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# Prognosis of adults admitted to medical departments with community-acquired bacteremia

PhD dissertation

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Health
Aarhus University
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Preface:

This thesis is the result of studies carried out during my PhD position at the Faculty of Health Sciences, Aarhus University and the Department of Infectious Diseases, Aalborg University Hospital.

I am deeply indebted to a number of persons. First and foremost I would like to thank my supervisors. Henrik C. Schønheyder helped me find my way to Aalborg where he enthusiastically introduced me to research. He is a giant in bacteremia research and naturally his insight was pivotal. Henrik Nielsen has continuously encouraged and supported me. His mentorship, input and feedback has been invaluable. Reimar W. Thomsen inspired me. He deftly and patiently taught me many lessons on clinical epidemiology and biomedical writing.

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Michael Dalager-Pedersen, March 2014

This PhD thesis is based on the following four studies:

I) Dalager-Pedersen M, Søgaard M, Schønheyder HC, Nielsen H, Thomsen RW. Risk for myocardial infarction and stroke after community-acquired bacteremia: A 20-year population-based cohort study. *Circulation*. Feb 12 2014 [Epub ahead of print]

II) Dalager-Pedersen M, Søgaard M, Schønheyder HC, Thomsen RW, Baron JA, Nielsen H. Venous thromboembolism after community-acquired bacteraemia: A 20-year Danish cohort study. *PLoS One*. 2014; 9:e86094.

III) Dalager-Pedersen M, Koch K, Thomsen RW, Schønheyder HC, Nielsen H. The effect of community-acquired bacteraemia on return to workforce, risk of sick leave, permanent disability pension and death: a Danish population-based cohort study. *BMJ Open*. 2014; 4:e004208.

IV) Dalager-Pedersen M, Thomsen RW, Schønheyder HC, Nielsen H. Functional status and quality of life after community-acquired bacteraemia: A matched cohort study. [Manuscript in preparation]

List of abbreviations:

| | |
|---|---|
| Adj. | Adjusted |
| ACS | Acute coronary syndrome |
| ADL | Activities of daily living |
| AIS | Acute ischemic stroke |
| AMI | Acute myocardial infarction |
| CAB | Community-acquired bacteremia |
| CI | Confidence interval |
| CNS | Central nervous system |
| COPD | Chronic obstructive pulmonary disease |
| CRP | C-reactive protein |
| CRS | Civil Registration System |
| CVD | Cardiovascular disease |
| DAMP | Damage associated molecular pattern |
| DVT | Deep venous thrombosis |
| DIC | Disseminated intravascular coagulation |
| DREAM | [The register-based evaluation of the extent of marginalization] |
| EPCR | Endothelial protein C receptor |
| EQ-5D | European quality of life 5 dimensions (questionnaire) |
| HRQOL | Health-related quality of life |
| HDR | Hospital Discharge Registry |
| HR | Hazard rate ratio |
| IADL | Instrumental activities of daily living |
| ICD | International classification of diseases |
| ICU | Intensive care unit |
| IQR | Inter-quartile range |
| MODS | Multi organ dysfunction syndrome |
| OR | Odds ratio |
| PAMP | Pathogen associated molecular pattern |
| PE | Pulmonary embolism |
| PRR | Pattern recognition receptor |
| QOL | Quality of life |
| RD | Risk difference |
| RR | Relative risk |
| RTI | Respiratory tract infection |
| SF-36 | Short form 36 (questionnaire) |
| SIRS | Systemic inflammatory response syndrome |
| TFPI | Tissue factor pathway inhibitor |
| TNF | Tumor necrosis factor |
| TLR | Toll-like receptor |
| UTI | Urinary tract infection |
| VTE | Venous thromboembolism |
| WBC | White blood cell count |
| WHO | World Health Organization |

# Contents

# 1. Introduction to thesis

Community-acquired bacteremia (CAB) is a major healthcare problem. In recent decades, the incidence of hospital admissions for CAB has increased by 50%.[1,2] Meanwhile, CAB mortality has remained virtually unchanged and high.[3–11] Today, CAB is one of the most prominent causes of death in the Western world.[12–14] Because the incidence of CAB has increased while mortality has been stable, the proportion of CAB survivors in Western populations is increasing.[15]

Many studies have described death following CAB, arguably the most serious outcome of any disease. Still, there are many other potential adverse outcomes of CAB, including but not limited to other disease, disability, decline in quality of life, and impoverishment. Knowledge on these other outcomes after CAB is of high import for patients, families, health care providers, and policy makers.

The four studies on which this thesis is based were conducted to examine the prognosis of medical patients with CAB. Two studies detail the risk of arterial and venous thromboembolic events, respectively, after CAB. The third study describes return to work, duration of sick leave, and risk for disability pension and death after CAB among patients of working-age. Finally, the fourth study portrays the effect of CAB on functional status and quality of life.

# 2. Introduction to bacteremia

*"But every observer who has worked with processes of actual observation of the blood and tissues of man is agreed as to the absence from them of micro-organisms, save in disease"*

*Sir Alexander Ogston (1882)*

## 2.1 Definitions

Bacteremia is defined as viable bacteria in the bloodstream (the suffix "–emia" refers to the blood), normally evidenced by growth in blood cultures.[16–18] During the formative period of clinical bacteriology no taxonomic division was made between bacteria and fungi, and hence the term bacteremia also included fungemia from the outset.[16] A key issue when interpreting a positive blood culture is to judge the credibility of the result, i.e. is it true-positive (bacteremia) or false-positive (contamination). In theory, contamination can occur in any step from blood culture bottle manufacture to the final subculture.[19] However, with high quality modern day manufacturing methods, contamination typically occurs during the blood-sampling procedure.[20] The microbial culprit provides important interpretative information. For example, *Streptococcus pneumoniae* and *Escherichia coli* are rarely contaminants while members of the normal skin flora (e.g. coagulase-negative staphylococci, diphtheroids) can contaminate during the venipuncture procedure.[17,21] Clinical findings are also important for the interpretation, does the patient (still) appear to have an infection and, if so, is the cultured microorganism compatible with the suspected infection. There are several other tools that may guide interpretation of blood culture results and these are reviewed elsewhere.[22,23]As bacteria can be introduced into the bloodstream after minimal trauma, such as catheterization and endoscopy, it is relevant to distinguish between transient and more sustained bacteremia.[19] Under normal circumstances transient bacteremias remain clinically silent and inconsequential, as circulating microorganisms are removed by the host immune system within minutes to hours.[22] Still, on rare occasions host defenses fail to clear the bloodstream and microorganisms may find a *locus minoris resistentiae* (a place of less resistance) and cause disease.[19] A well-known example is endovascular infection following tooth brushing or dental procedures.[24] More sustained bacteremia occurs when bacteria are released from an infected site into the blood, or when the infection is intravascular. In daily practice, joint microbiological and clinical expertise is called upon to decipher whether bacterial or fungal isolates that grow in blood cultures have etiological significance and cause a more sustained and medically relevant bacteremia.[16,17,19]

There are many ways to classify bacteremia. Of chief relevance for this thesis is that bacteremia can be classified according to the place of acquisition. It can be community-acquired, i.e. arise in the community, or hospital-acquired (nosocomial), i.e. arise during hospital stay. The word nosocomial is derived from Greek

(*nosos*: disease, *komein*: to take care of, *nosokomein*: hospital). In 1988, the US Centers for Disease Control used a number of criteria to define nosocomial "laboratory-confirmed bloodstream infection and clinical sepsis" including that there must be no evidence that the infection was present or incubating at the time of hospital admission.[25] As first done by McGowan et al. in 1975, many studies have defined nosocomial bacteremia as clinically significant positive blood cultures drawn after more than 48 hours of hospitalization.[17,26–28] In contrast, infections are deemed community-acquired if diagnosed or incubating in the community or within 48 hours after hospital admission.[17,29] Additional criteria for community-acquired infections are increasingly used, including no history of recent hospital stay, to distinguish "true" community-acquired infections from health-care associated infections with community-onset.[7,10,30–34] In the studies on which the present thesis is based, community-acquired bacteremia is defined as a clinical entity with positive and clinically relevant blood cultures within 48 hours of hospital admission and no hospital stay in the previous 30 days.

Bacteremia episodes may also be classified according to causative pathogen (microbial isolate/s) and focus of infection. Different types of pathogens and foci are closely associated with each other and with types of place of acquisition. The distribution of microbial isolates and foci of infection in community-acquired bacteremia in North Denmark from 1992 to 2010 are shown in Figure 1 and 2, respectively, which are based on original data from the North Denmark Bacteremia Research Database.[16] Of note, *E. coli, S. pneumoniae,* and *Staphylococcus aureus* were the three most common pathogens isolated in monomicrobial bacteremia-episodes, accounting for 35.7%, 21.4%, and 7.5% of episodes respectively (Figure 1). These three pathogens are similarly ranked in a range of comparable studies from other Western countries.[21,30,31,34–40] They are also frequent causes of CAB in Africa and Asia, although Salmonella isolates are more commonly encountered in these continents.[41,42] In contrast, enterococci, *Pseudomonas aeruginosa*, and coagulase-negative staphylococci, which are uncommon in CAB (1.5%, 1.0%, and 0.7% of episodes locally), are relatively more common as causes of health-care related and hospital-acquired bacteremia, and so is *S. aureus*.[1,21,28,31,34,40] Generally, pathogens that cause CAB are less resistant to antibiotics than causative pathogens in health-care related and hospital-acquired bacteremia.[31–33] Although most bacterial pathogens can cause a number of different infections, the identification of a given causative pathogen may be an important clue in the search for an infectious focus. For instance, *E. coli* is closely associated with urinary tract infection and *S. pneumoniae* with respiratory tract infection. *S. aureus* commonly cause infection of skin, bone and joint but should, in accord with Keefer's Dictum, also prompt consideration of endocarditis.[19,43] Knowing the rank order of CAB-pathogens, and their predilection for certain infectious foci, it comes as no surprise that urinary tract infection (33.5% of CAB episodes) and respiratory tract infection (20.4% of episodes) are the most common infectious foci in CAB in North Denmark (Figure 2).

**Figure 1. Causative pathogen(s) in 5076 episodes of CAB, North Denmark, 1992-2010.**

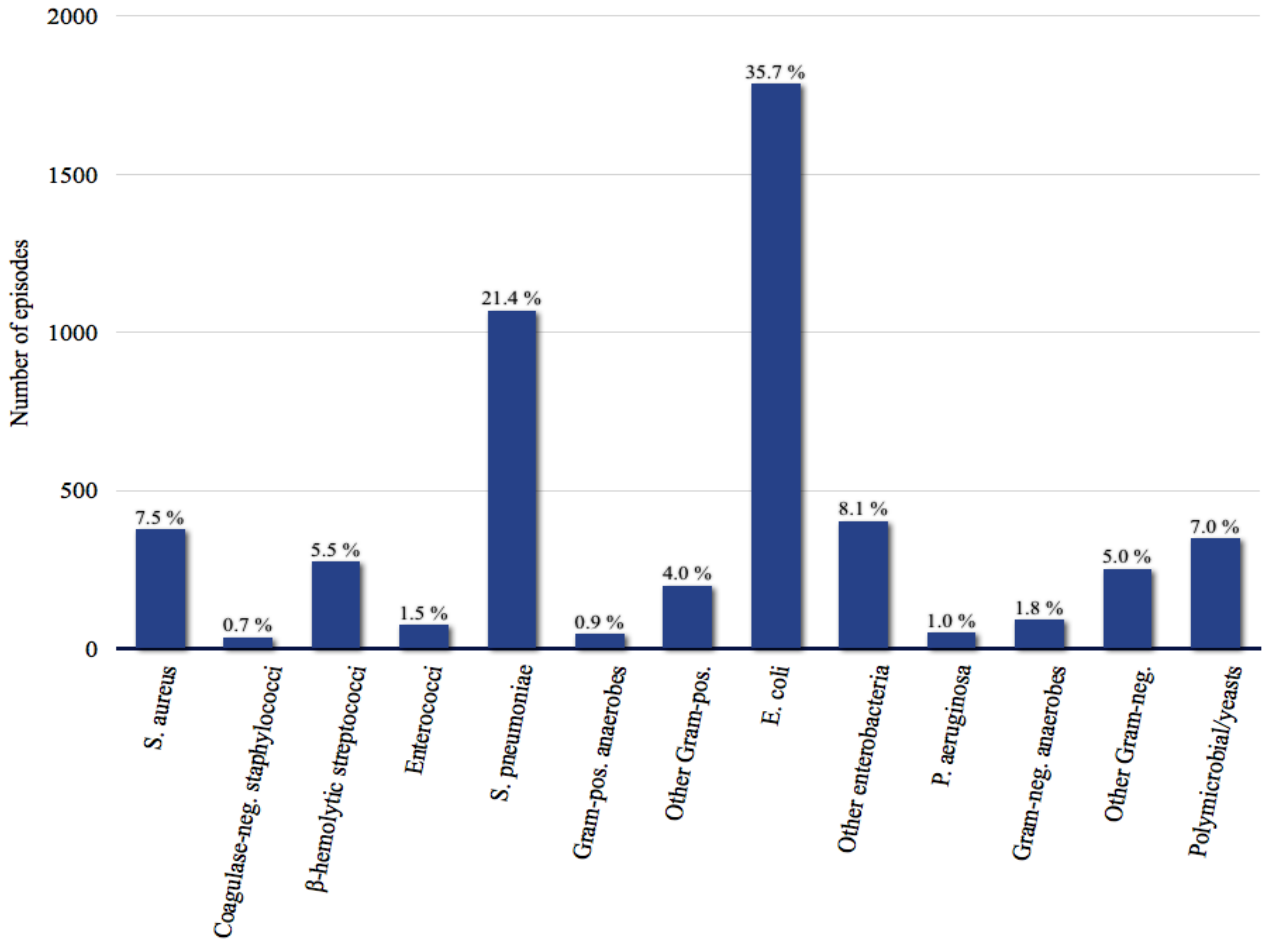
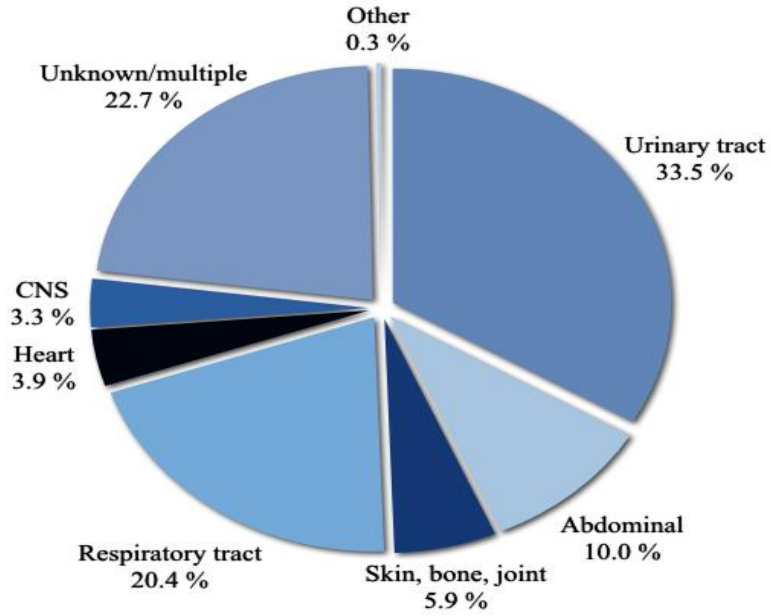



**Figure 2. Focus of infection in 5076 episodes of CAB, North Denmark, 1992-2010.**



## 2.2 Burden of bacteremia and risk factors

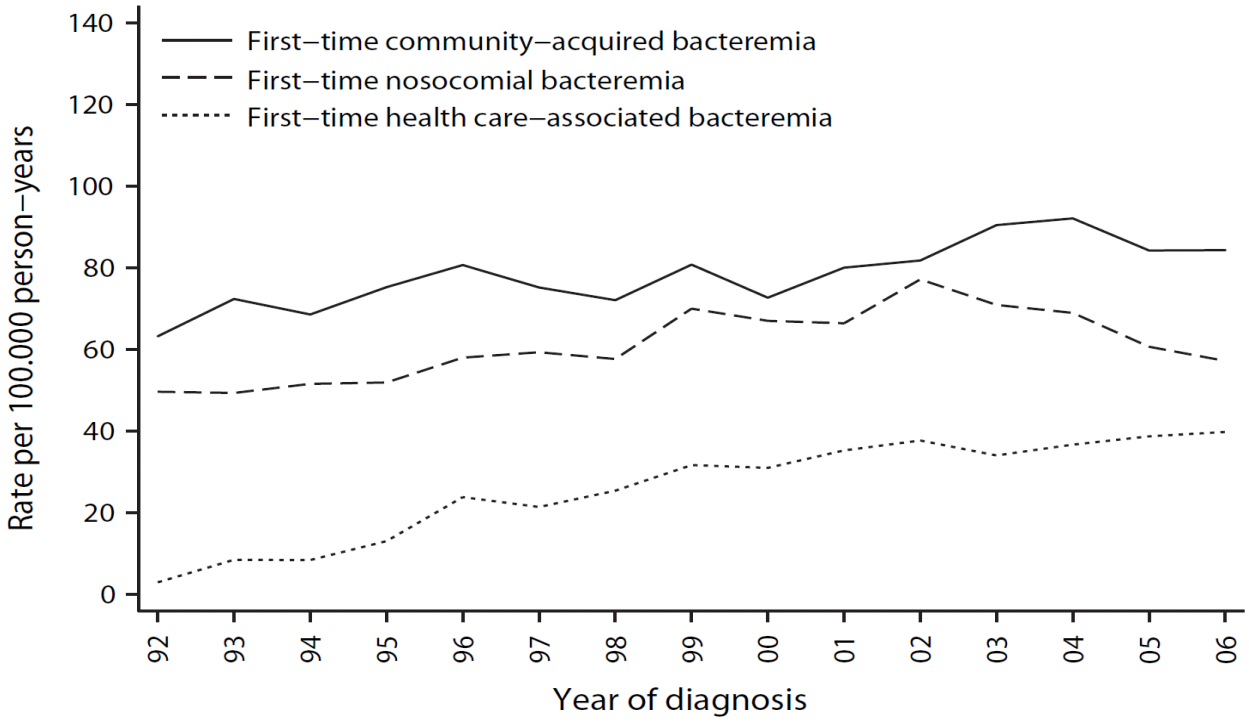
In Denmark and other Western countries, studies have found an increasing incidence rate of hospitalization for CAB and other severe acute bacterial infections (e.g. sepsis) in recent decades.[1,2,13,44–49] Figure 4 shows the bacteremia hospitalization rate in North Denmark from 1992-2006. It illustrates a 50% increase in incidence rate over the study period and that the most common place of acquisition is the community (approximately 50% higher rate than for nosocomial bacteremia). In 2006, the incidence of first-time hospitalization with bacteremia was 166 per 100.000 person years, and for CAB it was approximately 90.[1] As such, the incidence of hospitalized CAB is similar to that of hospitalized acute myocardial infarction in Denmark.[50] Studies from other countries have depicted a similar bacteremia incidence rate, e.g. in Canada where Laupland et al. reported an average community-onset bacteremia incidence rate of 82 per 100.000 person years between 2002 and 2004 in Calgary[30], and 101 per 100.000 years during 1998-2005 in Victoria.[39]

Several factors – *risk factors* – affect the risk of hospital admission with bacteremia and may have influenced the increasing bacteremia rate. Age is one important risk factor. Approximately a third of adult patients hospitalized for first-time CAB are of working-age (15-64 years old).[1] However, the incidence of hospitalization with CAB increases markedly with increasing age.[1,37,49] When considering all types of hospitalized bacteremia episodes in Finland, Skogberg et al. found an incidence rate of 932 per 100.000 person years in persons ≥85 years of age.[49] Like increasing age, many other risk factors for bacteremia are associated with biomedical progress, e.g. a rising prevalence of people surviving with chronic disease and an increasing use of chemotherapeutics, other immunosuppressive agents, and surgical interventions. Studies from North Denmark have found that diabetes mellitus, and hematological malignancies are risk factors for bacteremia, as are other cancers, heart disease, lung disease, alcoholism, and HIV.[38,51–53] Socioeconomic factors and institutionalization are also important risk factors (Kristoffer Koch et al., accepted for publication in American Journal of Epidemiology 2014).[54] In addition to an increased prevalence of risk factors, the recent rise in diagnosed bacteremia incidence may also in part be explained by a lowered threshold for blood culture draw (ascertainment bias) and changes in blood culture methodology.[55] Because average life expectancy and the prevalence of people living with disease is projected to increase in Denmark and worldwide[56], it is likely that the incidence of bacteremia will continue to rise.

A discussion of the burden of bacteremia is not complete without emphasizing that bacteremia is a common cause of death. Bacteremia (septicemia) is estimated to be the 11$^{th}$ most common cause of death in the US.[57] However, these estimates are based on death records and focus on the one *underlying* cause of death. Therefore, the true bacteremia-associated death-burden may be far higher if *contributory* causes of death are taken into account.[13,58,59] As an example, older studies that examined "causes of death in cancer patients"

found that infection was by far the most common cause of death (38% of deaths were associated with bacteremia, and up to 68% with infection).[60,61] A more recent study estimated that 43% of deaths in hospitalized medical patients in Aalborg in 2008 were associated with infection, and that 17% of these deaths were associated with a diagnosed bacteremia episosde.[62] Indeed, Goto and Al-Hasan recently estimated 1900 annual deaths from bacteremia in Denmark making it the 7th leading cause of death while Raoult and Richet have suggested that bacteremia may be the 4th leading cause of death in Europe (following cardiac disease, lung cancer, and cerebrovascular disease).[13,59] In total, North America and Europe face an estimated 2 million bacteremia episodes and one-quarter of a million bacteremia-related deaths annually.[13]

**Figure 4. Age- and sex-standardized incidence-rates of hospital-diagnosed bacteremia in North Denmark, 1992-2006. With kind permission from Mette Søgaard**[1]



## 2.3 A history of bacteremia and related terms

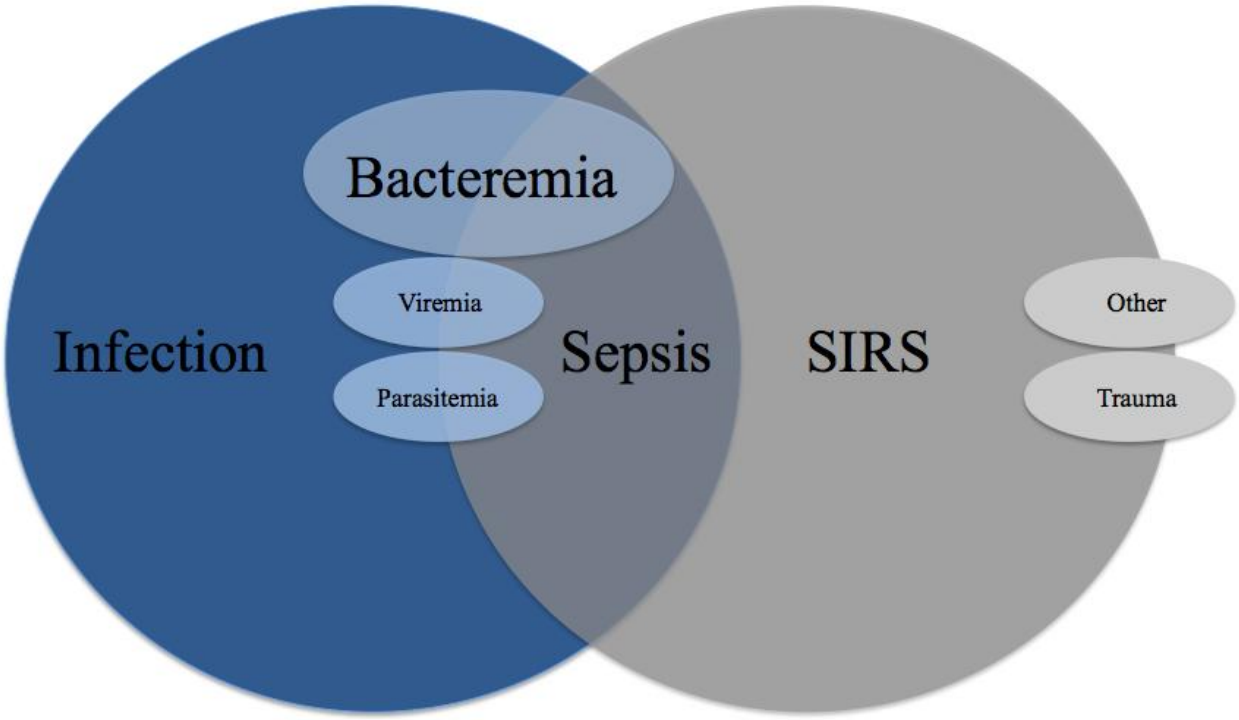
> *Everyone has a vague notion of what the terms bacteremia, septicemia, sepsis, the sepsis syndrome, and septic shock mean. Too often, however, these words are used interchangeably in speech and in professional literature, which can lead to considerable bewilderment.*
>
> *Roger C. Bone (1991)*

The medical literature is full of terms that are closely related to bacteremia, which may hamper the understanding of bacteremia. It is fruitful to briefly consider the history of bacteremia and related disease syndromes, most importantly sepsis. Sepsis is derived from the Greek and refers to the decomposition of animal, vegetable or organic material – the verb *sepo* means "I rot".[63] The term was used in a medical context in the poems of Homer (circa 700 BC), and later in Hippocrates' Corpus Hippocratum. Fast forward to the 17th century, when Antonie Philips van Leeuwenhoek produced a microscope of adequate quality to make the first observations of single-cell organisms and thereby paved the way for the development of the germ theory of disease (reviewed elsewhere).[64,65] A century later the Danish zoologist and botanist Otto Friderich Müller was the first to suggest taxonomy for bacteria including the names Proteus, Vibrio and Monas.[66]

In 1850, the French physician Casimir Joseph-Davaine unequivocally linked bacteria in blood (*Bacillus anthracis*) to animal disease and soon thereafter his compatriot, Edmé Vulpain, invented the term *Bactériémie* (bacteremia).[67] In the early1880's Sir Alexander Ogston, a Scottish Surgeon, published a series of seminal papers on suppurative infections due to "micrococci" including both staphylococci and streptococci. Ogston realized that local and phlegmonous infections formed a continuum with "blood-poisoning", "pyemia" and "septicemia", but he saw blood merely as a vehicle of dissemination.[68–70] The Austrian surgeon Anton Freiherr von Eiselberg was probably the first to point out the utility of blood culture for demonstrating "Eitercoccen" (i.e. pyogenic cocci).[71] Blood culture featured as a new diagnostic test in the 2nd edition of William Osler's Textbook of Medicine published in 1898.[72] However, the clinical and academic interest in bacteremia was primarily centered on patients with typhoid fever or endocarditis. The advent of serum therapy for pneumococci in the 1910's and sulfaphyridine therapy in the 1930's meant a greater utility of culture-based diagnoses and this development continued after the 2nd World War with two significant boosters: Cumulated data on blood culture pathogens drew attention to the development of resistance to new antibiotics such as tetracyclines and streptomycin[73], and studies by Waisbren and collaborators drew attention to the link between Gram-negative bacteremia and septic shock.[74] The latter studies inaugurated an important series of studies including the first two papers on severity of underlying disease and mortality after bacteremia by McCabe and Jackson and the first population-based bacteremia studies from the US Carolinas.[28,75–78] With direct reference to contemporary advances in clinical epidemiology, two seminal papers by Weinstein and colleagues appeared in 1983 that have laid the foundation for studies to come.[17,18]

Meanwhile the ancient word sepsis began to lose its connotation with rottenness and instead came to suggest infection, more specifically the systemic response to invading microorganisms of all types.[79–81] Because of increasingly complex terminology, the American College of Chest Physicians/Society of Critical Care Consensus Conference was held to develop a uniform set of definitions (published in 1992).[80,82,83] At this conference, Roger C. Bone et al. coined the term "systemic inflammatory response syndrome" (SIRS) to signify the underlying systemic response to infection and similar noninfectious disorders (e.g. trauma).[82] Criteria for SIRS were two or more abnormalities in body temperature (<36°C or >38°C), heart rate (>90 beats/minute), respiratory function (respiratory rate >20 breaths/minute or arterial oxygen tension<32 mmHg), white blood cell count (>12*10^9/L, <4*10^9/L, or >10% immature neutrophils). Sepsis was labeled as SIRS caused by *confirmed* infection and it was suggested that the term septicemia should be discarded. Moreover, severe sepsis was defined as sepsis complicated by organ dysfunction, and septic shock as sepsis plus hypotension despite adequate fluid resuscitation (e.g., a systolic blood pressure below 90 mmHg in adults). The interrelationship between SIRS, sepsis and bacteremia is shown in Figure 3.

**Figure 3. The interrelationship between infection, systemic inflammatory response syndrome (SIRS), sepsis, and bacteremia. Modified from Bryan et al.[19] and Bone et. al.[82]**



The SIRS term was soon criticized, among other things for being overly sensitive and too non-specific[83,84], and in 2001 a new consensus conference was convened by five societies to renew the terminology.[85] The SIRS concept was abandoned and the diagnostic criteria for sepsis were changed to *confirmed or suspected* infection plus "some" signs (later defined as "one" sign[86]) of systemic inflammatory response to infection, while definitions of severe sepsis and septic shock were essentially unaltered.[85] Still, the SIRS term has proven hard to rid and to this day it is used in numerous studies, review articles and in clinical guidelines on the management of sepsis.[87–95] Other highly influential papers on sepsis use the more recently outlined non-SIRS based criteria for sepsis.[86,96–98] As may be evident, sepsis is hard to define and difficult to diagnose, and therefore the risk of misdiagnosis is considerable.[99–101] As noted by one prominent sepsis researcher "Sepsis is a real phenomenon…but it is too generic (diverse) to have a meaningful pathophysiological description or definition".[102] It is noteworthy that during recent decades of changing diagnostic criteria for sepsis, the definition and diagnostic criteria of bacteremia (presence of viable bacteria in the bloodstream) have remained unchanged. While bacteremia and sepsis are not the same, they are closely related and often discussed simultaneously.[54,103–107] As a case in point, 85% of medical patients with pneumococcal community-acquired bacteremia may have sepsis (using the SIRS based criteria for sepsis) and 50% severe sepsis.[108] In comparison, bacteremia may be found in 20% of hospitalized sepsis patients, 30% of severe sepsis patients, and more than 50% of septic shock patients.[86,109–113] The relatively low percentage of sepsis patients with positive blood cultures may in part be explained by the administration of antibiotics prior to blood cultures being obtained in these severely ill patients.[22,111,114,115] The close association between bacteremia and sepsis is also evident in the highly influential Surviving Sepsis Campaign Guidelines, which focus on the management of severe sepsis and septic shock.[116] These guidelines have continuously stressed the need for early blood culture draw and subsequent antibiotic/antifungal therapy. However, not until their third edition, in 2012, did they address other infectious agents that may cause sepsis and their treatment (e.g. viral agents and antiviral therapy).[96–98]

*"Formerly, and in a surgical sense, the term "Septicæmia" was used to designate the invasion of the blood and tissues of the body by the organisms of suppuration, but in the medical sense the term may be applied to any condition in which, with or without a local site of infection, there is microbic invasion of the blood and tissues, but in which there are no foci of suppuration. Owing to the great development of bacteria in the blood, and in order to separate it sharply from local infectious processes with toxic invasion of the body, it is proposed to call this condition bacteræmia; toxæmia denotes the latter state."*

*William Osler. The Principles and Practice of Medicine. D. Appleton & Co., New York, 3rd Ed. 1898. Pp. 161*

## 2.4 The pathophysiology of bacteremia

### 2.4.1 Inflammation

Every day the human body is exposed to vast numbers of commensal and pathogenic microorganisms that may potentially cause infection. However, surface epithelia and other defense mechanisms present an effective barrier to infection. If bacterial/fungal pathogens manage to successfully evade these barriers they may cause localized infection or disseminate and replicate in the bloodstream. Sustained and clinically relevant bacteremia may ensue that may eventually lead to the clinical syndrome sepsis - the host systemic inflammatory response to invading microorganisms.[22,79,80,117–119] This host response is complex. What follows is but a brief overview of the host-pathogen interactions in sepsis, including effects that these interactions may have on the coagulatory and cardiovascular systems. Initially, innate immune cells recognize invading microorganisms through a limited number of pattern-recognition receptors (PRRs), such as the Toll-like receptor family (TLRs), see Table 1.[120,121] PRRs sense common microbial structures (pathogen-associated microbial patterns, PAMPs), e.g. lipopolysaccharide from Gram-negative bacteria (Table 1).[120,121] In addition to PAMPs, PRRs are also triggered by endogenous danger signals such as fibrinogen, hyaluronic acid, and high-mobility group box-1 (a nuclear protein present in most eukaryotic cells) that may be released after trauma or burns. These endogenous molecules have been named danger-associated molecular patterns (DAMPs) and also "alarmins".

**Table 1. Examples of pattern recognition receptors and their ligands, modified from Takeuchi et al.**[121]

| Pattern-recognition receptors | Localization | Ligand | Origin of ligand |
|---|---|---|---|
| **Toll-like receptors (TLRs)** | | | |
| TLR1 | Plasma membrane | Triacyl lipoprotein | Bacteria |
| TLR2 | Plasma membrane | Lipoprotein, lipoteichoic acid, peptidoglycan, high-mobility group box-1 | Bacteria, viruses, parasites, self |
| TLR3 | Endolysosome | dsRNA | Viruses |
| TLR4 | Plasma membrane | Lipopolysaccharide, mannan, high-mobility group box-1 | Bacteria, fungi, self |
| TLR5 | Plasma membrane | Flagellin | Bacteria |
| **C-type lectin receptors** | | | |
| Dectin-1 | Plasma membrane | β-Glucan | Fungi |
| **Retinoic acid-inducible gene (RIG)-I-like receptors** | | | |
| RIG1 | Cytoplasm | Short dsRNA, 5'triphosphate dsRNA | Viruses |
| **Nucleotide-oligomerization domain (NOD) leucine-rich repeat proteins** | | | |
| NOD2 | Cytoplasm | Muramyl dipeptide | Bacteria |

Triggering of PRRs on macrophages, dendritic cells, and neutrophils activates intracellular signal transduction pathways (e.g. Nuclear Factor-κβ activating pathways and caspase-1 activating platforms termed "inflammasomes") that in turn up-regulates the production of an array of proteins involved in the inflammatory response (e.g. proinflammatory cytokines, such as interleukin (IL)-1 and 6 and tumor necrosis factor alpha (TNF), and chemokines such as IL-8).[120–123] Secreted cytokines and chemokines initiate an inflammatory cascade with further production of pro-inflammatory proteins, recruitment of other cells of the immune system, and localized stasis and edema.[86,118,124] The ensuing inflammatory response may eliminate the invading microorganism(s) but it also leads to collateral host tissue damage. Thus, signal amplification come into play with DAMPs further triggering PRRs and pro-inflammatory proteins begetting more pro-inflammatory proteins – potentially a cytokine storm. However, a concurrent release of anti-inflammatory cytokines (e.g. IL-10 and 13 and transforming growth factor beta) regulates the inflammatory repsonse.[122] In recognition that sepsis is more than "just" a pro-inflammatory response to infection (SIRS), Roger C. Bone proposed the terms "compensatory anti-inflammatory syndrome" and "mixed antagonists response syndrome" before his death in 1997.[125] While these terms never really caught on, sepsis is now widely considered a misbalance between pro-inflammatory reactions and anti-inflammatory responses.[119,120] The host inflammatory response can be balanced, with killing of microorganisms, repair of damaged tissues, no/few symptoms of infection and full recovery.[119] Or, it can be aberrant and unbalanced with either apoptosis of immune cells and immune suppression or hyperinflammation and coagulation activation.[119,126]

### 2.4.2 Coagulation

Activation of the coagulation system occurs in most patients with bacteremia and sepsis.[119,126,127] The endothelial lining of vessel walls, activated by IL-1 and TNF, plays a pivotal role in the inflammatory response and the accompanying activation of the coagulation system.[127,128] Historically, many significant and parallel discoveries have been made concerning the inflammation and coagulation cascades.[64] In an early study Nawroth et al.[129] showed that IL-1 induced endothelial production of a procoagulant named tissue factor. During inflammation, tissue factor is also produced by monocytes/macrophages. It is expressed constitutively in subendothelial tissues and may bind to coagulation factor VIIa for initiation of the extrinsic pathway of the coagulation system. This leads to increased thrombin and fibrin generation – crucial constituents of blood clots (thrombi). Thrombin itself is a key activator of platelets. Pro-inflammatory cytokines may bring about endothelial perturbation, detachment, apoptosis, and release of von Willebrand factor thereby allowing activated platelet to adhere to subendothelial surfaces and clot formation.[124,127] Vessel-wall neutrophil extracellular traps - tangles of extracellular DNA (e.g. histones) from apoptotic immune and endothelial cells and trapped red blood cells - may also form a surface for clot formation.[128,130]

Blood clotting is inhibited by three major anticoagulants: tissue factor pathway inhibitor (TFPI) produced by endothelial cells, (activated) protein C, and antithrombin. For protein C to be activated, endothelial protein C

receptor (EPCR) and thrombomodulin expressed by endothelial cells are needed. During inflammation, endothelial TFPI, EPCR, and thrombomodulin is down regulated (hence diminished protein C activation), and plasma antithrombin is low.[118,127,130] When blood clots have been formed, components of the fibrinolytic system (e.g. plasmin) inhibit their growth and promote their dissolution. Inflammatory stimuli increase endothelial production of plasminogen inhibitor type-1, which inhibits the conversion of plasminogen to plasmin.[118,127,130] Thus, systemic inflammation may induce activation of platelets, up-regulation of pro-coagulant pathways, down-regulation of anti-coagulants, and inhibition of fibrinolysis.[118–120,126–128,130,131] To complicate matters further, coagulation factors may trigger endothelial cell and monocyte protease activated receptors, which further increase the production of pro-inflammatory cytokines and hence coagulation.[127,131] The net result is a pro-thrombotic state, which may be considered physiologically advantageous in confining inflammatory activity to the site of infection. However, a deviant pro-thrombotic state during infection may lead to widespread microvascular thrombosis (known as disseminated intravascular coagulation, DIC).

The mechanisms described above have focused on the host response to invading microorganisms. Still, microbial factors influence the host response during infection.[119] Virulence factors of pathogenic microorganisms may cause direct damage to numerous host cells including endothelial cells.[132] Pore-forming cytotoxins, such as hemolysin produced by many bacteria and fungi may disrupt membranes and lyse host cells (with further indirect tissue damage through release of DAMPs).[133–135] Cytotoxins can also affect the vascular resistance through direct stimulation of thromboxane A2 and leukotrien production (vasoconstrictors), and indirectly through endothelial NO release (a vasodilator).[133,136] Some bacteria, such as *S. aureus*, may also directly activate platelets thereby supporting the pro-thrombotic state in sepsis.[137–139]

### 2.4.3 Organ failure

*When death occurs* in patients with bacteremia and sepsis it is often due to organ failure.[118,130] Typically, patients will first develop a single organ failure and if the disease process is not controlled, further organ failure may follow (multi organ dysfunction syndrome, MODS).[118] As an illustration, heart failure is common in patients with sepsis. Early studies by Calvin et al. and Parker and Parrillo et al. showed that patients with sepsis have reversible myocardial depression lasting several days to weeks, and that the mechanism may involve cytokine-induced (TNF and IL-1) inhibition of cardiomyocyte contraction amplitude and velocity.[64,140–142] Other mechanisms of heart failure during infection may include hypotension, hypoxemia, red blood cell deformability, and mitochondrial dysfunction.[143–145] It may also include, inflammation-induced cardiac arrhythmia such as atrial fibrillation, perhaps through triggering of PRRs (TLR).[146–148] Finally, it may be due to myocardial infarction.[149] Irrespective of the underlying mechanism, heart failure may lead to further organ failure, MODS, and death.

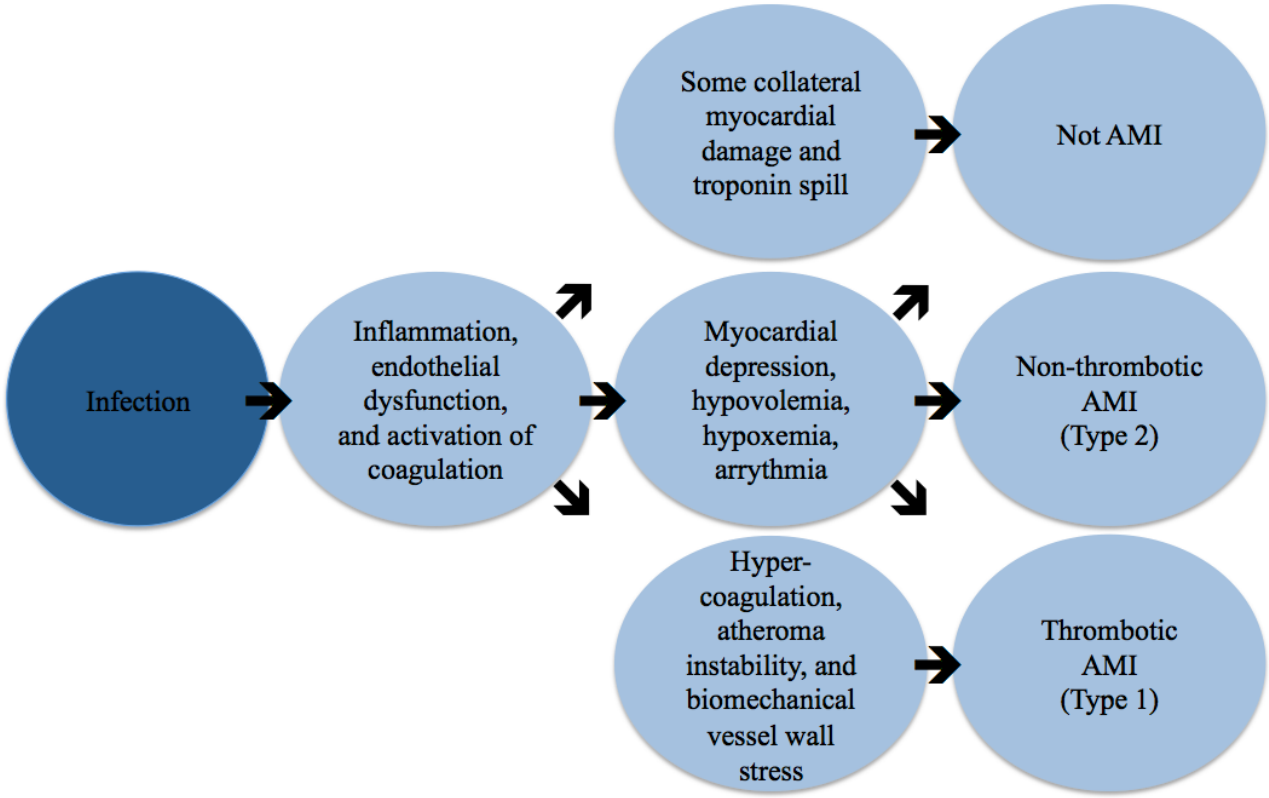
*When death does not occur* (quickly) in patients who suffer from severe infection, recovery is not instantaneous nor may it be complete. As illustrated above, myocardial dysfunction may last for weeks after infection. However, it is not just the heart that may suffer during and after severe infection. Severe infection may induce prolonged or permanent unspecific brain dysfunction, cognitive impairment, renal failure, myopathy and muscle atrophy with prolonged limb and respiratory muscle weakness.[150–152] Patients who have been discharged after hospitalization for pneumonia may experience long-lasting (subclinical) inflammation.[153]

### 2.4.4 Thromboembolic events

The most common thromboembolic events encountered in clinical practice are acute myocardial infarction (AMI), acute ischemic stroke (AIS), and venous thromboembolism (VTE).

AMI is defined as acute myocardial necrosis in the setting of myocardial ischemia.[154] Current diagnostic criteria for AMI include an elevated blood troponin measurement plus at least one more criterion among the following: symptoms of ischemia, electrocardiographic changes indicative of new ischemia (e.g. ST-segment elevation, ST-segment depression, new left bundle branch block), development of electrocardiographic Q-waves, imaging with evidence of new loss of viable myocardium. The archetypical AMI is one with sudden rupture of an atherosclerotic plaque and thrombosis in a cardiac artery (type 1 AMI). Other types of AMI may occur, including AMI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary embolism, hypotension, or arrhythmia (type 2 AMI). For management purposes, patients with chest pain may be categorized as having acute coronary syndrome or not. Acute coronary syndrome is an umbrella term for AMI with ST-segment elevation (STEMI), AMI with non-ST-segment elevation (NSTEMI), and unstable angina pectoris.[155] Infection may invoke some collateral myocardial injury and troponin spill without actual AMI (Figure 5).[154,156,157] However, systemic inflammatory activity, myocardial depression, hypotension, and arrhythmia may also lead to severe myocardial ischemia and a non-thrombotic acute myocardial infarction (a type 2 AMI).[141,143,145,149,154,158–161] Moreover, inflammation-induced endothelial dysfunction, hypercoagulation, and atheroma instability as well as biomechanical vessel wall stress may provoke atherosclerotic plaque rupture, fissuring, or dissection with superimposed thrombosis (a type 1 AMI).[149,154,162]

**Figure 5. Potential mechanisms by which acute infection may trigger acute myocardial infarction**




The collective term "stroke" was recently defined as embracing many different cerebrovascular events that cause CNS infarction.[163] CNS infarction denotes brain, spinal cord, or retinal cell death attributable to ischemia, based on pathological, imaging, other objective evidence, and/or clinical symptoms.[163] Clinical symptoms must persist ≥24 hours or until death, and other etiologies must be excluded.[163] AIS is CNS infarction due to focal ischemia and cell death that occurs within the perfusion territory of an artery that is stenosed or occluded.[163] Similar to AMI, AIS may be triggered by infections because of hypotension, endothelial dysfunction and hypercoagulation.[164] On top of this, infection-related atrial fibrillation or hypokinetic cardiac wall motion may lead to intracardiac formation of thrombotic material and embolization to cerebral vessels.[165,166] Likewise, vegetations in infective endocarditis may dislodge and result in stroke.[164,167,168] Infections that directly affect the cerebrum and/or adjacent tissues, e.g. bacterial meningitis, may also cause localized vasculitis and thrombosis.[164,169]

A VTE is any thromboembolic event that occurs within the venous system.[170] It most commonly starts in the calf veins and may propagate proximally (deep venous thromboembolism, DVT). Furthermore, it may dislodge and travel to the lungs to cause a pulmonary embolism (PE). Because approximately 25% of adults have a patent foramen ovale (average diameter 5 mm), fragmented clot material may also travel to the arterial side where it may cause cerebral (AIS) or coronary embolization (type 2 AMI).[171–174] In the early 19$^{th}$

century, inflammation of the veins (phlebitis) was considered the major cause of venous thrombosis (thrombophlebitis).[175] Rudolf Virchow (1821-1902) was incensed by the idea that inflammation caused venous thrombosis and instead proposed a triad of endothelial damage, hypercoagulability, and venous stasis as the underlying mechanism.[175] In recent years, scientists have again suggested that inflammation and infection may be a cause of VTE, partly because of an operating Virchow's triad.[176–181] Infection-associated endothelial damage and hypercoagulability is detailed above. Venous stasis may be the result of heart failure during infection or prolonged bed rest and immobilization during and after infection.[182]

Previous studies have detailed that AMI, AIS, and VTE are associated events and that they may share many risk factors, examples of which include age, male gender, history of a previous thromboembolic event, thrombophilia (e.g. Factor V Leiden), hypertension, dyslipidemia, diabetes mellitus, smoking, chronic obstructive pulmonary disease, chronic renal disease, obesity, immobility, and cancer.[183–190] Acute infection can activate a number of pathophysiological mechanisms that may ultimately trigger thromboembolism. Thus, acute infection may be yet another shared risk factor for AMI, AIS, and VTE.

# 3. Introduction to epidemiology

*For epidemiology is the simplest and most direct method of studying the causes of disease in humans, and many major contributions have been made by studies that have demanded nothing more than an ability to count, to think logically, and to have an imaginative idea*

*Sir Richard Doll (1987)*

This thesis is based on studies in which we used epidemiological methods. The words *epidemeion* and *endemeion* were used by Hippocrates at the school of Cos (circa 400 BC) to incorporate a community outlook into the understanding of disease. Their purpose was to differentiate diseases that visit the community from those that reside in it (*epidemeion*: to visit). Later, epidemiology (*demos:* the people, *logos:* word, or a principle of order and knowledge) has been coined as the study of the occurrence and distribution of health-related states or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control the health problems.[191] The cohort design is an important epidemiological study design. The word cohort is derived from Latin (a combination of *co:* together, and, *hortus:* enclosure, meaning: to be together in the same enclosure) and was used by Roman General and statesman Gaius Marius to designate an infantry unit (one tenth of a legion), circa 100 BC. In a cohort study a group of study subjects who share a common characteristic is followed forward in time – from exposure to outcome.[192,193] In observational cohort studies, in contrast to an experimental design or trial, the researcher does not assign the exposure. Moreover, the cohort study design is widely considered the best design for answering questions regarding prognosis and course of disease.[193–195] Cohort studies can be divided into prospective and retrospective cohort studies based on investigator perspective or data-record timing.[196,197] From the investigator perspective, cohort studies are "truly" prospective only if study subjects are followed forward in time after the investigator initiates the study. From the perspective of data-recording, cohort studies are prospective if information about exposure was recorded before the outcome occurred. The timing of data-recording has real validity consequences. For example, if study subjects are asked about their previous exposure history at the end of follow-up, it is possible that the occurrence of an outcome event can influence exposure recording, which may bias the study results (recall bias).[196] Therefore, the order of data-record timing is now considered the best way to differentiate between retrospective and prospective studies.[198]

All four studies in this thesis use the cohort design and all rely on prospectively collected data.

# 4. Introduction to prognosis research

Foreseeing the future has been an indispensable aspect of human life since before Pythia, the Oracle of Delphi.[199] Prognosis is derived from the Greek words *pro* and *–gnosis*, the latter meaning "knowledge" in a very broad sense. Together with diagnosis, prognosis became a key concept of Hippocratic medicine, which is the origin of modern clinical medicine. Today, prognosis refers to the risk of future outcomes in people with a given disease or health state.[195,200] Outcomes of disease can be classified in many ways. Half a century ago, Jack Elinson proposed the "five D's": Death, Disease (or illness, the patient's experience of disease), Disability, Discomfort, and Dissatisfaction.[201,202] Shortly thereafter, John W. Williamson suggested a "sixth D", namely disruption or destitution – the socioeconomic consequence of disease.[201–203] All six outcomes are relevant to patients to a certain degree but some can be more pertinent than others. The overall aim of prognosis research is to understand and improve future outcomes in people with a given disease/health state. To inform patients and next of kin is a primary concern, but in many ways prognostic information is also relevant for clinicians, scientists (including trialists), and for healthcare policy makers.[195]

The typical prognostic study utilizes a cohort design. It may be conducted to describe future outcomes in people with disease in the context of current diagnostic and treatment practices (fundamental prognosis research) and to compare the prognosis with that of other cohorts, e.g. the healthy background population.[195] When comparing the prognosis of several cohorts with different diseases or conditions, stratifying or adjusting for known risk factors of the outcome (potential confounders) may help to identify the true influence of the disease (exposure) on prognosis. In this respect there may be a fine line between prognostic cohort studies and etiological cohort studies, i.e. studies that attempt to identify causes – *etiological factors* – of a given outcome (in this case typically the outcome is a disease).[204] It is important to note that in fundamental comparative prognostic studies and etiological studies, investigators often adjust for as many confounders as possible in order to isolate the effect of the exposure, while taking care not to adjust for an intermediate variable on a causal path from exposure to outcome.[205] As an example, in examining the risk of VTE among hospitalized patients with CAB on the day of admission compared with hospitalized controls, adjustment for severity of illness might blur the effect of CAB on VTE. Why? Because severe inflammation (severe illness) may be a mediator within the pathway from CAB to VTE. In examining mechanisms by which CAB affect the risk of VTE, adjustment for severity of illness would be worth considering.[204]

A prognostic study may also examine specific factors – *prognostic factors* – that may be associated with prognosis (prognostic factor research), or use these factors in the development of a model, also known as risk score, prognostic score, outcome score, or clinical prediction rule, to predict individual risk of an outcome

(prognostic model research).[195,206,207] A prognostic factor, in the broadest sense, is any measure – clinical or non-clinical – that is associated with a subsequent outcome among people with a given health condition.[195,206] The relative effect of one prognostic factor compared with another can be estimated by the relative risk (e.g. a risk ratio or a hazard rate ratio derived from a time-to-event analysis). Prognostic factors may help define disease at diagnosis (e.g. according to focus of bacteremia or microbial agent), inform clinical and therapeutic decisions (individually or as part of a risk score)[208,209], plus identify targets for clinical trials.[206]

## 4.1 Prognosis of bacteremia

Among the six outcomes of disease mentioned in the previous paragraph, death is by and far the most studied outcome of CAB. Fundamental prognosis research has shown that adults hospitalized with CAB have a 30-day mortality of 13 to 20%, a 1-year mortality of 25 to 45%, and a 3-year mortality of approximately 50%.[1,9,10,14,210] To paraphrase evolutionary biologist Stephen Jay Gould, average 30-day or 365-day mortality isn't the only message in prognostic CAB studies.[211] Information on the timing of death after CAB is also important. Figure 6 shows a mortality curve for patients with first-time CAB in North Denmark, 1992-2010. CAB mortality increases sharply within the first month (to 15%) and less so thereafter. Still, as is evident in Figure 6, patients with CAB have a considerable mortality risk of approximately 15% from day 31 to day 365 after blood culture draw.

**Figure 6. 1-year mortality in 5076 patients with first-time community-acquired bacteremia, North Denmark, 1992-2010.**

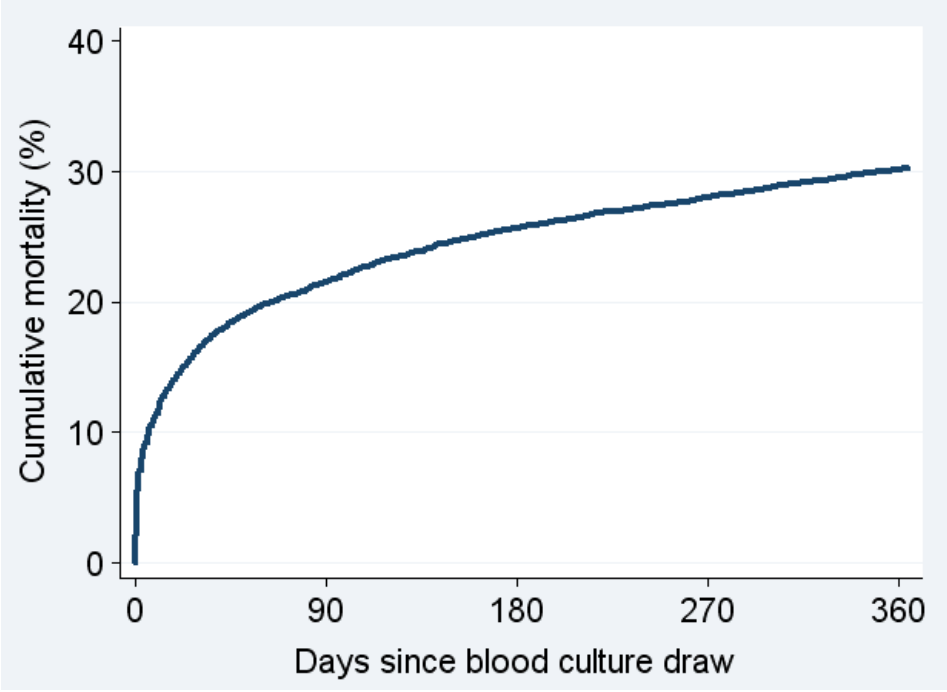
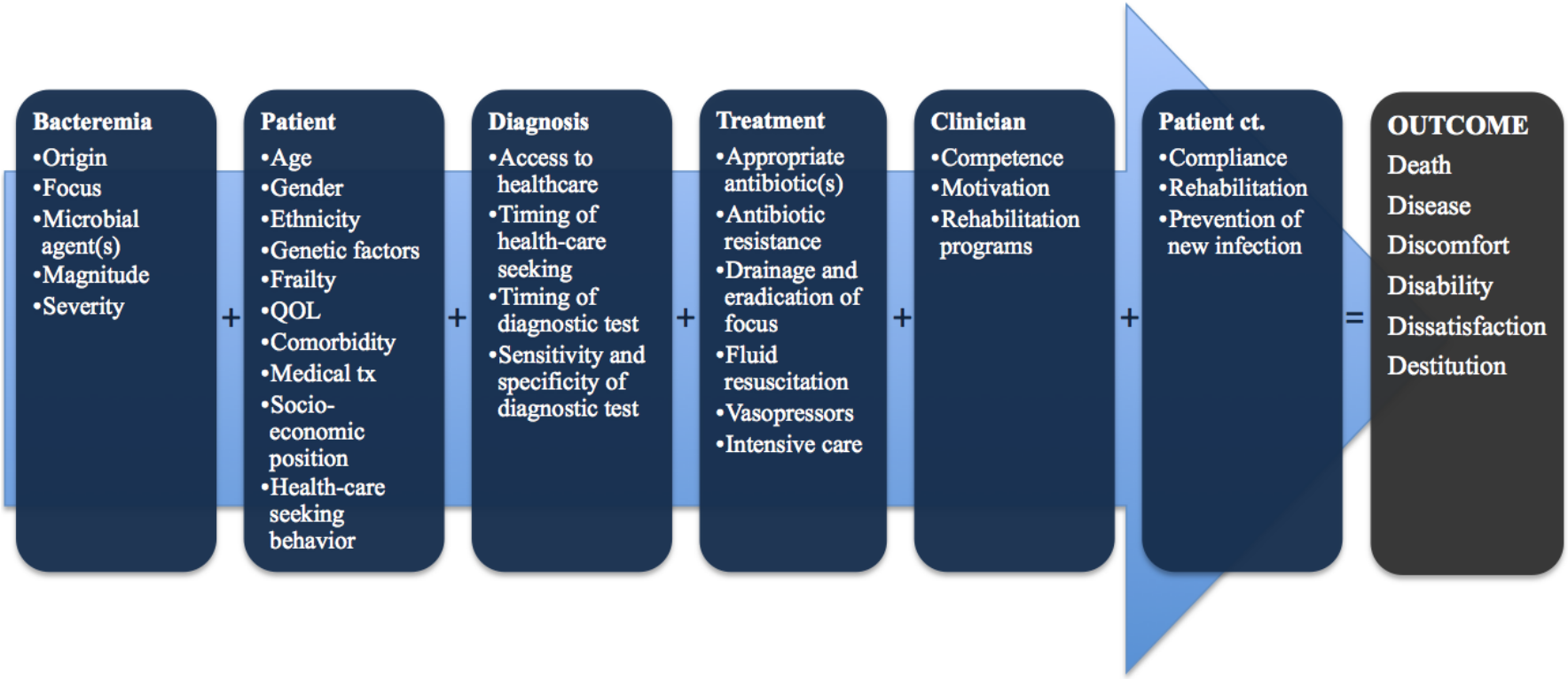


**Figure 7. Prognostic factors in bacteremia. Modified from Sackett et al.**[212]



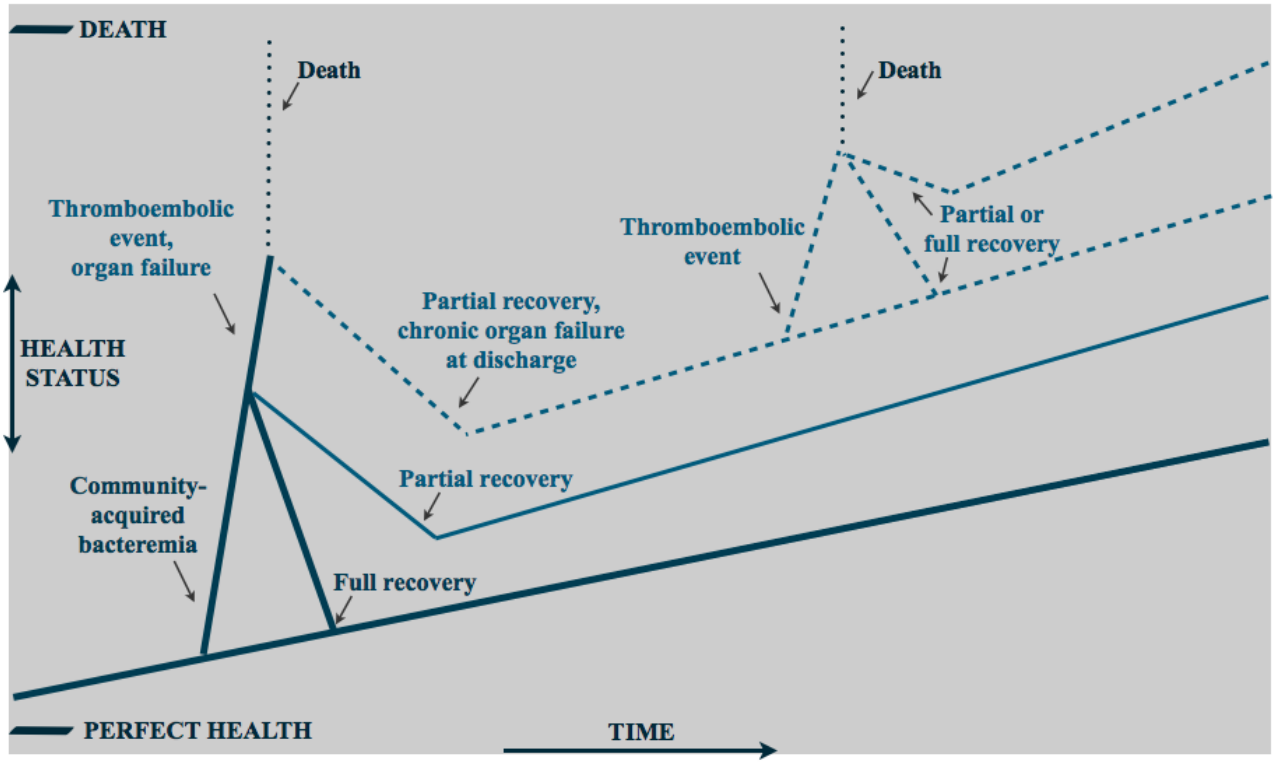
Factors that may affect the prognosis of CAB are shown in Figure 7 and many have been affirmed in observational studies from across the globe. This can be illustrated with recent data from North Denmark: old age (≥80 years of age vs. 15-64 years), high comorbidity level (Charlson score of >2 vs. 0), and low socioeconomic position (lowest tertile of annual income vs. highest tertile) is associated with a 50 to 80% increased hazard rate of death within 30 days.[8,213] Other studies from North Denmark have shown that diabetes mellitus, hematological malignancies, microbial agent(s), focus of infection, adequacy of empirical antimicrobial therapy, and pre-admission statin treatment are prognostic factors with regard to death after bacteremia.[3–6,8,51,213–217] Certain patient characteristics that are related to pre-existing disease, e.g. quality of life and functional status before hospital admission, have also been found to be prognostic factors in patients with bacteremia and/or sepsis.[218–221]

Comorbidity indices developed for use in research have been used frequently in bacteremia studies. In 1962, McCabe and Jackson developed a comorbidity classification system in a study on patients with Gram-negative bacteremia (also see "A history of bacteremia and related terms").[75,76] Patients were categorized as having "rapidly fatal disease" (e.g. acute leukemia and blastic relapse of chronic leukemia), "ultimately fatal disease" with suspected death within 4 years (e.g. chronic renal disease, chronic hepatic disease, and chronic leukemia), and "non-fatal disease" (e.g. diabetes mellitus). The McCabe and Jackson score has been used in many bacteremia studies, especially in studies from before the turn of the century.[104,221–223] A more recent comorbidity index, and perhaps the most widely used, was developed by Mary Charlson and coworkers for use in prognostic studies.[224] The Charlson Comorbidity Index includes 19 major disease categories. In the original study on 559 medical patients, a weight was generated for each comorbid condition based on the size of the relative risk of dying among patients with the condition vs. patients without. The Charlson score is the sum of these weights. The Charlson Comorbidity Index has been adapted for use with hospital discharge data and has been used in many studies on bacteremia.[225] From an infectious disease physicians point of view it may be of interest that HIV is not included in the McCabe and Jackson score (the score was developed prior to the discovery of HIV) and that HIV, along with metastatic solid cancer, receives the highest possible score of 6 in the Charlson Comorbidity Index (this index was developed before the introduction of effective therapy against HIV, highly active antiretroviral therapy). The HIV example serves the purpose of illustrating that prognosis and prognostic factors may change over time and that studies on new or modified comorbidity indices may continue to have a place in prognosis research.

In addition to comorbidity indices, numerous severity-of-illness scores, developed for use in the clinical setting, may have prognostic predictive capabilities with regard to short-term mortality after bacteremia. They include but are not limited to the Pitt Bacteremia score, CURB-65 score, Acute Physiology And Chronic Health Evaluation scores (APACHE, now in its fourth version), and the Mortality in Emergency Department Sepsis score.[208,209,221,226–230]

In a recent review, Leonard Leibovici suggested that physicians and scientists traditionally may have seen acute severe infection as a sharply defined event that can terminate in death or complete recovery with no permanent effect on patient's health status trajectory.[231] He also stressed that clearly it is not so and that there are many other outcomes of infection. Others have made the same point. Yende and Angus proposed a conceptual model of long-term outcomes after severe infection (Figure 8).[150] They point out that, while death and complete recovery are potential outcomes, it is likely that patients experience only partial recovery that may put them at increased risk for subsequent acute illness, hospitalization, lowered functional status and quality of life, and a shortened lifespan. In the following sections I address what is known about the non-death outcomes after CAB that I examine in this thesis.

**Figure 8. Model of long-term outcomes after severe infection. Modified from Yende & Angus.**[150]



### 4.1.1 Thromboembolic events

A systematic search of the literature in Medline through November 2013 was done to identify studies examining bacteremia as a risk factor for AMI, AIS, and VTE. The primary search was conducted using the following search terms, with no language or publication date restrictions:

- ("Bacteremia"[Mesh] OR Bloodstream infection) AND (“Myocardial infarction”[Mesh] OR “Stroke”[Mesh] OR “Venous thromboembolism”[Mesh]) [yielded 234 articles]

Because this search methodology yielded very few observational studies on the association between bacteremia and thromboembolic events, we conducted further searches using the MeSH term “Sepsis” instead of bacteremia/bloodstream infection. Next, we did non-MeSH searches using various combinations of the following terms: bacteremia/bacteraemia, bloodstream infection, sepsis, septicemia, infection, myocardial infarction, coronary disease, acute coronary syndrome, cardiovascular diseases, stroke, ischemic stroke, venous thromboembolism, thromboembolism, deep venous thrombosis, pulmonary embolism. We identified 12 recent reviews[139,149,158,160,164,181,232–237] on acute infection and cardiovascular events and a range of laboratory studies on the association between infection and cardiovascular disease, some of which are referenced in the section on the pathophysiology of bacteremia. In addition, we found several case reports on an association between bacteremia and AMI/AIS. Although this thesis concerns the prognosis of bacteremia in adults, case reports on bacteremia in neonates and subsequent transmural myocardial infarction (very rare in infants) are of interest from an etiological point of view,[238] as are studies detailing that one third of acute ischemic strokes in children are preceded by acute infection such as sepsis.[239] Also of interest, several case reports have detailed dog-bite induced *Capnocytophaga canimorsus* bacteremia in healthy young adults and subsequent development of myocardial infarction in the absence of hypotension and endocarditis.[240] Overall, data from cohort studies were scarce and most papers investigated only the relationship between pneumonia and AMI, meningitis and stroke, or endocarditis and stroke. Table 2 shows previous epidemiological studies on the association between bacteremia/sepsis and thromboembolic events. Table 3 shows selected studies on various acute infections and risk of thromboembolic events. For the selected studies, focus was on studies that were large (> 2500 subjects), recent (last five years), or concerned infections of bacterial etiology (very few studies relied on laboratory results). For an overview of smaller/older studies, please see the above mentioned review articles.

**Table 2. Studies on bacteremia or sepsis and risk of myocardial infarction, stroke, and venous thromboembolism**

| Authors, year | Design | Study subjects | Outcome | Risk (%) | Relative risk (95% CI) |
|---|---|---|---|---|---|
| Svanbom et al.,[241] 1980 | Cohort | 151 patients hospitalized with septicemia | AMI | In-hospital: 4.0 | - |
| Levine et al.,[242] 2008 | Cohort from clinical trials database | 2649 intensive care unit patients with severe sepsis | ACS<br>AIS<br>DVT<br>PE | 28-day: 0.9<br>28-day: 1.1<br>28-day: 0.5<br>28-day: 0.5 | - |
| Corrales-Medina et al.,[243] 2009 | Self-controlled case series | 41 patients hospitalized with *S. aureus* bacteremia patients and AMI | AMI | - | Days 0-2: IR=35.3 (16.7-74.7)<br>Days 0-15: IR=7.9 (3.9-15.9) |
| Walkey et al.,[166] 2011 | Cohort | 49 082 patients hospitalized with severe sepsis and 3 095 705 hospitalized with no severe sepsis | AIS | In-hospital: 0.8 | In-hospital: OR = 6.0 (5.4-6.7) |
| Vardi et al.,[244] 2012 | Cohort | 1080 patients hospitalized with sepsis in internal medicine departments | VTE | On-admission: 0.65<br>In-hospital: 1.29<br>Post-discharge and within 1 year: 0.65 | - |
| Mejer et al.,[245] 2013 | Cohort | 15 669 patients hospitalized with *S. aureus* bacteremia and 156 690 population controls | VTE | 1-year: 1.2 vs. 0.3 | Days 0-30: HR = 15.6 (10.3-23.5)<br>Days 31-180: HR = 5.5 (4.1-7.3)<br>Days 181-365: HR = 4.5 (3.2-6.2) |

IR, incidence rate ratio; OR, odds ratio; HR, hazard rate ratio; AMI, acute myocardial infarction; AIS, acute ischemic stroke; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; ACS, acute coronary syndrome. The collective term ACS includes unstable angina and stroke includes non-ischemic events.

**Table 3. Selected studies on acute infection and risk of myocardial infarction, stroke, or venous thromboembolism**

| Authors, year | Design | Study subjects | Outcome | Risk (%) | Relative risk (95% CI) |
|---|---|---|---|---|---|
| Anderson et al.,[167] 2003 | Cohort | 707 patients hospitalized with endocarditis | Stroke | In-hospital: 9.6 (risk-period not clearly specified) | - |
| Smeeth et al.,[246] 2004 | Self-controlled case series | >20 000 patients with systemic respiratory tract infection and >10 000 with urinary tract infection seen by a general practitioner | AMI<br>Stroke | - | AMI: Days 1-3: IR = 4.95 (4.43-5.53) for RTI and 1.66 (1.8-2.14) for UTI<br>Stroke: Days 1-3: IR = 3.19 (2.81-3.62) for RTI and 2.72 (2.32-3.20) for UTI<br>For both types of infection there was a gradual decrease in relative risk for later periods |
| Smeeth et al.,[177] 2006 | Self-controlled case series | 3375 patients with systemic respiratory tract infection and 2258 with urinary tract infection seen by a general practitioner | VTE | - | Weeks 0-2: IR = 1.91 (1.49-2.44) for RTI and 2.10 (1.56-2.82) for UTI infection<br>For both types of infection there was a gradual decrease in relative risk for later periods |
| Clayton et al.,[247] 2008 | Case-control | 11 155 patients hospitalized for AMI and 9208 hospitalized for stroke and population control for each case | AMI<br>Stroke | - | AMI:<br>0-7 days: OR = 2.10 (1.38-2.10) for RTI<br>Stroke:<br>0-7 days: OR = 1.92 (1.24-2.97) for RTI |
| Murdoch et al.,[248] 2009 | Cohort | 2781 patients hospitalized for endocarditis | Stroke | In-hospital: 17.0 (risk-period not clearly specified) | - |
| Corrales-Medina et al.,[249] 2009 | Cohort | 206 patients hospitalized with bacterial community-acquired pneumonia and 395 hospitalized controls | ACS | 15-day: 10.7 vs. 1.5 | Days 0-15: OR = 7.8 (3.1-19.4) |
| Corrales-Medina et al.,[249] 2009 | Self-controlled case series | 37 patients hospitalized with bacterial community-acquired bacteremia and ACS (part of the above cohort study) | ACS | - | Days 0-15: IR = 47.6 (24.5-92.5) |
| Clayton et al.,[178] 2011 | Case-control | 11 557 patients hospitalized for VTE and one population control for each case | VTE | - | Weeks 0-4: OR = 2.64 (1.62-4.29) for RTI |
| Elkind et al.,[250] 2011 | Cohort | 5639 patients in the Cardiovascular Health Study with no history of stroke of which 2387 were hospitalized for infection (exposure) | AIS | 90-day: 1.2 | Days 0-14: 3.9 (1.9-7.9)<br>Days 0-30: 2.4 (1.3-4.4)<br>Days 0-90: 2.4 (1.6-3.4) |
| Elkind et al.,[250] 2011 | Case-crossover | 669 patients hospitalized with infection and AIS from the above cohort | AIS | - | Days 0-14: OR = 8.0 (1.6-77.3)<br>Days 0-30: OR = 7.3 (1.9-40.9)<br>Days 0-90: OR = 3.4 (1.8-6.5) |

**Table 3 continued.**

| Authors, year | Design | Study subjects | Outcome | Risk (%) | Relative risk (95% CI) |
|---|---|---|---|---|---|
| Perry et al.,[251] 2011 | Cohort | 50 119 patients hospitalized with pneumonia | AMI<br><br>Stroke | 30-day: 1.2<br>90-day: 1.5<br>30-day: 0.1<br>90-day: 0.2 | - |
| Corrales-Medina et al.,[252] 2012 | Cohort | 1343 inpatients and 944 outpatients with community-acquired pneumonia | AMI | 30-day: 3.1 for inpatients and 0.1 for outpatients | - |
| Chen et al.,[253] 2012 | Cohort | 745 patients with a principal ICD-code for pneumococcal pneumonia and 1490 population controls | Stroke | 3-month: 3.2 vs. 0.5<br>1-year: 7.5 vs. 2.3<br>2-year: 10.7 vs. 4.9 | Event in the 1st year: HR= 3.65 (2.25-5.90)<br>Event in the 2nd year: HR = 0.91 (0.53-1.59) |
| Schut et al.,[254] 2012 | Cohort | 696 patients hospitalized with bacterial community-acquired meningitis | Stroke | In-hospital: 9.0 had definite stroke and a further 16.0 had probable stroke | - |
| Schmidt et al.,[255] 2012 | Case-control | 15 009 patients hospitalized with VTE and 150 074 population controls | VTE | - | Weeks 0-2: OR = 5.6 (5.2-6.0) overall for infection vs. no infection<br>Weeks 0-2: OR = 8.7 (3.2-23.7) for hospital-diagnosed septicemia<br>For all types of infection there was a gradual decrease in relative risk for later periods |
| Rogers et al.,[180] 2012 | Case-crossover | 399 patients hospitalized for VTE (participants in the Health and Retirement Study) | VTE | Infection was the most common trigger of VTE hospitalization. It occurred in 52.4% of pre-VTE risk periods | Days 0-90: ÏR = 2.90 (2.13-3.94) for all infection vs. no infection, and 6.92 (4.46-10.72) for infection with a hospital stay or healthcare facility stay |

IR, incidence rate ratio; OR, odds ratio; HR, hazard rate ratio; AMI, acute myocardial infarction; AIS, acute ischemic stroke; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; ACS, acute coronary syndrome; RTI, respiratory tract infection; UTI, urinary tract infection. The collective term ACS includes unstable angina and stroke includes non-AIS events.

As is evident from tables 2 and 3, acute infection may be associated with AMI, AIS, and VTE. Still, the magnitude and duration of the increased cardiovascular risk is not clarified. The cumulated evidence from previous cohort, case-only, and case-control studies indicate that arterial thromboembolic events may predominantly occur within a few days after infection-onset, while infection may be associated with a more prolonged increased risk of venous thromboembolic events.[158,242,245,255,256] Cohort studies have reported short-term absolute risks of AMI, stroke, and VTE varying from 0.1% to more than 10% after hospitalized pneumonia, sepsis, endocarditis, or meningitis.[166,167,242,244,248–251,253,254,257,258] Case-only studies have suggested a 10- to 50-fold increased within-person risk for AMI or stroke shortly after hospitalized infection,[243,249,250] and a 2- to 5-fold increased risk of AMI, stroke, and VTE shortly after infection diagnosed by general practitioners.[177,246] Three cohort studies have found that bacterial pneumonia may be associated with an 8-fold increased 15-day risk for AMI and severe sepsis with a 4- to 6-fold increased in-hospital risk for stroke, when compared with hospitalized patients without those infections.[166,249,250] Only one cohort study on risk of VTE after infection has included a comparison group. Mejer et al. found that patients with *S. aureus* bacteremia had a 15-fold increased 30-day risk of new hospitalization with VTE when compared with population controls and an approximately 5-fold increased long-term risk (31-180 days and 181-365 days).[245] Similarly, in a case-control study by Schmidt et al., infection remained associated with an increased risk for VTE throughout 1 year.[255] We are aware of few studies that used microbiological test results to define exposure (infection).[243,245,249,254,257] Lack of laboratory confirmation of infection may have falsely inflated the effect estimates in previous studies if thromboembolic events were initially misdiagnosed as infections. The risk of misdiagnosis is relevant for all thromboembolic events due an overlap in the clinical presentation with certain types of infection, e.g. AMI and pneumonia, AIS and meningitis, PE and pneumonia, and DVT and skin infection.

### 4.1.2 Return to work, risk of sick leave and disability pension

We performed a systematic Medline search through November 2013 with no language or publication date restrictions:

- ("Bacteremia"[Mesh] OR Bloodstream infection) AND ("Work"[Mesh] OR "Employment"[Mesh] OR "Retirement"[Mesh] OR "Pensions"[Mesh] OR "Sick leave"[Mesh] OR "Disability evaluation"[Mesh]) [yielded 4 articles]

None of these four articles examined return to work, sick leave, or disability pension after infection, so we added the MeSH term “Sepsis” (yielded 19 articles) and conducted further non-MeSH searches.

We identified a few observational studies that reported on the chance of return to work after severe infection with conflicting results. In a study at the general ICU of Rigshospitalet, Copenhagen, Denmark, Poulsen et al. found that 43% (10 /23) of survivors of septic shock returned to work within one year.[259] In contrast,

Cuthbertson et al. detailed a 93% chance of return to work within 3.5 years among survivors of ICU-treated severe sepsis.[260] In another ICU-based study by Longo et al., 90% (9/10) of patients with severe sepsis who were treated with activated protein C had returned to work within 1 month and 100% within 7 months. One non-ICU based study of patients hospitalized for community-acquired pneumonia found that 68% of survivors had returned to work within 30 days.[261]

We did not find any study that examined return to work after CAB. Because previous studies on infection and return to work are predominantly ICU-based, little is known about return to work among patients with infection treated in medical departments. No previous study on return to work after infection has accounted for the possibility of retirement. Moreover, no study has examined risk of long-term sick leave or disability pension after CAB or other severe bacterial infection.

### 4.1.3 Functional status and health-related quality of life

In the constitution of the World Health Organization (WHO), health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[262] Health-related quality of life (HRQOL) is a holistic concept that is determined by the quality of each of these aspects of a person's health.[263] The terms HRQOL, quality of life (QOL), and health status are frequently used interchangeably with the former term being used in this thesis.[264,265] It could be said that measuring HRQOL is in essence evaluating the health status of individuals, both mental and physical, together with their own sense of well being.[266] Functional status is an individual's ability to perform normal daily activities required to meet basic needs, perform usual roles, and maintain health and well-being. [267,268] Both functional status and HRQOL can be assessed by questionnaires. With regard to functional status, questionnaires detail the individual's capacity to manage basic activities of daily living (ADL), e.g. eating or bathing, and/or instrumental activities of daily living that are not necessary for fundamental functioning (IADL), e.g. shopping. With regard to HRQOL, questionnaires detail the subjective quality of physical, mental, and social dimensions of daily life.[269] Before evaluating the prognosis of bacteremia with regard to functional status and HRQOL, it is important to realize that many different instruments can be used - and have been used - in the assessment of these outcomes. Today more than 100 generic instruments, i.e. disease non-specific instruments, are described in the Patient Reported Outcome and Quality of Life Instruments Database.[270] A commonly used instrument for assessment of functional status is the Barthel index, which was introduced by Dorothea Barthel in 1955.[271] It includes 10 items (bowel control, bladder control, grooming, toileting, bathing, dressing, feeding, walking on level surface, walking on stairs, and moving from bed to chair) each of which is scored by health-care professionals or by individuals themselves.[272] Since its inception, various modifications have been made to the original Barthel index including a 100-point scale version by Shah et al. (Barthel-100) and a 20-point version by Collin and Wade et al. (Barthel-20).[267,272–274] In both versions, a score of 0 indicates total dependence on others for all ADL and higher scores indicates better functional

status (greater independence). In studies on HRQOL after severe infection, two questionnaires have predominantly been used; the Short Form-36 and the European Quality of Life measure questionnaire (EQ-5D).[275] The SF-36 contains 36 questions used to assess HRQOL pertaining to eight dimensions (physical functioning, role limitation due to physical problems, bodily pain, social functioning, mental health, role limitations due to emotional problems, vitality, and general health perception). Responses for each SF-36 dimension can be linearly transformed into a value of 0 to 100, with a high score reflecting a good HRQOL. In contrast the EQ-5D, which is used in this thesis, consists of a descriptive system and a visual analogue scale (VAS).[264,265,272] The descriptive system, comprises five different dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is divided into three levels (1=no problems, 2=some problems, and 3=severe problems). Hence, 243 health states exists ($=5^3$) ranging from "11111" ("no problems" in all dimensions) to "33333" ("severe problems" in all dimensions). Each health state may be converted into a single summary EQ-5D index score by applying preference weights derived from a representative sample from a given background population. EQ-5D index scores range from +1 ("no problems" in all dimensions) to somewhere between -1.0 and 0 ("severe problems" in all dimensions). An index score of 0 corresponds to the health state "dead" – in other words, there are health states that the background population consider worse than being dead. Finally, the 20-cm VAS is a self-rating of overall health anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). It is noteworthy that many questionnaires on HRQOL, including SF-36 and EQ-5D, include an assessment of the individuals' functional status, e.g. question on "usual activities" in EQ-5D.

To study existing literature concerning changes in functional status and HRQOL after bacteremia we conducted a systematic search of the literature in Medline through November 2013:

("Bacteremia"[Mesh] OR Bloodstream infection) AND ("Activities of daily living"[Mesh] OR "Quality of life"[Mesh]) – which gave 31 hits.

To recover more studies we also used the MeSH terms "bacterial infections", "sepsis", and "rehabilitation". We identified two review articles on acute severe infections and subsequent functional status and HRQOL.[275,276] Table 4 summarizes previous cohort studies on bacteremia/sepsis and functional status and HRQOL.

**Table 4. Previous cohort studies on bacteremia/sepsis in hospitalized patients and long-term changes in functional status and quality of life**

| Authors, country, year | Study subjects and type of infection | Outcome measurement tool (Pre-admission status assessed) | | Duration of follow-up, months | Control group (confounder adjustment) | Key findings |
|---|---|---|---|---|---|---|
| | | HRQOL | Functional status | | | |
| Perl et al.,[223] USA, 1995 | 100 patients with suspected Gram-negative bacteremia. 66% with positive blood cultures, 57% of infections were nosocomial | SF-36, Health Opinion Poll (No) | Barthel-100, Functional Status Questionnaire, Eastern Cooperative Oncology Group score (No) | 24 to 72 | No (-) | Outcome assessment in 38/40 survivors. Compared with population norms, survivors reported lower perceived HRQOL (esp. for general health, physical dysfunction, problems with work). Scores for perceived emotional health were higher in sepsis patients. Mean Barthel-100 was 85 (100=total independence) at time of survey |
| Longo et al.,[277] Canada, 2007 | 35 activated protein C treated and 63 standard care severe sepsis ICU patients (28-day survivors) | SF-36 (No, but baseline assessment) | - | 6 | Yes (Yes) | Activated protein C treated patients had better HRQOL (physical component score) at baseline and at follow-up when compared with standard care patients. Both study groups experienced gradual improvement in HRQOL throughout follow-up |
| Hofhuis et al., [278] Netherlands, 2008 | 170 medical and surgical ICU patients with severe sepsis | SF-36 (Yes, by proxies) | - | 6 | No (-) | HRQOL assessed in 95/103 survivors. Sepsis survivors reported lower HRQOL (physical functioning, role-physical, general health) at follow-up than pre-admission and had worse HRQOL pre-ICU and at follow-up when compared with population norms |
| Karlsson et al.,[279] Finland, 2009 | 470 ICU patients with severe sepsis. Bacteremia in 128 (27%). 39% nosocomial infections | EQ-5D (Yes, in 252 patients, 62% of these were by proxies) | - | Median 17 (range 12-20) | No (-) | 98 of 251 survivors with both pre- and post-sepsis HRQOL assessment. Compared with population norms, survivors had lower HRQOL before severe sepsis and at follow-up. Among sepsis survivors there was no difference in EQ-VAS between baseline and follow-up. |

**Table 4 continued.**

| Authors, country, year | Study subjects and type of infection | Outcome measurement tool (Pre-admission status assessed) | | Duration of follow-up, months | Control group (confounder adjustment) | Key findings |
|---|---|---|---|---|---|---|
| | | HRQOL | Functional status | | | |
| Poulsen et al.,[259] Denmark, 2009 | 172 ICU patients with septic shock | SF-36 (No) | - | 12 | No (-) | HRQOL assessed in 70/80 survivors who reported a lower HRQOL especially in physical dimensions when compared with the background population |
| Iwashyna et al.,[280] USA, 2010 | 516 survivors of severe sepsis hospitalization and 4517 survivors of non-sepsis hospitalization | - | Unnamed questionnaire on functional disability (Yes) | Up to 100 | Yes (Yes, for within group comparison) | Survivors of severe sepsis acquired more new functional limitations than survivors of non-sepsis hospitalization (≈1.5 vs. ≈0.5 new functional limitations, $p<0.001$). |
| Nesseler et al,[281] France, 2013 | 96 medical and surgical ICU patients with septic shock, community-onset in 34% | SF-36 (Yes, in 42%) | - | 6 | No (-) | Patients with septic shock had a lower HRQOL at baseline and at 6 months when compared with the background population. In 23 patients for whom HRQOL was assessed at baseline and 6 months, HRQOL was significantly better at follow-up for bodily pain and vitality |
| Cuthbertson et al.,[260] UK, 2013 | 439 ICU patients with severe sepsis | SF-36 (No) | - | 60 | No (-) | 3.5 and 5 year survivors had significantly lower physical HRQOL than the background population |
| Orwelius et al.,[282] Portugal, 2013 | 313 six-month survivors of ICU stay, 91 with community-onset sepsis and 222 without | EQ-5D (No) | - | 6 | Yes (No) | 313 of 599 six-month survivors returned EQ-5D questionnaires. Patients with sepsis and those without reported similar median EQ-5D index and VAS scores |

If nothing is stated about site of onset then it is not reported in the article. Some studies on HRQOL have drawn comparisons to available data from a background reference population of similar age and gender (see "Key findings")

With regard to functional status, Perl et al. showed that 2 to 6-year survivors of suspected gram-negative bacteremia had a median Barthel-100 score of 85 with no comparison made to pre-admission status or a control group. Two recent studies have used register-data from the Health and Retirement study to assess changes in ADL and IADL after severe sepsis and pneumonia, respectively.[280,283] Iwashyna et al. detailed that survivors of severe sepsis hospitalization were burdened with more new functional limitations than survivors of non-sepsis hospitalization (≈1.5 vs. ≈0.5 new functional limitations).[280] Likewise, Davydow et al. found that hospitalization for pneumonia was associated with ≈1.0 new limitations in ADL and IADL.[283] In general, more studies have examined HRQOL after infection than functional status after infection. When compared with reference values from a background population, patients with sepsis have a low HRQOL before hospital admission and at various time points after hospitalization, especially with regard to physical dimensions of HRQOL.[223,259,260,278,279,281] However, patients treated for sepsis syndromes in ICUs may have similar HRQOL to non-sepsis ICU patients after 6 to 72 months.[282,284–286] Only a few studies have examined HRQOL-changes in sepsis survivors over time and with conflicting results. In a study from the Netherlands, Hofhuis et al. found that HRQOL in ICU-treated sepsis patients as measured by SF-36 may gradually improve from ICU-discharge to 6 months after discharge.[278] However, sepsis survivors still had worse physical functioning, general health perception, and more limitations due to physical problems at 6 month follow-up compared with their pre-ICU HRQOL. In contrast, Karlsson et al found that sepsis survivors reported similar HRQOL pre-admission and at 12-20 month follow-up (as assessed by EQ-5D VAS),[279] and Nesseler et al. found better HRQOL at 6-month follow-up than pre-admission among septic shock survivors.[281]

The review article by Winters et al. includes further cross-sectional studies on HRQOL after sepsis. In fact, some of the studies detailed in Table 4 may just as well be labeled as cross-sectional surveys[223,259,282] because study subjects are included at some point in time after infection and are then questioned on their present HRQOL (with no assessment of pre-infection HRQOL). Thus, these studies offer very little insight into the effect of infection on functional status and HRQOL. Of importance for this thesis, we did not identify any study on changes in functional status and HRQOL after CAB and, in general, studies on functional status and HRQOL changes after non-ICU treated infection are very few (see Table 4).

# 5. Aims of the thesis

**I.** To assess the short- and longer-term risks of acute myocardial infarction and acute ischemic stroke among medical patients with community-acquired bacteremia compared with the background population and with other acutely admitted patients.

**II.** To assess the short- and longer-term risks of symptomatic venous thromboembolism in a cohort of hospitalized medical patients with microbiologically confirmed community-acquired bacteremia compared with acutely hospitalized controls and with the background population.

**III.** To examine return to work and risk for long-term sick leave, disability pension, and death after medical hospitalization with first time community-acquired bacteremia compared with blood culture negative controls and matched population controls

**IV.** To examine the short- and longer-term risk of deterioration in functional status and health-related quality of life among medical non-cancer patients with first time community-acquired bacteremia compared with blood culture negative controls

# 6. Materials and methods

*An English judge speaking to a young Sir Harold Cox: "…Cox, when you are a bit older, you will not quote Indian statistics with that assurance. The Government are very keen on amassing statistics - they collect them, add them, raise them to the nth power, take the cube root and prepare wonderful diagrams. But what you must never forget is that every one of those figures comes in the first instance from the chowkidar (village watchman), who puts down whatever he pleases."*

*As recounted by Sir Josiah Charles Stamp. Stamps Law of Statistics: the data source may easily be the weakest link*

## 6.1 Data sources

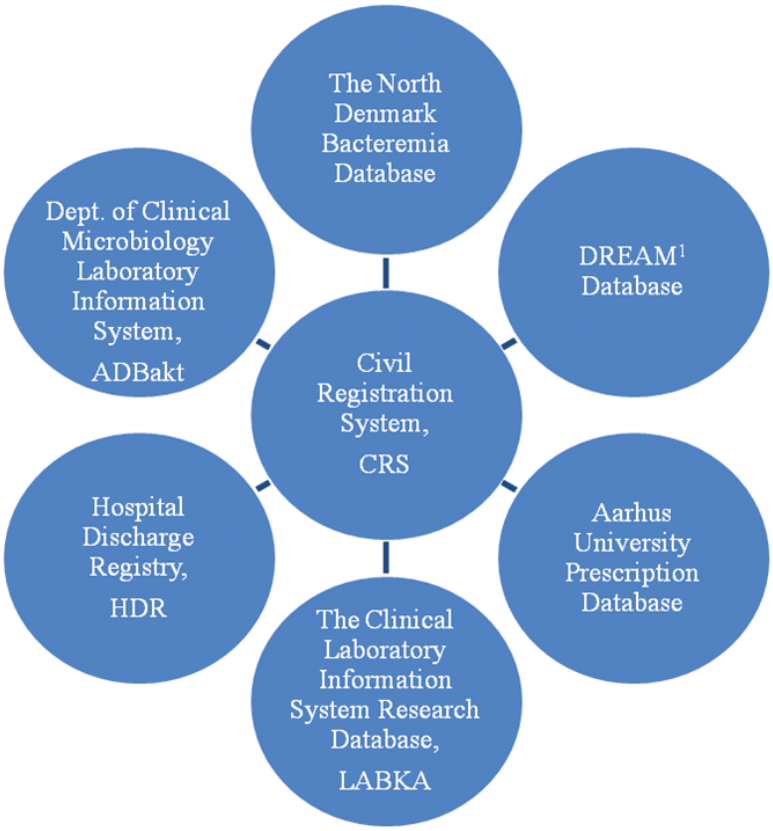
### 6.1.1 Study I to III

**Studies I to III** in this thesis are population-based cohort studies conducted in North Denmark Healthcare Region, within a population of approximately 600.000 inhabitants. Denmark is a welfare state, with tax-financed universal access to health services, free at the point of delivery. Individual's contact with Danish health services are recorded in national registries and these data may be used for research purposes. **Studies I-III** are based on data obtained from seven such registries, which are described below (see Figure 9). For each registry, specific codes used in this thesis are detailed in the Appendix.

1. The Civil Registration System (CRS)

In Denmark, all residents have been registered electronically in the CRS since 1968.[287] The CRS holds information on date of birth, gender, marital status, place of residence, vital status, and date of death, updated daily. At birth or immigration a Danish resident is provided with a 10-digit unique personal identification number, the CRS number. The CRS number format is DDMMYY-XXXX where the first six digits (DDMMYY) is the date of birth, the final four digits (XXXX) encode century of birth, and the final digit is even for females and odd for males. It may be used to identify individuals in Danish registries and facilitates linkage of data. It was used in **studies I-III**.

**Figure 9. Data sources used in registry based studies, Study I-III.**




[1]DREAM is a Danish acronym for "Den Registerbaserede Evaluering Af Marginaliseringsomfanget", which translates into "the register-based evaluation of the extent of marginalization".

2. The North Denmark Bacteremia Database

The North Denmark Bacteremia Database has recorded all culture-confirmed bacteremia episodes in the region since 1981, prospectively since 1992.[16] It is maintained by the Department of Clinical Microbiology at Aalborg University Hospital, upon which all regional hospitals relied for blood culture analyses. Three different systems for blood culture inoculation were used during the study period. In the early part of 1992 blood was sampled for culture in transport tubes and later inoculated into multiple bacteriological culture media. This was replaced by the Colorbact broth culture system (Statens Serum Institut, Copenhagen, Denmark) from August 1992 to 1995. Since 1996, the BacT/Alert system (bioMérieux, Marcy l'Etoile, France) has been used.[16] Blood cultures are incubated for 7 to 14 days and examined thrice daily. Positive blood cultures are investigated by microscopy (motility in wet-mount, gram-stain reaction, and bacterial arrangement and morphology), and after subculture by other conventional and commercial methods as

appropriate.[3,16,288,289] In addition, physicians in charge of patient care are notified twice by physicians from the Department of Clinical Microbiology through telephone contact. The first notification is given on the basis of direct microscopy, while the second notification is given on grounds of a tentative/definitive bacteriological diagnosis and antibiogram. The telephone contacts with attending physicians allow individual patients and blood culture findings to be jointly assessed and the information is recorded in the database, including CRS number, date of blood culture draw, number of positive culture bottles, causative pathogen/s, focus of infection and susceptibility pattern.[16] A less extensive assessment is initiated when blood culture contamination is suspected and these episodes are not recorded in the database.[16,17,21] The bacteremia database was used in **studies I-III**.

3. The Dept. of Clinical Microbiology Laboratory Information System (ADBakt)

A computerized laboratory information system (ADBakt, Autonik, Sköldinge, Sweden) has been utilized by the Dept. of Clinical Microbiology, Aalborg, since 1996.[290] It contains prospectively recorded basic information on all blood cultures examined including CRS-number, date of blood culture draw, length of incubation, bacterial/fungal species, and antiobiograms. It was used in **study III**.

4. The Hospital Discharge Registry (HDR)

The HDR covers all somatic hospitalizations in Denmark since 1977.[291] Initially only hospital admissions were recorded but since 1995 outpatient visits have been entered as well (i.e. planned ambulatory care visits and emergency department contacts). Key variables in HDR include CRS-number, date and time of hospital arrival/departure, hospital department, and one primary discharge diagnosis and up to 20 secondary diagnoses which are assigned by physicians at the treating hospital department. The primary diagnosis refers to the condition that prompted patient admission and the main condition responsible for the completed diagnosis and treatment course. The secondary diagnoses refer to conditions that affect the diagnosis and treatment course. HDR had used two versions of the World Health Organization's International Classification of Diseases (ICD): ICD-8 until the end of 1993 and ICD-10 thereafter. HDR was used in **studies I-III**.

5. The Clinical Laboratory Information System Research Database (LABKA)

The LABKA database is maintained by the Department of Clinical Epidemiology at Aarhus University Hospital. It contains NPU (Nomenclature, Properties, Units) coded information on laboratory results from blood samples obtained during hospital visits in North and Central Denmark Region, since 1997 and 2000 respectively.[292] In addition, CRS-number and date of venipuncture is recorded. In **study I** we obtained data on white blood cell count (WBC; NPU02593) and C-reactive protein (CRP; NPU19748).

6. Aarhus University Prescription Database

This pharmaco-epidemiological database is maintained by the Department of Clinical Epidemiology at Aarhus University Hospital. It holds individual-level (CRS-number) data on date of sale of reimbursed prescriptions in North and Central Denmark, with coverage of North Denmark since 1991.[293] Of note, not all drugs sold in Denmark are prescription-only and/or reimbursable. Still, of the many drugs that we obtained information on, only aspirin could be legally purchased without a prescription (<20% of aspirin sold since 2003). In the database, type of drug is coded according to the Anatomical Therapeutic Chemical (ATC) classification. This database was used in **studies I-III**.

7. DREAM Database.

The DREAM Database is administrated by the National Labor Market Authority [Arbejdsmarkedsstyrelsen] and accessed through Statistics Denmark.[294–296] It contains weekly updated individual-level data on all public transfer payments to Danish residents since 1991. Danes who are part of the workforce (employed or unemployed) can receive paid sick leave during temporary illness for a maximum of 52 weeks (with the possibility for extension) within an 18 month period. People whose illness causes a lasting reduced ability to work can receive permanent disability pension. In addition to information on social transfer benefits, the database also includes data on immigrant status. The DREAM database was used in **study III**.

### 6.1.2 Study IV

In **study IV**, which examined health and functional status changes among CAB patients and blood culture-negative controls, we used electronic medical records and personal interviews to obtain basic information on study subjects: age, sex, pre-existing disease, medication use, vital signs, and laboratory findings. Moreover, information on the study subjects' functional status and HRQOL was obtained during direct patient and proxy contact by validated questionnaires. We used a questionnaire version of the Barthel-20 index to assess functional status and the European Quality of Life measure 3 level version questionnaire (EQ-5D) to assess HRQOL.[264,265,267,272,297] Barthel-20 and EQ-5D have previously been translated into Danish and are recommended for assessment of functional status and HRQOL in Denmark. [267,298,299] For further detail on Barthel-20 and EQ-5D see the section entitled "Prognosis of bacteremia – functional status and health-related quality of life". In addition to Barthel-20 and EQ-5D, questionnaires contained items on employment status, place of residence, and home based care.

## 6.2 Study design

Table 5 gives an overview of the design of the four cohort studies included in this thesis. The study designs are discussed in more detail below. All studies were approved by the Danish Data Protection Agency (2011-41-5864); **study IV** was also approved by the Science Ethical Committee (N-20100102).

**Table 5. Design of the cohort studies in this thesis**

| Study | Setting, period | Study population | Outcome(s) |
|---|---|---|---|
| **I** | North Denmark, 1992-2011 | - All adult medical patients with a first episode of hospitalized CAB<br>- Matched population controls<br>- Matched hospitalized controls | 30-day, 31-180 day, and 181-365 day AMI and AIS |
| **II** | North Denmark, 1992-2011 | - All adult medical patients with a first episode of hospitalized CAB and no previous VTE<br>- Matched hospitalized controls<br>- Matched population controls | 90-day and 91-365 day VTE |
| **III** | North Denmark, 1996-2011 | - All working-age medical patients with first time blood culture draw and no recent hospitalization (CAB patients and culture-negative controls)<br>- Matched population controls | Return to work, sick leave for ≥4/≥52 weeks, 365-day disability pension, 30-day and 365-day mortality |
| **IV** | Department of Medicine, Aalborg University Hospital, 2011-2013 | - Adult medical patients with blood culture draw within 48 hours of admission, no history of bacteremia, and no recent admission or cancer | 90-day risk of declining functional status and HRQOL |

### 6.2.1 Study I and II

We conducted two 20-year (1992-2011) population-based cohort studies in North Denmark to assess the short- and longer-term risks of AMI, AIS and VTE among medical patients with CAB. Eligibility criteria for inclusion for all study subjects were age ≥15 years, no hospitalization within the previous 30 days, no record of previous bacteremia (since 1981), and study area residence for ≥1 year. In **study II** we employed a further eligibility criterion of no history of VTE. We used the North Denmark Bacteremia Research Database to identify patients with CAB during 1992-2010 and for information on date of blood culture draw, etiological agent(s), focus of infection, and number of blood culture bottles that were positive (the latter in **study I** only). We defined CAB as the presence of viable bacteria or fungi in the bloodstream, determined by blood cultures performed *on the day of admission*, among clinically ill patients who were not admitted to the hospital within the previous 30 days. We only studied CAB patients with positive blood cultures on the day of admission (and not within 48 hours of admission) because we wanted to be confident that CAB preceded thromboembolism in patients who had been given a discharge code of AMI, AIS, or VTE. In addition, we examined convenience samples of cases with available medical files and discharge files, i.e. all CAB patients

with index-hospitalization VTE since 1994 (n=22 [of 26 patients since 1992]), and all CAB patients with an index-hospitalization and a primary discharge code of AMI/AIS since 2003 (n=21 [of 60 patients since 1992]). We found no indication of reverse causation in any patient. Next, we assembled comparison cohorts using the CRS and HDR registries. Because bacteremia was community-acquired, we assembled a cohort of unexposed controls from the general population (up to 10 for each CAB patient). As hospitalization in itself may affect the risk of thromboembolism, we further assembled comparison cohorts of acutely admitted medical patients without CAB (up to 5 subjects for each CAB patient). In **study I** we identified hospitalized controls with no primary diagnosis of cardiovascular disease or rehabilitation (ICD-8: 390-458; ICD-10: DI00-99, DZ50) and in **study II** hospitalized controls with no primary diagnosis of VTE (see Appendix for ICD codes). Background population controls and hospitalized controls were individually matched to CAB patients on sex, exact year of birth, and calendar-time (date of CAB patient blood culture draw [the index date] for population controls, and, year of hospital admission for hospitalized controls). For CAB patients and controls, we used the HDR and the prescription database to retrieve information on pre-existing conditions and medication use that may affect the risk for AMI, AIS, or VTE.[189,190] In **study I** we obtained information from the LABKA database on index-date WBC and CRP level for CAB admissions since 1998. Information on outcomes – primary and secondary discharge codes of AMI, AIS, and VTE from hospital stays - was obtained from the HDR (AMI = ICD-8: 410; ICD-10: I21, AIS = ICD-8: 432-434; ICD-10: I63-I64 (except I63.6), VTE = ICD-8: 450.99, 451.00, 451.08, 451.09, 451.90, 451.92, 451.99, 452-453; ICD-10: I26, I80.1-9, I81-82). In **study II** we also considered VTE codes from hospital outpatient clinic visits as outcome events. However, we chose not to consider AMI, AIS or VTE-diagnoses from emergency room visits because these codes may have a low positive predictive value.[300–302]

### 6.2.2 Study III

We conducted a 16-year (1996-2011) population-based cohort study in North Denmark to examine return to work, risk of sick leave, risk for permanent disability pension, and mortality after medical hospitalization with CAB. To assure that patients could return to the workforce and were at risk of sick leave and disability pension, we focused on patients of working-age (20-58 years) who were part of the workforce in the four weeks before hospital admission (i.e. did not receive permanent disability benefits, were not retired, and received sickness absence benefits for a maximum of three weeks within four weeks prior to admission). Further eligibility criteria were no history of blood culture draw (since 1995), no history of bacteremia (since 1981), no hospital stay within the previous 30 days, and residence within the study area for ≥1 year. We defined CAB as the presence of viable bacteria or fungi in the bloodstream, determined by blood cultures performed within 48 hours of admission, among clinically ill patients who were not admitted to the hospital within the previous 30 days. We used the bacteremia database and the laboratory information system (ADBakt) to identify all patients who had a first-time blood culture taken within 48 hours of admission,

1996-2010, and to categorize subjects as CAB patients or as blood culture-negative controls. Furthermore, for each CAB patient, we used the CRS and HDR to sample 10 eligible population controls who were alive on the date of hospital admission of the CAB patient and with no recent hospitalization, matched on sex and year of birth. We used the bacteremia database for information on CAB episodes (etiological agent, focus of infection). For all study subjects, we used the HDR for data on hospital contacts and comorbidities that may affect the risk of sick leave, disability pension, and death, including the 19 disease categories in the Charlson Comorbidity Index and alcohol-related disorders.[224,303] The prescription database was used for information on medication use. We used the DREAM database for information on social transfer benefits and categorized DREAM codes as work-ready codes (employed and unemployed), sick leave codes, and permanent disability pension codes (see Appendix). We defined long-term sick leave as lasting at least 4 consecutive weeks after the index date.[304] Finally, the CRS registry was used for information on death.

### 6.2.3 Study IV

We conducted a prospective matched cohort study at Aalborg University Hospital to examine changes in functional status and HRQOL throughout 1 year after medical hospitalization with first-time CAB. We included subjects from subspecialty wards within the hospitals Department of Medicine (152 beds) that directly partakes in acute medical admissions (Infectious Diseases, Hematology, Pulmonology, Nephrology, Gastroenterology, and Endocrinology) from June 1 2011 to June 30 2013 and we followed them for 3 months. Eligibility criteria for study inclusion were age ≥18 years, medical hospitalization, no hospital stay within the previous 30 days, no history of bacteremia, no cancer within the last 10 years, and blood culture draw within 48 hours of admission. Moreover, patients had to be clinically stable (not destined to die during the hospitalization as judged by treating physicians) and included within 7 days of blood culture draw. Baseline questionnaires encouraged study subjects to recall their health/functional status as it were 1 month prior to hospitalization while questionnaires pertained to the day of contact at 3-month follow-up.

## 6.3 Statistical analyses

In all four cohort studies we followed patients from the index date (date of blood culture draw for CAB patients and the same date for their matched population controls, date of blood culture draw for culture-negative controls, and date of hospitalization for hospitalized controls) until emigration, death, an outcome of interest (e.g. AMI, AIS, VTE, or disability pension), or end of 1-year follow-up. Stata 11.2 for Windows (Stata Corp., College Station, TX) was used for all data analyses. All relative risk (RR), odds ratio (OR), hazard rate ratio (HR), and risk difference (RD) estimates were obtained with corresponding 95% confidence intervals (CIs). For Cox models the proportional hazards assumption was checked with log-minus-log plots

In **studies I and II** we expected the risk of thromboembolism to be greatest shortly after onset of infection. Therefore, we split the 1-year follow-up after the index date into three time periods in **study I** (days 0-30, 31-180, and 181-365) and two time periods in **study II** (days 0-90 and 91-365). For each time period we computed absolute risks for first AMI/AIS (and AMI and AIS separately) and VTE among at-risk CAB patients and their at-risk matched controls. In **study I** we used conditional Poisson regression with robust variance estimation to compute RRs for any hospital admission with AMI/AIS within 0-30 days (index-admission included),[305] and in **study II** we used conditional logistic regression for ORs of VTE within 0-90 days. We used Cox proportional hazards models and "stsplit" in Stata to compare hazard rates of hospital admission with AMI/AIS/VTE during later time periods among CAB patients still alive and at risk of first incident AMI/AIS/VTE on day 31/181 and 91, respectively, and their "at risk" matched controls. To account for the matched design, Cox models were stratified on matched sets.[305–307] Because death was a competing risk for thromboembolism, we modeled cause-specific hazards of thromboembolism by censoring on death.[308] Because AMI/AIS or VTE might have preceded CAB in some patients despite our sample validation results, we performed supplementary sensitivity analyses in which CAB patients (and their matched controls) were excluded if they had a primary discharge code of AMI/AIS or VTE. In **study I** we further examined the risk of AMI/AIS after restriction to CAB patients with no endocarditis. In **study II** we computed the VTE risk after restriction to study subjects without recent surgery/trauma (previous 90 days) or hospital admission (previous 180 days), cancer history or new cancer in the following 365 days, or pregnancy in the 365 days surrounding the index date (here, termed "classic" risk factors for VTE). In both studies, regression models controlled for a priori potential confounders (**study I**: age, gender, calendar-time, marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular diseases, other comorbidity, and use of medications for cardiovascular disease, and, **study II**: age, gender, calendar-time, cancer, cardiovascular disease, other comorbidity, and recent hospital contact). In both studies we examined the risk of thromboembolism in CAB subgroups (age group, gender, study period, etiologic agent and focus of infection). In **study I** we further examined the risk of AMI/AIS according to CAB patients' degree of inflammation on admission (as assessed by some/all blood culture bottles positive, normal/elevated/highly elevated CRP, low/normal/elevated WBC) and in strata of previous cardiovascular disease. Analyses within strata of previous cardiovascular disease required that we ignored the matching, so we used modified Poisson regression.[309–311] In **study I and II** subgroup and stratified analyses were controlled for age, gender, and calendar-time (plus any comorbidity in **study I**). In **studies I and II** we conducted supplementary sensitivity analyses in which we excluded matched groups if the patient with CAB had a primary discharge code of AMI/AIS or VTE. Moreover, in **study I** we used "episensi" in Stata to assess how much a potential strong unmeasured confounder might have influenced the observed association between CAB and AMI/AIS when using "healthy" population controls as the comparison group.

In **study III** we first computed the median number (and inter-quartile range, IQR) of weeks that patients were on paid sick leave during the year before and after blood culture draw. We then computed the risk of being on paid sick leave for at least 4 and for 52 consecutive weeks, respectively, beginning in the week of blood culture draw. Log-binomial regression was used to compute the RD and RR of 4 weeks and 52 weeks of consecutive sick leave after the index date for CAB patients versus culture-negative controls.[310,311] Next, we constructed cumulative incidence curves for permanent disability pension (using "stcompet" in Stata)[312] and Kaplan-Meier curves for mortality. We used the pseudo-value approach (a "leave one out" resampling technique) to compute the cumulative incidence of permanent disability pension and death at fixed points in time after the index date.[313,314] Pseudo-values were generated for each study subject using "stpci" and "stpsurv" in Stata. Next, the pseudo-values were analyzed in generalized linear models to compute crude and adjusted RDs and RRs of permanent disability pension and mortality for CAB patients versus controls. Death was considered a competing risk for permanent disability pension in all time-to-event analyses. In regression analyses, we adjusted for potential risk factors for sick leave, disability pension and death: age, gender, Charlson score, alcoholism-related disease (including disulfiram use), medication use (antidiabetics, drugs for cardiovascular disease and pulmonary disease), marital status and immigrant status. Analyses pertaining to CAB patients versus population controls were only adjusted for age and gender because of few events among population controls. In subgroup analyses we examined the risk for the outcomes of interest according to etiologic infectious agent and focus of infection. We also stratified analyses by gender, age group, and employment status in the 4 weeks prior to admission.

In **study IV** we used EpiData Entry 3.1 (The EpiData Assoc., Odense, Denmark) for data. First, the "eq5d" command in Stata was used to compute EQ-5D index scores.[315] We then computed the absolute risk of deterioration in functional status (a lower Barthel-20 index score) and HRQOL (a lower EQ-5D index score, a drop ≥10 in EQ-5D VAS score) at 3 months compared with baseline under the assumption that subjects who were lost to follow-up (1 in each group) had unchanged functional status/HRQOL. We also used the patient's report to compute the risk of a worse functional status and HRQOL (yes/no) at follow-up compared with baseline. Log-binomial regression was used to compute RDs and RRs of deterioration in functional status and HRQOL for CAB patients vs. controls with adjustment for age, gender, and any comorbidity (yes/no). Next, we used Spearman's rank correlation coefficient to examine the correlation between patient's report of a worse functional status/HRQOL and deterioration in Barthel-20/EQ-5D scores at follow-up compared with baseline. This computation was performed among subjects who were not dead or lost at follow-up. We then computed the median and inter-quartile range (IQR) of EQ-5D index score, EQ-5D VAS score, and Barthel-20 index score at baseline and at follow-up for CAB patients and controls. Box plots were used to depict the distributions of EQ-VAS scores and EQ-5D index scores. For within group comparisons of functional status and HRQOL at baseline and follow-up, we used the Wilcoxon signed rank test and the McNemar test (presented as ratios of proportions with CIs).

# 7. Results

The main results of the four cohort studies are outlined below.

## 7.1 Study I.

### Risk for AMI and AIS after CAB

We included 4389 CAB patients who were matched to 43 831 population controls and 21 893 hospitalized controls. The majority of study participants were women (53.5%) and the median age was 73 years (IQR, 61-82 years). CAB patients had a burden of pre-existing disease similar to other hospitalized patients, e.g. among CAB patients 7.3% had previous AMI and 13.2% had previous cerebrovascular disease and for hospitalized controls the percentages were 7.1% and 12.1%. Background population controls had a considerably lower burden of disease (5.3% had previous AMI and 8.3% had previous cerebrovascular disease). For CAB patients the 30-day, 180-day, and 365-day mortality was 15.7%, 24.8%, and 29.4% - the corresponding percentages for hospitalized controls were 7.9%, 18.1%, and 23.9%, and for population controls 0.3%, 2.7%, and 5.8%.

When compared with matched controls, patients with CAB had an increased risk for AMI/AIS within 30 days (3.6% vs. 0.2% for population controls, adj. RR, 20.86; 95% 15.38-28.29, and, vs. 1.7% for hospitalized controls, adj. RR, 2.18; 95% CI, 1.80-2.65), Table 6. Similar relative risk increases were found when AMI and AIS were analyzed separately (Table 6). During 31-180 days, CAB was associated with an increased hazard rate of AMI/AIS (adj. HR, 1.64; 95% CI, 1.18-2.27) and AIS (adj. HR, 1.90; 95% CI, 1.26-2.89), but not AMI, when compared with population controls. No differences in risk of AMI/AIS were seen during 181-365 days after the index date.

The short-term risk increase of AMI and AIS was evident in most subgroups that we examined. Still, certain subgroups were associated with particularly high relative risk estimates. As an example, within 0 to 30 days, high relative risk estimates of AMI and AIS were found among patients with CAB who had elevated levels of markers of inflammation, especially when compared with matched population controls (e.g. low WBC, adj. RR, 4.80; 95% CI, 0.43-53.32, normal WBC, adj. RR, 15.09; 95% CI, 7.46-30.50, elevated WBC, adj. RR, 26.03; 95% CI, 17.52-38.67). Moreover, patients with *S. aureus* bacteremia were at increased risk for AIS when compared with hospitalized controls during 0-30 days (adj. RR, 2.85; 95% CI, 1.47-5.54) and also 31-181 days (adj. HR, 7.12; 95% CI, 1.63-31.03) after the index date.

CAB remained associated with AMI/AIS in sensitivity analyses. We excluded 61 matched groups in which the CAB patients had a primary discharge diagnosis of AMI/AIS, which lowered the adjusted 0-30 day RR

of AMI/AIS to 1.36 (95% CI, 1.08-1.72) vs. hospitalized controls, and to 12.98 (95% CI, 9.33-18.06) vs. population controls.

We estimated that if a strong unmeasured confounder had a prevalence of 5% among population controls and 50% in patients with CAB, and independently increased the 30-day AMI/AIS risk by a factor of 20, the true risk for AMI/AIS following CAB would still be increased 5.73- fold increased vs. population controls.

**Table 6. Risk and adjusted relative risk for acute myocardial infarction and acute ischemic stroke among patients with community-acquired bacteremia and their matched population and hospitalized controls, Northern Denmark, 1992-2010.**

| | Risk, % (n/N) | | | Adjusted relative risk (95% CI)* | |
|---|---|---|---|---|---|
| | **CAB patients** | **Population controls** | **Hospitalized controls** | **CAB patients vs. population controls** | **CAB patients vs. hospitalized controls** |
| **AMI/AIS risk** | | | | | |
| 0-30 days | 3.6 (160/4389) | 0.2 (72/43 831) | 1.7 (365/21 893) | 20.86 (15.38-28.29) | 2.18 (1.80-2.65) |
| 31-180 days | 1.4 (49/3589) | 0.7 (247/35 676) | 1.2 (201/16 187) | 1.64 (1.18-2.27) | 0.95 (0.69-1.32) |
| 181-365 days | 1.2 (38/3188) | 0.9 (277/30 873) | 1.2 (162/13 007) | 0.98 (0.68-1.40) | 0.83 (0.57-1.21) |
| **AMI risk** | | | | | |
| 0-30 days | 1.7 (73/4389) | 0.1 (37/43 831) | 0.8 (166/21 893) | 17.70 (11.33-27.64) | 2.32 (1.71-3.13) |
| 31-180 days | 0.2 (20/3645) | 0.3 (126/36 265) | 0.6 (104/16 757) | 1.42 (0.86-2.34) | 0.90 (0.54-1.49) |
| 181-365 days | 0.5 (18/3250) | 0.4 (132/31 570) | 0.6 (77/13 392) | 0.88 (0.52-1.50) | 0.91 (0.52-1.60) |
| **AIS risk** | | | | | |
| 0-30 days | 2.1 (91/4389) | 0.1 (37/43 831) | 0.9 (206/21 893) | 25.82 (16.72-39.89) | 2.41 (1.84-3.15) |
| 31-180 days | 0.9 (33/3641) | 0.4 (130/36 218) | 0.6 (107/16 694) | 1.90 (1.26-2.89) | 1.25 (0.82-1.91) |
| 181-365 days | 0.6 (20/3238) | 0.5 (156/31 437) | 0.7 (92/13 301) | 0.97 (0.58-1.59) | 0.71 (0.42-1.20) |

*Relative risk is risk ratio for 0-30 day estimates and hazard rate ratios for 31-180 and 191-365 day estimates. The relative risk is controlled for age, gender, calendar-time, marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular diseases, other co-morbidities, and medications for cardiovascular disease.

## 7.2 Study II.

### Risk for VTE after CAB

The study included 4213 CAB patients, 20 084 matched hospitalized controls, and 41 121 matched population controls. The median age of all study participants was 73 years (IQR 61-82). As in **study I**, CAB patients and hospitalized controls had a similar burden of pre-existing disease (e.g. history of cancer among 16.0% and 14.8%, respectively) while population controls had a lower burden (history of cancer in 9.7%). Among CAB patients the 90-day mortality was 20.5%, nearly twice that of hospitalized controls (12.5%), and after one year it was 29.3% (vs. 5.6% for population controls and 21.6% for hospitalized controls).

Patients with CAB had an increased risk for VTE within 90 days when compared with matched population controls (1.1% vs. 0.0%, adj. OR, 23.4; 95% CI, 12.9-42.6) and hospitalized controls (1.1% vs. 0.6%, adj. OR, 1.9; 95% CI, 1.4-2.7) (Table 7). During 91-365 days, CAB remained associated with a moderately increased risk of VTE (vs. population controls, adj. HR, 1.9; 95% CI 1.4-2.7, and, vs. hospitalized controls, adj. HR, 1.4; 95% CI 0.8-2.5) (Table 7). Among patients with CAB caused by Gram-positive organisms, the 0-90 day relative risk for VTE vs. hospitalized controls was higher than what seen among patients with Gram-negative CAB (adj. OR, 2.5; 95% CI 1.6-4.1, and, adj. OR, 1.2; 95% CI 0.7-2.1, respectively). *S. aureus* infection was associated with a particularly high 90-day risk of VTE (3.6%), whereas a lower risk was found among patients with *S. pneumonia* infection (0.7%). A high 90-day risk for VTE was also found among patients with CAB who had skin or bone/joint infection (5.1%). However, among patients with skin or bone/joint infection, the 0-90 day VTE-risk was high among those with *S. aureus* infection (7.2%) and relatively low among those with infection caused by β-hemolytic streptococci (0.8%). After exclusion of patients with CAB who had a primary diagnosis of VTE at the index admission, CAB remained associated with an increased 90-day risk for VTE (OR vs. hospitalized controls, 1.6; 95% CI 1.1-2.3).

**Table 7. 0-90 and 91-365 day risk of a first VTE among patients with first hospital admission for CAB and matched hospitalized controls and population controls, Northern Denmark, 1992-2010**

| | Risk, % (n/N) | | | Adjusted relative risk (95% CI)* | |
|---|---|---|---|---|---|
| | **CAB patients** | **Population controls** | **Hospitalized controls** | **CAB vs. population controls** | **CAB vs. hospitalized controls** |
| **0-90 days** | 1.1 (45/4213) | 0.0 (18/41 121) | 0.6 (112/20 084) | 23.4 (12.9-42.6) | 1.9 (1.4-2.7) |
| **91-365 days** | 0.5 (15/3316) | 0.2 (72/32 022) | 0.3 (45/13 920) | 1.9 (1.0-3.3) | 1.4 (0.8-2.5) |

*Computed by conditional logistic regression (0-90 days) and Cox' regression (91-365 days). Controls matched for age, sex and calendar time act as reference groups. All relative risk estimates are controlled for matching factors and cancer, cardiovascular diseases, other comorbidities, and recent hospital contact.

## 7.3 Study III.

### The effect of CAB on return to workforce, risk of sick leave, permanent disability pension and death

In **study III** we included 450 CAB patients, 6936 blood culture-negative controls, and 3765 matched population controls of working age (20-58 years) who were part of the workforce in the previous 4 weeks. In the year before blood culture draw, study subjects were on sick leave for a median of 0 weeks (IQR 0-1 week for CAB patients and culture-negative controls, and 0-0 weeks for population controls). CAB patients were older than culture-negative controls (median age in years 47.7 vs. 41.4, $p<0.001$). The burden of pre-existing disease was relatively low in CAB patients (Charlson score of 0 in 79.3%) and culture-negative controls (Charlson score of 0 in 78.8%). Still, the disease burden was even lower among population controls (Charlson score of 0 in 90.7%).

One year after the index date, 78.0% of CAB patients, 85.7% of culture-negative controls, and 96.8% of population controls were alive and part of the workforce. During 1 year of follow-up, 50% of CAB patients were on sick leave for at least 4 weeks (median 4, IQR 0-14 weeks). In contrast, 50% of culture-negative controls were on sick leave for 0 weeks (median 0, IQR 0-7 weeks). Patients with CAB experienced an increased risk of sick leave for ≥4 consecutive weeks (40.2% vs. 23.9%, adj. RR, 1.51; 95% CI, 1.34-1.70) and ≥52 weeks (5.8% vs. 2.6%, adj. RR, 1.96; 95% CI, 1.31-2.93) when compared with culture-negative controls (Table 8). Still, patients with CAB and culture-negative controls had a similar 1 year risk for disability pension, 2.7% for CAB patients and 2.6% for culture-negative controls (adj. RR, 0.99; 95% CI, 0.48-2.02) (Table 8 and Figure 10). Patients with CAB had an increased risk for 1-year disability pension when compared with population controls (2.7% vs. 0.6%, adj. RR, 5.20; 95% CI, 2.16-12.50), see Table 8. Table 8 also shows the 30-day and 1-year mortality among patients with CAB who were part of the workforce compared with controls. Patients with CAB had a 4.0% 30-day mortality (vs. 1.4% for culture-negative controls, adj. RR, 1.87; 95% CI 1.03-3.40, and 0 for population controls) and a 1-year mortality of 8.0% (vs. 3.9% for culture-negative controls, adj. RR, 1.52; 95% CI 1.10-2.10, and, 0.2% for population controls, adj. RR, 37.83; 95% CI 15.67-91.29).

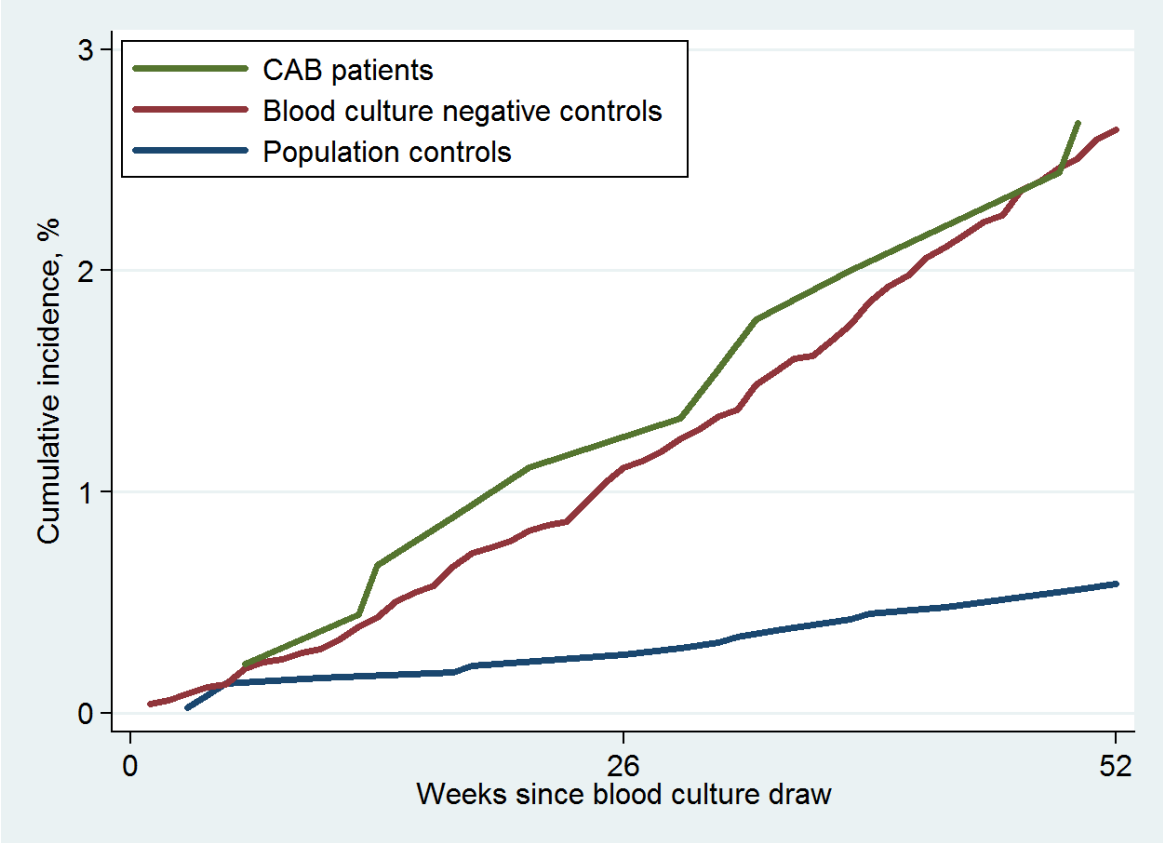
Patients with CAB caused by *S. pneumoniae* had the lowest level of comorbidity (85% with Charlson score of 0), the lowest mortality (30-day, 1.7%, and, 1-year, 4.5%), and the highest 1-year risk for permanent disability pension (3.4%). Patients with *S. aureus* infection and polymicrobial CAB had high mortality (30-day mortality: *S. aureus*, 9.7%, and polymicrobial CAB, 21.4%; 1-year mortality: *S. aureus*, 16.1%, and polymicrobial CAB, 28.6%) and a high proportion of patients were on sick leave for a long period of time after infection (e.g. 19.4% of patients with CAB caused by *S. aureus* were on sick leave for 52 consecutive weeks) but the 1-year risk for disability pension was 0.

**Table 8. Sick leave, disability pension, and mortality among CAB patients (N=450) and blood culture-negative controls (N=6936).**

| | | Risk, % (# of events) | | Adjusted risk difference*, % (95% CI) | Adjusted relative risk* (95% CI) |
|---|---|---|---|---|---|
| | | CAB patients | Controls | | |
| **Sick leave**† | **≥4 weeks** | 40.2 (181) | 23.9 (1658) | 14.1 (9.5-18.7) | 1.51 (1.34-1.70) |
| | **≥52 weeks** | 5.8 (26) | 2.6 (181) | 3.0 (0.8-5.2) | 1.96 (1.31-2.93) |
| **Disability pension** | **1-year** | 12.7 (12) | 2.6 (183) | -0.5 (-2.1-1.0) | 0.99 (0.48-2.02) |
| **Mortality** | **30-day** | 14.0 (18) | 1.4 (99) | 2.2 (0.4-4.0) | 2.34 (1.22-4.50) |
| | **1-year** | 8.0 (36) | 271 (3.9) | 3.1 (0.6-5.6) | 1.73 (1.18-2.55) |

*Relative risk and risk difference computed by log-binomial regression (sick leave analyses) and regression analyses based on pseudo-values (disability pension and mortality analyses). Estimates are adjusted for age, gender, Charlson score, alcoholism-related disease, medication use, marital and immigrant status. Because of few events, 30-day mortality estimates were not adjusted for medication use, marital and immigrant status. Risk difference estimates for sick leave were not adjusted for immigrant status because of failure to converge. †Sick leave for ≥4 and ≥52 consecutive weeks after the index date.

**Figure 10. Cumulative incidence of permanent disability pension in workforce CAB patients, blood culture-negative controls, and population controls, North Denmark, 1996-2011.**



## 7.4 Study IV.

### Functional status and HRQOL after CAB

In **study IV** we included 71 patients with CAB and 71 matched culture-negative controls. Patients with CAB and controls were of comparable age (63 vs. 64 years) and pre-hospitalization functional status as assessed by Barthel-20 (median Barthel-20 index score of 20 [range 1-20] for patients with CAB and median score 20 [range 2-20] for controls). However, more CAB patients than controls were previously healthy (23% vs. 10%) and employed before admission (38% vs. 24%). Two percent of baseline questionnaires were completed by proxies. At 3 month follow-up, 7% (5/71) of patients with CAB and 4% (3/71) of controls had died and 1 patient in each group did not respond to questionnaires.

Patients with CAB had a 5-fold increased risk for deterioration in functional status (as assessed by Barthel-20) when compared with controls (Table 9). CAB was associated with a 37 to 39% risk for deterioration in HRQOL (as assessed by EQ-5D index score and VAS), which was not significantly greater than among controls (Table 9).

For all Barthel-20 items, except walking on stairs, the proportion of CAB patients who needed assistance was greater at follow-up than at baseline (ratio of proportions for help with bathing, 2.3; 95% CI, 1.1-4.7, and, for help with dressing, 2.3; 95% CI, 1.0-5.4). Likewise, the proportion of patients with CAB with HRQOL problems was increased in all five EQ-5D dimensions at follow-up compared with baseline, and significantly so for usual activities and pain/discomfort (ratio of 2.3, 95% CI, 1.4-3.6, and, ratio of 1.7, 95% CI, 1.2-2.5). Among controls, a similar proportion of subjects had problems in Barthel-20 items and EQ-5D dimensions at baseline and at follow-up.

**Table 9. Risk for deterioration in functional status and HRQOL among patients with CAB and culture-negative controls.**

| | Risk for deterioration, % (n/N) | | Adj. risk difference* | Adj. risk ratio* |
|---|---|---|---|---|
| **Deterioration in** | **CAB patients** | **Controls** | **% (95% CI)** | **(95% CI)** |
| **Functional status** | | | | |
| **Barthel-20 score** | 14 (10/71) | 3 (2/71) | 11 (3-19) | 5.1 (1.2-22.3) |
| **Patient's report**† | 9 (6/71) | 3 (2/71) | - | 2.9 (0.6-13.3) |
| **HRQOL** | | | | |
| **EQ-5D index score** | 37 (26/71) | 28 (20/71) | 10 (-5-25) | 1.3 (0.8-2.1) |
| **EQ-5D VAS**‡ | 39 (28/71) | 27 (19/71) | 12 (-3-28) | 1.4 (0.9-2.3) |
| **Patient's report**† | 32 (23/71) | 18 (13/71) | 14 (1-28) | 1.9 (1.0-3.4) |

Abbreviations: CAB, community-acquired bacteremia. *Estimates are adjusted for age and gender. Estimates pertaining to deterioration in HRQOL are also adjusted for any pre-existing disease (yes/no). A (-) denotes that no adjusted estimate was computed because of failure to converge. †Patient's report of worse functional status and HRQOL at follow-up compared with baseline. ‡Deterioration in VAS of at least 10 points.

# 8. Limitations of the studies

There are six ways for an exposure to be associated with an outcome in an epidemiological study: 1) selection bias, 2) information bias, 3) confounding bias, 4) chance, 5) reverse causation, and, 6) causation. All types of bias, chance, and reverse causation are important threats to the validity of observational studies and need to be considered in the context of **studies I to IV**.

***Selection bias***

Selection bias arises from inappropriate selection of study subjects and/or factors that affect study participation (informative/non-random censoring). It entails that the association between exposure and outcome differs between included study subjects and those potentially eligible for study. Inappropriate selection of subjects and informative censoring will be discussed separately.

In **studies I and II** patients with CAB who also had thromboembolism may have been more likely to be hospitalized (and diagnosed) than patients with CAB who did not have thromboembolism. This may have inflated the observed association between CAB and thromboembolism when patients with CAB were compared with population controls.[316] Inappropriate selection of controls is a possibility. In **study I and II** we included hospitalized controls who did not have a primary diagnosis of AMI/AIS or VTE from the index admission to avoid hospitalized controls who were hospitalized solely for thromboembolism. This could lead to falsely inflated relative risk estimates of thromboembolism for patients with CAB vs. hospitalized controls. Still, CAB remained associated with a significantly increased risk of thromboembolism after exclusion of matched groups in which the patient with CAB had a primary diagnosis of thromboembolism. In **study IV** patients were asked if they would like to participate in the study which may have lead to response bias, i.e. subjects who participated and answered questionnaires at follow-up may differ from those who did not chose to participate at baseline or at follow-up. The potential effect of response bias is difficult to decipher.

Informative censoring occurs when study subjects are lost to follow-up due to reasons related to the study. In **studies I to III** loss to follow-up was negligible because we used Danish population-based registries with prospectively collected data to obtain information on study subjects. In **study IV** only 1 subject in each group did not respond to follow-up questionnaires.

A special type of informative censoring occurs when study subjects are lost to follow-up due to a competing event – a competing risk for the outcome under study.[308] Informative censoring by a competing event may not be a weakness *per se* but it complicates the interpretation of the findings in **studies I to IV**. In all four studies death was a competing event because subjects who died during follow-up were no longer at risk for AMI, AIS, VTE, long-term sick leave, disability pension, or deterioration in functional status or HRQOL (as

assessed by questionnaires). In cohort studies with non-informative (random) loss to follow-up and no competing risk, the Kaplan-Meier method is frequently used to compute the cumulative risk of an outcome event. However, if a competing risk is present, the Kaplan-Meier method will falsely inflate the risk of an outcome event (if the competing event occurs). Because follow-up was practically complete for all study subjects in **studies I to IV**, with the exception of informative censoring by death, the absolute risk (cumulative incidence) of an outcome event could be calculated by dividing the number of new outcome events by the total number of subjects who were included in each group.[198] Still, when considering the risk of an outcome event in **studies I to IV** it is important to also consider the risk of the competing event, death, in each group. This is especially important in **studies I and II** in which we computed the cause-specific hazard of AMI/AIS (during 31-180 and 181-365 days of follow-up) and VTE (during 91-365 days of follow-up). The cause-specific hazard can be computed by simply censoring deaths because the instantaneous hazard rate of an event (here thromboembolism) is the instantaneous rate among those actually at risk (e.g. those event-free and not dead).[317] Cause-specific Cox models can be used to compute hazard rate ratios of thromboembolism, again, because it compares the instantaneous hazard among those actually at risk of an event. Because the usual 1-1 correspondence between rate and risk is lost in a competing risk setting[308], the same Cox model cannot be used to compute the cumulative incidence of an event. The implication is that covariates, such as CAB, may not have the same effect on the hazard rate of thromboembolism as on the risk of thromboembolism. In **study III** the risk of long-term sick leave was conditional on long-term survival. Mortality was greatest among patients with CAB and therefore RD and RR estimates of long-term sick leave and mortality should be considered simultaneously. Similarly, in **study IV** the risk of deterioration in functional status/HRQOL was conditional on being alive at 3-month follow-up and mortality was greatest in patients with CAB. Theoretically, if a new/improved treatment only affected mortality after CAB, patients with CAB could experience a further increase in risk for long-term sick leave, disability, and deterioration in HRQOL.

***Information bias***

Information bias may have affected the findings in **studies I to IV** due to non-differential or differential measurement errors.[198,318] Non-differential misclassification occurs when misclassification is the same across the groups to be compared. If misclassification differs between groups, it is differential.

Mistakes in exposure classification are inevitable. Differential misclassification of the exposure causes an unpredictable effect on the measure of association and may explain a non-null result. In contrast, non-differential misclassification of a dichotomous exposure has a predictable effect on the measure of association (typically towards the null) and can rarely explain a non-null finding.[196] In the studies on which this thesis is based, CAB was the exposure. In **studies I and II** we included medically hospitalized controls without CAB and in **studies III and IV** we included medical patients with negative blood cultures as

controls. Some of these controls may have had bacteremia or developed it during follow-up, which could affect our risk estimates towards the null-hypothesis.

Mistakes in the classification of non-death outcomes are also inevitable. Misclassification of the outcome with regard to exposure status is possible in **studies I to IV**. In **studies I to II** we used ICD codes from the hospital discharge registry to identify thromboembolic events. The codes used in the studies have been shown to have a positive predictive value of 92% for AMI, 86 to 90% for AIS, and 75% for VTE.[300–302] If patients with CAB were more likely than controls to be diagnosed with thromboembolism (differential misclassification of the outcome) then our relative risk estimates are biased away from the null. Patients with CAB were already under medical surveillance and therefore potentially more likely to be diagnosed with AMI/AIS or VTE than population controls. Possible troponin spill or fibrin D-dimer increase during infection could further increase CAB patients' risk estimates compared with controls.[156,157] However, the AMI risk was similar before and after troponin measurements became routinely used in clinical practice. In **study III** we may have the underestimated the true duration of sick leave among hospitalized subjects, especially the lower quartile values of sick leave (0 in both groups), because sick leave of short duration is underreported to the Danish social services. However, data on long-term sick leave (>14 days) has been found to be highly valid.[296] Still, patients with CAB were older than culture-negative controls and may have waited for voluntary early retirement instead of applying for disability pension[319], thereby falsely increasing risk estimates for long-term sick leave and falsely decreasing risk estimates for disability pension. In **study IV** interviewer bias may have an effect if the study investigator (the author of this thesis) recorded information on functional status and HRQOL differently among exposed and unexposed. To diminish the risk of interviewer bias I did not go through each subject's data before follow-up contact was made. A bias related to interviewer bias is possible if study participants in any way responded differently to questionnaires according to their exposure status (a Hawthorne effect). It is my impression that study subjects paid very little attention to the result of the blood culture examination – they were all hospitalized and they all felt sick. Another issue with regard to **study IV** is that the questionnaires do not perfectly measure functional status and HRQOL. For Barthel-20 especially, but also EQ-5D, we found that a large proportion of subjects responded with the maximum score at baseline and follow-up (a ceiling effect). The questionnaires may therefore not have been very sensitive to change among our study subjects with the possibility of non-differential misclassification of the outcome among patients with CAB and controls. When measuring changes in HRQOL over time it is necessary to consider adaptation (a response shift), i.e. individuals who survive a debilitating disease may adapt to new health states and therefore "reset the bar" when the time comes for renewed HRQOL assessment.[266] We did see possible examples of adaptation in **study IV**, among them one previously healthy patient who was immobilized in an ICU at follow-up and reported little change in HRQOL (as assessed by EQ-5D).

### *Confounding bias*

Confounding bias, often just called *confounding*, has been deemed "the most important cause of spurious associations in observational epidemiology".[320] Confounding is derived from the Latin, *confundere*, meaning to mix together. It is a mixing of effects due to the presence of a common cause of exposure and outcome.[321] It may be conceptualized as a difference in risk among exposed and unexposed arising from a factor(s) other than the exposure. As defined by Miguel Hernán, a *confounder* is any variable that when stratified on or adjusted for will eliminate/diminish the spurious component of the association between exposure and outcome.[321] Using this definition, a confounder is not necessarily a common cause of exposure and outcome. A proxy variable, which may not be a common cause of exposure and outcome, is also a confounder if adjustment for the proxy variable diminishes confounding. In **studies I to IV** we controlled for confounding by multiple a priori potential confounders in the design phase (restriction and matching) and in analyses (stratification and adjustment). Still, uncontrolled, residual, and unmeasured confounding remains possible. Uncontrolled confounding is a possibility in all four studies in this thesis. Here it implies information on a potential confounder which is measured but not used in an attempt to diminish confounding. In general we had plenty of data on potential confounders in each study. However, limited sample size and/or few outcome events in main analyses or subgroup analyses meant that not all confounder data could be used in analyses. **Study IV** is a good example. It concerned 142 study subjects and less than 70 outcome events in individual analyses, which limited the opportunity for extensive multivariate adjustment. Residual confounding may be due to use of (too) crude categories of confounders leading to loss of information. It may be due to categorization of continuous variables (such as age) or dichotomous classification of pre-existing disease (as done in **studies I to IV**). As an example, pre-existing diseases (confounders) could be classified in many ways from mild through moderate to severe and/or according to duration of disease, which would be more informative and might further diminish confounding when compared with simple dichotomization (e.g. any previous cancer yes/no). For several reasons we did not broaden the classification of confounders, amongst them the abovementioned issues related to sample size and number of outcome events. It is important to note that confounder variables may also be misclassified (see "Information bias" above). If a dichotomous confounder variable is non-differentially misclassified (as would be expected in the present studies) then the problem can essentially be viewed as one of residual confounding (i.e. confounding left after control of the available confounder data).[196] Unmeasured confounding, known and unknown, is of import and a few examples deserve mention. In **study I** we did not have information on smoking history but instead relied on proxy variables for smoking (such as chronic obstructive pulmonary disease). We performed a deterministic sensitivity analysis in **study I**, which showed that an unmeasured confounder would have to be extremely strong to nullify our findings. In **study II** we did not have data on intravenous drug abuse, which has been shown to be associated with *S. aureus* bacteremia and VTE and could account for some of the high risk for VTE associated with CAB in our study.[245] In addition, thrombophilia could confound the observed

association between CAB and thromboembolism. Moreover, anticoagulants for thromboprophylaxis among hospitalized patients could have lowered the risk for thromboembolism and we may therefore have underestimated the VTE risk increase associated with CAB in the absence of this treatment, particularly versus population controls. In **studies I and II** we found no adjusted risk increase for thromboembolism after 180 and 90 days, respectively, which argues against considerable unmeasured confounding. In **study III** we lacked data on psychiatric and orthopedic disorders, which are risk factors for sick leave and disability pension. Whether these disorders are unevenly distributed among patients with CAB and their culture-negative controls, and how they may affect our risk estimates, is guesswork at present. All four studies lacked data on lifestyle factors and some socioeconomic factors (e.g. educational level). Marital status, a marker of socioeconomic status, was considered a confounder in **studies I and IV** and used in multivariate analyses. In summary, confounding could – to some extent - be a cause of spurious associations in **studies I to IV**.

***Chance***

In contrast to bias described above, chance can be minimized (statistical precision can be improved) in epidemiological studies by increasing the sample size of any given study. The cohorts presented in this thesis constitute some of the largest cohorts on acute infection and the outcomes under study. Still, statistical precision was only modest to good in **studies I to IV**. Some may argue that **studies I and II** show very wide confidence intervals (a large amount of random error) for many short-term relative risk estimates. However, when considering the width of the confidence interval, one has to look at the magnitude and the direction of the effect measure. As an example, consider the 30-day risks for AMI/AIS which were 3.6% for CAB patients vs. 0.2% for population controls. The adjusted relative risk was 20.86 and the 95% confidence interval was 15.38 to 28.29, which may seem wide. If we flip the analysis and compare the risk among population controls with the risk among patients with CAB we would get an adjusted relative risk of 0.05 and a confidence interval from 0.03 to 0.06, which seems less wide. Precision was generally good in **studies I and II**. In **study IV** the risk of deterioration in HRQOL as assessed by EQ-5D VAS was 39% among patients with CAB and 27% among controls, which may seem a clinically relevant difference but our study lacked power to identify a statistically significant difference (adj. RD, 12%; 95% CI, -3-28, and, adj. RR, 1.4; 95% CI, 0.9-2.3). Hence, in **study IV**, our smallest study, our findings may be due to chance alone.

***Reverse causation***

Reverse causation is frequently overlooked as a threat to the validity of cohort studies, perhaps because the temporal sequence of events is clear-cut in many studies (e.g. studies on infection and mortality). Still, for studies with a close temporal association between exposure and a non-death outcome, reverse causation may be of paramount importance. In **studies I and II**, and other observational studies on infection and

thromboembolism, it is possible that some thromboembolic events preceded infection. Studies have shown that the risk of nosocomial infection shortly after AMI and stroke is somewhere between 2 and 16%.[322–325] To decrease the effect of reverse causation, we only included patients with CAB who had positive blood cultures taken on the day of hospital admission. Furthermore, we reviewed a convenience sample of medical records of patients with CAB who had a thromboembolism discharge diagnosis from the index admission and found no indication of reverse causation. Still, we cannot firmly rule out that reverse causation may have inflated our relative risk estimates in the main analyses. In supplementary analyses we excluded matched groups in which the patient with CAB had a primary diagnosis of thromboembolism and CAB remained associated with a significantly increased risk of thromboembolism.

Bias, confounding, chance, competing risk, and to some extent reverse causation are issues that affect the interpretation and validity of **studies I to IV**. However, the very same issues are unavoidable when discussing the existing literature as will be done in the following section.

# 9. Discussion in relation to the existing literature

## Thromboembolism after CAB

Few studies have examined the risk of thromboembolism after microbiologically verified bacterial infection. Our short-term absolute risk estimates for AMI (1.7% within 30 days), AIS (2.1% within 30 days), and VTE (1.1% within 90 days) are consistent with findings from previous cohort studies. Levine et al. pooled data from three clinical trials in patients with severe sepsis and septic shock and found that 0.5-1.5% had AMI, 1.0-2.7% had AIS, and 0.5-0.9% had VTE within 28 days.[242] In that study, approximately 54% of subjects received prophylactic heparin. [242,326] Thus, the true risk of thromboembolism after severe sepsis and septic shock may be higher in the absence of heparin prophylaxis. In support of that notion, a study from Israel by Vardi et al. found an in-hospital risk of VTE of 1.3% among patients with sepsis admitted to a Department of Internal Medicine (18% received anticoagulant therapy).[244] In the largest cohort study conducted to date, Perry et. al detailed the risk of AMI and stroke among 50 119 patients admitted for pneumonia.[251] In total, 1.2 % of patients experienced a first-time AMI and 0.2% a first-time stroke within 30 days following admission. Other studies on patients with pneumonia have found a higher risk of AMI within 30 days (up to 7%).[232] However, reverse causation may be an issue in some studies that detail a high risk.[249,257] In our study, endocarditis and meningitis were associated with particularly high risks for AIS. Still, other studies have detailed a greater risk (≥ 10%) of stroke after these infections, in part because they included hemorrhagic stroke outcomes.[167,248,254,258]

Very few cohort studies on the association between infection and thromboembolic events have included a comparison group or have had adequate long-term follow-up. We found that patients with CAB had an approximately 2-fold increased short-term risk for AMI, AIS and VTE when compared with hospitalized controls, and that the risk was increased more than 20-fold when compared with population controls. Patients with CAB caused by *S. aureus* had a particularly high risk for AIS and VTE. However, all types of CAB increased the risk of thromboembolism. One small cohort study compared 208 patients hospitalized for pneumonia with 395 hospitalized controls and found an 8-fold risk increase for acute coronary syndrome within 15 days.[249] Similarly, a large register-based study from the US found that patients hospitalized for severe sepsis had a 6-fold increased risk of in-hospital AIS compared with hospitalized controls.[166] Reverse causation may have accounted for some of the increased risk in these studies.[327] A recent study from Denmark by Mejer et al. examined the risk of VTE after *S. aureus* bacteremia and detailed a 15-fold increased risk (HR) of VTE within 30 days of blood culture draw when compared with population controls.[245] Because events during bacteremia hospitalization were ignored, the study findings are not biased by reverse causation but by immune person-time (immortal-time bias) and the true risk increase may therefore be greater.[328] As in our study, Mejer et al. and Schmidt et al. found that skin and soft tissue

infections were potential high-risk infections for VTE.[245,255] Case-only study designs, especially the self-controlled case series method, have been used to examine short-term risks of thromboembolic events after infection. In this type of study, subjects are included if they have both a transient exposure (infection) and an acute outcome of interest (thromboembolism) during an observation period and the outcome-risk is then compared for different time periods, with each patient serving as his/her own control. The following 14-day risk-increases have been reported from case-only studies: hospitalization with *S. aureus* bacteremia was associated with a 35-fold increased risk of AMI[243], hospitalization with pneumonia was associated with a nearly 50-fold increased risk of AMI[249], and hospitalization for infection was associated with an 8-fold increased risk of stroke.[250] Moreover, self-controlled case series studies by Smeeth et al. found that RTI and UTI diagnosed in the community were associated with a 2 to 5-fold increased risk for AMI, AIS, and VTE.[177,246] The big advantage with the self-controlled case series method is that time-invariant confounders (e.g. sex and genetics) are controlled for implicitly.[329] Disadvantages include that absolute risk estimates cannot be computed and that some of the assumptions behind the method may be hard to satisfy (e.g. the occurrence of an outcome event must not alter the probability of subsequent exposure).[329] In a Lancet Infectious Diseases review, Corrales-Medina inferred from case-only studies by Smeeth et al. that pneumonia is associated with a greater risk of acute coronary syndrome than UTI.[149] However, such a conclusion cannot be drawn from case-only data. While some infections may be associated with a higher risk of thromboembolism than others, the findings from **studies I and II** and other previous studies suggest that a wide range of infections are associated with an increased short-term risk of thromboembolism when compared to other hospitalized patients or the background population.

## The effect of CAB on return to workforce, risk of sick leave, permanent disability pension and death

To the best of our knowledge, our study is the first population-based cohort study to examine return to work and risk of sick leave and disability pension among patients with CAB. Only a few studies have examined return to work after severe bacterial infection and mostly in secondary analyses. In a small study from Denmark, Poulsen et al. examined physical outcomes in 1-year survivors of ICU-treated septic shock.[259] After 1 year, 43% (10/23) of previously employed patients had returned to work, which is considerably fewer than the approximately 80% of patients with CAB who were in the workforce after 1 year in our study. The discrepancy between our findings may owe to differences in study populations. The study by Poulsen et al. included ICU patients who could retire with benefits (a competing event), which the medical patients in our study could not. Other studies on ICU-treated severe sepsis have found that the proportion of patients who had returned to work was 90% (9 of 10 patients) after 1 month and 93% after 3.5 years.[260,277] In a US

study on patients with pneumonia, Fine et al. followed 2287 patients for thirty days, including 539 previously employed outpatients and 218 previously employed inpatients.[261] Among less sick outpatients, 95.3% of the previously employed had returned to work at day 30. Among patients who were admitted to hospital, 68.1% of previously employed had returned to work at day 30 and the median time to return to work was 22 days, which is comparable with our results.

This is also the first study to examine the mortality in adults who were part of the workforce immediately before onset of CAB. We found a relatively low mortality among patients with CAB of 4% within 30 days and 8% within 1 year. In a recent population-based cohort study from Denmark, Koch et al. examined mortality according to socioeconomic status among 8653 patients with bacteremia who were 30 to 65 years of age.[213] The authors reported the highest 30-day mortality (19.7%) in the subgroup that had the lowest income and most disability pensioners. Other studies have found a similar and high short-term mortality among working-age patients with CAB.[8,9] Considering that we excluded approximately 30% of 20 to 58 year old patients with CAB because of disability pension or recent long-term sick leave, it does seem likely that the higher mortality described in previous studies owes to the inclusion of comorbid patients from outside the workforce.

## Functional status and HRQOL after CAB

Our prospectively conducted cohort study is the first to assess changes in functional status and HRQOL after CAB. It corroborates and extends on findings from previous studies on acute infection and changes in functional status/HRQOL, including two large studies from the US that relied on data from the Health and Retirement Study and Medicare. Davydow et al. showed that hospitalization for pneumonia was associated with new disabilities in ADL and IADL.[283] In the subgroup with no baseline disability, patients with pneumonia suffered significantly more new functional disabilities than patients hospitalized for AMI and fewer than patients hospitalized for stroke.[283] Similarly, Iwashyna et al. found that survivors of severe sepsis hospitalization were burdened with significantly more new functional disabilities than survivors of non-sepsis hospitalization.[280] Few cohort studies have examined changes in HRQOL from before ICU admission with severe sepsis to various time points after hospitalization with conflicting results. Hofhuis et al. used the SF-36 among 6-month severe sepsis survivors (95 of 103 responded) and found a lower HRQOL at follow-up compared with pre-admission, especially in dimensions pertaining to physical functioning.[278] We found that a greater proportion of patients with CAB had problems with usual activities and pain/discomfort (follow-up vs. baseline) as assessed by EQ-5D, and our study thus corroborates that severe infection may particularly affect the more physical dimensions of HRQOL. Karlsson et al. used the EQ-5D and found that 98 severe sepsis survivors reported similar EQ-5D VAS before and 17 months (range 12 to 20 months) after

infection, while the index score was lower after infection .[279] The study by Karlsson et al. was limited by considerable loss to follow-up (>40%). Nesseler et al. found that in 23 patients with septic shock, for whom SF-36 data was obtained at baseline and at 6 month follow-up, HRQOL improved in bodily pain and vitality dimensions.[281] However, with regard to HRQOL analyses, lack of baseline data and loss to follow-up was also an issue in this study (>50%). None of the abovementioned studies on changes in HRQOL included a comparison group *per se*. However, they did compare HRQOL among sepsis patients with HRQOL reference values from the background population and found that sepsis survivors had lower HRQOL at baseline and at follow-up. Because patients with severe infection have a low HRQOL *before* hospital admission, I will not discuss our findings in relation to results from cohort and cross-sectional studies that "only" report on HRQOL at one point in time after severe infection (and generally find HRQOL low when compared with the background population).[275] Summarizing the findings from our study and previous studies with little loss to follow-up, CAB and other severe acute infections may be associated with an increased risk of deterioration in functional status when compared with other hospitalized patients and a high risk of worsened HRQOL, especially in physical dimensions.

# 10. Main conclusions

## Study I

We conclude that patients admitted with CAB had a transient increased risk of AMI and AIS when compared with matched hospitalized and population controls. The risk of AMI/AIS was greatest during the first 30 days after CAB. Still, a modestly elevated risk in particular for AIS was observed for 6 months post-infection when compared with population controls. While CAB was associated with an increased risk of AMI and AIS the absolute short-term risks of these events were low to moderate.

## Study II

Patients with CAB have an increased short-term risk for VTE when compared with matched controls. However, with the possible exception of *S. aureus* bacteremia, the absolute risk for VTE within 90 days following CAB is low.

## Study III

Our study shows that CAB is a debilitating condition in adults who are part of the workforce. CAB is associated with a high risk for long-term sick leave when compared to hospitalized culture-negative controls. Still, in this somewhat healthy population, the risk for permanent disability pension and death after CAB was relatively low.

## Study IV

Medical patients with first-time CAB have a high risk for deterioration in functional status and HRQOL from pre-admission until 3 months after blood culture draw. When compared with blood culture-negative medical patients, CAB is associated with an increased risk for reduced functional status.

# 11. Perspectives

The studies presented in this thesis underscores that patients with CAB are at high risk of serious outcomes.

**Studies I and II** substantiated that patients with CAB have an increased risk for AMI, AIS and VTE when compared with hospitalized controls and population controls. While the absolute risk of thromboembolism may be only low to moderate, CAB and other severe acute infections may account for a large proportion of all thromboembolic events (e.g. up to 10% of all AMIs and strokes).[180,330] But what can we do about it? Bacteremia and other infections may be preventable. Vaccination efforts may impact the risk of infection (e.g. pneumococcal infection) and thereby the risk of thromboembolic events.[331] The interest in vaccinology has been revived and multiple vaccines are in the pipeline.[332] Still, there are several challenges related to prevention, diagnosis, and optimal management of thromboembolic events *during* infection, which deserves mention. Prevention of thromboembolic events in patients hospitalized for CAB and other acute infection is somewhat hampered by the fact that most thromboembolic events occur very early, especially arterial events.[158,242] Patients rarely present in the incipient phase of infection but rather when the inflammatory and coagulatory response is well underway. In medical patients, the routine use of heparin for thromboembolism prophylaxis is controversial but may be beneficial in certain high-risk patients such as patients with CAB.[333–336] The appropriateness of "cardioprotective" therapy, with agents such as β-blockers, statins and aspirin, in patients with CAB is not clear.[217,337–341] Early antibiotic treatment may lead to reduced prothrombotic activity during infection[342], which gives us another incentive for early initiation of appropriate antimicrobial therapy. Still, on a population level, a lowered threshold for (very) early antibiotic treatment in patients with any suspected infection seems hard to justify when considering the negative effects of antibiotic treatment (e.g. resistance to antimicrobial agents). Diagnosis of AMI, AIS, and VTE in patients with CAB may be challenging because of clinical mimicry (i.e. dyspnea and chest pain in pneumonia and AMI and PE, redness and soreness of the leg in skin infection and DVT, focal neurologic abnormalities in meningitis and stroke). Moreover, elevated troponin and fibrin D-dimer levels during CAB may have little to do with a thromboembolic event.[157,343] Optimal management of thromboembolism during CAB is debatable. As an example, because AMI during CAB may be predominantly non-thrombotic (type 2), it is uncertain to what extent cardiac catheterization is called for. Future experimental and observational studies should clarify the mechanisms that link CAB to thromboembolic events. In addition, there is a need for further delineation of which infections confer a high risk of thromboembolism and the effect of heparin prophylaxis and "cardioprotective" therapy in the management of these infections. Such knowledge may improve prevention, early diagnosis, and targeted management of thromboembolism in patients with CAB. In the meantime, clinicians need to be aware of the possible link between CAB and thromboembolism.

**Studies III and IV** provided evidence that CAB is associated with long-term sick leave within 1 year and a high short-term risk of a decline in functional status and quality of life. Hence, they highlight the importance of evaluating non-death outcomes in patients with CAB. Previous studies have shown that the indirect costs (e.g. temporary and permanent morbidity, work absence and productivity loss) of sepsis and bacteremia may outweigh the direct costs (e.g. medical expenses related to hospitalization) by 100%.[344,345] The incidence of CAB is expected to increase because of aging populations[1,6,56,346], and therefore the socioeconomic burden of CAB may be substantial in decades to come. There are few data on the effect of CAB on sick leave, functional status, and HRQOL. Thus, there are several reasons why future studies are needed. Our findings of an increased risk of sick leave and worsened functional status among patients with CAB need verification in other studies. The tendency towards a higher risk of deterioration in HRQOL among patients with CAB versus culture-negative controls needs further evaluation in larger studies. Furthermore, an even longer duration of follow-up future should preferably be incorporated in future studies on the subject matter. At the present time, 1-year follow-up in **study IV** is ongoing.

An important next step for future research may be the identification of prognostic factors among patients with CAB that may predict a poor prognosis pertaining to death, thromboembolism, sick leave, functional status or HRQOL. We hope to elucidate some of these prognostic factors by the use of population-based health-care databases such as the North Denmark Bacteremia Database, Danish health-care registries, and hospital information systems.

# 12. Summary

Community-acquired bacteremia is a devastating infectious disease. In adults, it is associated with a 30-day mortality of approximately 15% which has been stable in recent decades. Recent studies have found increasing bacteremia rates in the western world. This translates to an increasing number of bacteremia survivors in western populations. Death is a very important outcome of CAB. Still, there are many other potential outcomes, including but not limited to risk of other disease, deterioration in functional status or health-related quality of life (HRQOL), and financial destitution. For patients, families, health care providers, and policy makers, knowledge on these other bacteremia outcomes are of high import.

**The aims** of this thesis were to examine 1) the short- and longer-term risks of acute myocardial infarction (AMI) and acute ischemic stroke (AIS) in CAB patients compared with the background population and with other acutely admitted patients (**study I**), 2) the short- and longer-term risks of symptomatic venous thromboembolism (VTE) in CAB patients compared with acutely hospitalized controls and with the background population (**study II**), 3) return to work and risk for long-term sick leave, disability pension, and death after CAB compared with blood culture-negative controls and matched population controls (**study III**), and, 4) the risk of deterioration in functional status and HRQOL in CAB patients compared with blood culture-negative controls (**study IV**).

**This thesis is based on four cohort studies** conducted in North Denmark. The first three studies are based on data from up to seven high-quality population based registries including the North Denmark Bacteremia Research Database. The fourth study is based on information obtained from patient interviews during which validated instruments were used to assess functional status (questionnaire version of the Barthel-20 index) and HRQOL (EQ-5D questionnaire).

In **study I** we included 4,389 CAB patients, 43,381 matched population controls, and 21,893 matched hospitalized controls. The risk for AMI/AIS was greatly increased within 30 days of CAB: 3.6% vs. 0.2% among population controls (adjusted relative risk, 20.86; 95% confidence interval, 15.38 to 28.29) and 1.7% among hospitalized controls (adj. RR, 2.18; 95% CI, 1.80 to 2.65). During 31 to 180 days after CAB, the risk remained increased vs. population controls (adj. RR, 1.64; 95% CI, 1.18 to 2.27) but not vs. hospitalized controls. During 181 to 365 days after CAB the risk was similar in all study cohorts. In **study II**, 4,213 CAB patients with no history of VTE were matched to 20,084 hospitalized controls and 41,121 population controls. Within 90 days, 1.1% of CAB patients experienced VTE as did 0.6% of hospitalized controls (adj. odds ratio, 1.9; 95% CI, 1.4 to 2.7) and 0.0% of population controls (adj. OR, 23.4; 95% CI, 12.9 to 42.6). No differences in VTE risk were seen after >3 months when compared with hospitalized controls. In **study III** we included 450 working-age CAB patients, 6,936 culture-negative controls, and 3,765 matched population controls. CAB was associated with a 40.2% risk for at least 4-week sick leave, a 2.7% 1-year risk

for disability pension, and a 1-year mortality of 8.0%. Approximately 80% of working-age CAB patients were back in the workforce after 1 year. Compared with culture-negative controls, CAB was associated with a more than 50% increased risk for long-term sick leave (adj. RR, 1.51; 95% CI, 1.34 to 1.70) whereas the 1-year risk for disability pension was similar. Compared with population controls, CAB was associated with a 5-fold increased for disability pension. In **study IV** we included 71 CAB patients and 71 matched culture-negative controls. CAB was associated with an increased risk for reduced functional status at 3 months as assessed by Barthel-20 score (14% vs. 3%, adj. RR, 5.1; 95% CI, 1.2 to 22.3). HRQOL was worse in 37% of CAB patients and 28% of controls by EQ-5D index score (adj. RR, 1.3; 95% CI, 0.8 to 2.1) and in 39% of CAB patients and 27% of controls by EQ-5D VAS (adj. RR, 1.4; 95% CI, 0.9 to 2.3).

**We conclude** that CAB is associated with an increased short-term risk of AMI, AIS, and VTE when compared with hospital and population controls, however, the absolute risks for these events are low. Medical patients with CAB are at increased risk for deterioration in functional status when compared with blood culture-negative controls. In adults who are part of the workforce, CAB is associated with a high risk for long-term sick leave but the risk for disability pension and death is relatively low. As the burden of bacteremia continues to grow, clinicians should be aware of the possible link between CAB and thromboembolic events and the high risk for deterioration in functional status and long-term sick leave after CAB. Prevention and improved therapy of CAB may have an impact on populations' health status.

# 13. Danish summary

Samfundserhvervet bakteriæmi (CAB) er en alvorlig infektion. Den er associeret med en 30-dages dødelighed på cirka 15 % blandt voksne, og dødeligheden har været stabil gennem de seneste årtier. Nylige studier har fundet en stigende incidens af bakteriæmi i den vestlige verden, hvilket har betydet en stigende forekomst af personer, der har overlevet bakteriæmi i befolkningen. Det er vigtigt at have kendskab til prognosen efter bakteriæmi hvad angår dødelighed, risikoen for anden sygdom, forværring af funktionsevne og livskvalitet samt tab af erhvervsevne.

**Formålet** med studierne i denne ph.d.-afhandling var at undersøge 1) risikoen for akut myokardieinfarkt (AMI) og iskæmisk apopleksi (AIS) på kort og længere sigt efter CAB sammenholdt med risikoen i baggrundsbefolkningen og blandt andre akut indlagte patienter (**studie I**), 2) risikoen for venøs tromboemboli (VTE) på kort og længere sigt efter CAB sammenholdt med risikoen i baggrundsbefolkningen og blandt andre akut indlagte patienter (**studie II**), 3) tilbagevenden til arbejde og risiko for langtidssygemelding, førtidspension og død efter CAB sammenholdt med risikoen blandt bloddyrkningsnegative patienter og baggrundsbefolkningen (**studie III**), og, 4) risikoen for forværring i funktionsevne og livskvalitet efter CAB sammenholdt med risikoen blandt bloddyrkningsnegative patienter (**studie IV**).

**Denne ph.d. bygger på fire studier** udført i Nordjylland. De første tre studier er baseret på data fra op mod syv registre af høj kvalitet heriblandt Den Nordjyske Bakteriæmidatabase. Det fjerde studie er baseret på information indhentet under personlige interviews med patienter, hvor der blev anvendt validerede spørgeskemaer til at bedømme funktionsniveau (Barthel-20) og livskvalitet (EQ-5D spørgeskemaet).

I **studie I** inkluderede vi 4389 CAB patienter, 43 381 matchede kontroller fra baggrundsbefolkningen samt 21 893 matchede akut indlagte kontroller. Risikoen for AMI/AIS var kraftigt forøget inden for 30 dage efter CAB: 3,6 % vs. 0,2 % blandt populationskontroller (justeret relativ risiko, 20,86; 95 % konfidensinterval, 15,38 til 28,29) og 1,7 % blandt indlagte kontroller (justeret RR, 2,18; 95 % konfidensinterval, 1,80 til 2,65). I perioden 31 til 180 dag efter CAB var risikoen forøget i forhold til baggrundsbefolkningen (justeret RR, 1,64; 95 % konfidensinterval, 1,18 til 2,27) men ikke i forhold til indlagte kontroller. I perioden 180-365 dage var risikoen ens i alle tre grupper. I **studie II** blev 4213 CAB patienter uden tidligere VTE matchet til 20 084 indlagte kontroller og 41 121 personer fra baggrundsbefolkningen. Inden for 90 dage oplevede 1,1 % af CAB patienter en VTE, og det samme gjorde 0,6 % af indlagte kontroller (justeret odds ratio, 1,9; 95 % konfidensinterval, 1,4 til 2,7) og 0,0 % af personer i baggrundsbefolkningen (justeret OR, 23,4; 95 % konfidensinterval, 12,9 til 42,6). Der var ingen forskel i VTE risiko på længere sigt blandt patienter med CAB og indlagte kontroller. I **studie III** inkluderede vi 450 CAB patienter, 6936 bloddyrkningsnegative kontroller og 3765 matchede populationskontroller. CAB var associeret med en 40,2 % risiko for mindst 4

ugers sygemelding, en 2,7 % risiko for førtidspension inden for 1 år og en 1-års dødelighed på 8,0 %. Cirka 80 % af hidtil erhvervsaktive CAB patienter var tilbage på arbejdsmarkedet efter 1 år. Sammenholdt med bloddyrkningsnegative kontroller var CAB associeret med en mere end 50 % øget risiko for langtidssygemelding (justeret RR, 1,51; 95 % konfidensinterval, 1,34 til 1,70) hvorimod risikoen for førtidspension var ens i de to grupper. Sammenholdt med populationskontroller var CAB associeret med en 400 % øget risiko for førtidspension inden for 1 år. I **studie IV** inkluderede vi 71 CAB patienter og 71 matchede bloddyrkningsnegative kontroller. CAB var associeret med en øget risiko for nedsat funktionsevne efter 3 måneder i forhold til kontroller (14 % mod 3 %, justeret RR, 5,1; 95 % konfidensinterval, 1,2 til 22,3). Livskvaliteten var forværret efter 3 måneder blandt 37 % af CAB patienter og 28 % af kontroller iht. EQ-5D indeks score (justeret RR, 1,3; 95 % konfidensinterval, 0,8 til 2,1) og blandt 39 % af CAB patienter og 27 % af kontroller iht. EQ-5D VAS (justeret RR, 1,4; 95 % konfidensinterval, 0,9 til 2,3).

**Vi konkluderer** at CAB er associeret med en øget risiko på kort sigt for AMI, AIS, og VTE når sammenholdt med andre indlagte og populationskontroller, men den absolutte risiko for tromboemboli er lav. Medicinske patienter med CAB har en øget risiko for forværring i funktionsniveau når sammenholdt med bloddyrkningsnegative kontroller. Blandt erhvervsaktive voksne er CAB associeret med en høj risiko for langtidssygemelding, men risikoen for førtidspension og død er forholdsvist lav. CAB byrden fortsætter med at stige, og sundhedspersonale bør være opmærksomme på den mulige sammenhæng mellem CAB og tromboemboli samt den høje risiko for forværring i funktionsevne og langtidssygemelding. Forebyggelse og forbedret behandling af CAB kan måske have en betydning for befolkningens helbredsstatus.

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# 15. Appendix

# Study I

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# Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study

**Running title:** *Dalager-Pedersen et al.; MI and stroke risk after CAB*

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**Abstract**

***Background*—**Infections may trigger acute cardiovascular events, but the risk after community-acquired bacteremia is unknown. We assessed the risk for acute myocardial infarction and ischemic stroke within 1 year of community-acquired bacteremia.

***Methods and Results*—**Population-based cohort study in Northern Denmark. We included 4389 hospitalized medical patients with positive blood cultures obtained on the day of admission. Patients hospitalized with bacteremia were matched with up to 10 general population controls and up to 5 acutely admitted non-bacteremic controls, matched on age, gender, and calendar-time. All incident events of myocardial infarction and stroke during the following 365 days were ascertained from population-based health-care databases. Multivariable regression analyses were used to assess relative risks (RR) with 95% confidence intervals (CI) for myocardial infarction and stroke among bacteremia patients and their controls. The risk for myocardial infarction or stroke was greatly increased within 30 days of community-acquired bacteremia: 3.6% vs. 0.2% among population controls (adjusted RR, 20.86; 95% CI, 15.38-28.29) and 1.7% among hospitalized controls (adjusted RR, 2.18; 95% CI, 1.80-2.65). The risks for myocardial infarction or stroke remained modestly increased from 31 to 180 days after bacteremia when compared to population controls (adjusted hazard ratio, 1.64; 95% CI, 1.18-2.27), but not vs. hospitalized controls (adjusted hazard ratio, 0.95; 95% CI, 0.69-1.32). No differences in cardiovascular risk were seen after more than 6 months. Increased 30-day risks were consistently found for a variety of etiologic agents and infectious foci.

***Conclusions*—**Community-acquired bacteremia is associated with increased short-term risk of myocardial infarction and stroke.

**Key words:** myocardial infarction, stroke, ischemic, infection, epidemiology

## Introduction

Each year, more than 1 000 000 Americans experience acute myocardial infarction (AMI) or acute ischemic stroke (AIS).[1] Any role of acute infection in triggering acute cardiovascular events is of major clinical and public health interest.[2–5] Infections may increase the risk of AMI and AIS[6–14] by inducing demand ischemia, decreasing myocardial contractility, or by causing endothelial dysfunction, coagulation disturbance, or direct platelet activation.[2–4,15–18] The magnitude and duration of the increased cardiovascular risk is debatable. Cohort studies have reported short-term risks of AMI and stroke varying from 0.2% to more than 10% after hospitalized pneumonia, sepsis, endocarditis, or meningitis.[7–11,19–21]

Case-only studies suggest a 10- to 50-fold increased risk for AMI or stroke shortly after hospitalized infection,[6,9,12] and a 2- to 5-fold increased risk shortly after infection diagnosed by general practitioners.[13,14] Only one cohort study of 206 patients with pneumonia included a comparison group[9], and we are aware of only three studies that included microbiological test results.[6,9,10] Lack of laboratory confirmation of infection may have falsely inflated the effect estimates if cardiovascular events were initially misdiagnosed as infections. Community-acquired bacteremia (CAB) is a well-defined clinical entity that embraces a wide range of mechanisms whereby infection may trigger cardiovascular events. We conducted a 20-year population-based cohort study in Denmark to assess the short- and longer-term risks of AMI and AIS among medical patients with CAB compared with the background population and with other acutely admitted patients.

## Methods

### Setting

The study was conducted in Northern Denmark from 1992 to 2011. This area had a stable

urban/rural catchment population of approximately 500 000 inhabitants who received universal tax-financed primary and secondary care, free at the point of delivery. Throughout the study period, Aalborg University Hospital was the only referral hospital, and all regional hospitals relied on its Department of Clinical Microbiology for blood culture analyses.

We used high-quality population-based databases with prospectively collected data: the Danish Civil Registration System (CRS), The North Denmark Bacteremia Research Database,[22] the Aarhus University Prescription Database,[23] the regional hospital discharge registry (HDR),[24] and the clinical laboratory information system research database.[25] The CRS contains general personal data for all citizens, updated daily. Unique CRS-numbers, assigned to every Danish resident and used for all healthcare contacts facilitated linkage between databases. The study was approved by the Danish Data Protection Agency (2011-41-5864).

**Bacteremia and control cohorts**

Eligibility criteria for study inclusion were age ≥15 years, no hospitalization within the previous 30 days, no record of previous bacteremia (since 1981), and study area residence for ≥1 year. We assembled three study cohorts. First, we used the Bacteremia Database to identify all adult patients who had a first-time positive blood culture taken on the day of admission to a medical ward during 1992-2010. We defined CAB as the presence of viable bacteria or fungi in the bloodstream, determined by blood cultures performed on the day of admission, among clinically ill patients who were not admitted to the hospital within the previous 30 days. The Bacteremia Database has registered all bacteremia cases in the study area since 1981, with prospective data collection since 1992, and is described in detail elsewhere.[22] It provided information on date of blood culture sampling, number of positive culture bottles, focus of infection, and etiologic agent(s). To assess level of inflammation, we retrieved information on index-date white blood

cell counts (WBCs) and C-reactive protein levels (CRPs) for admissions since 1998 from the laboratory database. We categorized WBC as decreased (<3.5×10^9/L), normal (3.5-10×10^9/L), or increased (>10×10^9/L), and the CRP level as normal (<10 mg/L), increased (10-100 mg/L), or highly increased (>100 mg/L).

Second, to assess the effect of hospitalization with CAB on the risk for AMI/AIS we used the CRS to assemble a matched population control cohort of individuals at risk for their first community-acquired bacteremia as of the admission date of their matched bacteremia patient (the index date). Up to 10 population controls were randomly selected for each bacteremic patient; matched for year of birth, gender, and calendar time.

Third, because acute medical hospitalization itself may increase the risk for subsequent AMI and AIS, we assembled an additional matched hospitalized control cohort of up to five randomly selected acutely admitted medical patients for each CAB patient. Hospitalized controls were patients who were acutely admitted for reasons other than a positive blood culture or a primary diagnosis of cardiovascular disease or rehabilitation (International Classification of Diseases (ICD), ICD-8: 390-458, ICD-10: DI00-99, DZ50). They were matched to CAB patients on sex, year of birth, and calendar year of hospital admission.

**Data on cardiovascular outcomes and comorbidity**

HDR provided data on all hospitalized events of AMI and AIS and on pre-existing comorbid conditions. It has recorded complete diagnosis codes from all inpatient hospitalizations and hospital outpatient clinic contacts in Denmark since 1977 and 1995, respectively. HDR uses two versions of the World Health Organization's International Classification of Diseases (ICD-8 until the end of 1993 and ICD-10 thereafter).

One primary discharge diagnosis and up to 20 secondary diagnoses are assigned by

physicians at the treating hospital department. The primary diagnosis refers to the condition that prompted patient admission and the main condition responsible for the completed diagnosis and treatment course. The secondary diagnoses refer to conditions that affect the diagnosis and treatment course.

To assess if AMI/AIS did precede CAB in some patients admitted with CAB and a primary diagnosis of AMI/AIS, we examined available electronic hospital files for 21 of the 60 bacteremic patients who had a primary discharge diagnosis of AMI or AIS. In all 21 patients AMI/AIS developed more than 24 hours after admission for suspected infection (n=7) or occurred on the day of admission in patients with ongoing infection (evidenced by microbiological tests performed by the patient's general practitioner, recent antibiotic prescriptions, and/or medical history taking [n=14]). Therefore, we used primary and secondary discharge diagnosis codes to identify episodes of AMI and AIS (**Supplemental Table 1**). For all three cohorts, we obtained data on pre-existing diseases recorded before the index date, including the 19 disease categories in the Charlson Comorbidity Index,[26] and other conditions described as risk factors for AMI/AIS in the literature.[1] Moreover, we used the Prescription Database to ascertain use of medications before the index date that may affect AMI/AIS risk. The database has Anatomical Therapeutic Chemical classification (ATC) codes on all reimbursed prescriptions since 1991 (**Supplemental Table 1**).[23]

**Statistics**

We followed all study subjects from the index date until first hospitalization for AMI/AIS, death, emigration out of Denmark, or January 1st 2012, whichever occurred first. Because we expected the risk of AMI and AIS to be highest shortly after onset of infection, we split follow-up into three time periods: 0-30, 31-180, and 181-365 days after the index date. For each time period we

computed absolute risks for our predefined outcome AMI/AIS, and for AMI and AIS separately. We also computed relative risks (RRs) of AMI/AIS, AMI, and AIS with 95% confidence intervals (CIs) for CAB patients versus their two matched control cohorts. Because the HDR does not include the exact date of AMI/AIS, we used conditional Poisson regression with robust variance estimation to compute RRs for any hospital admission with AMI/AIS within 0-30 days (index-admission included). We used Cox proportional hazards models and "stsplit" in Stata to compare hazard rates of hospital admission with AMI/AIS during 31-180 and 181-365 days after the index date among CAB patients still alive and at risk of first incident AMI/AIS on day 31 and 181, respectively, and their "at risk" matched controls. Because death was a competing risk for AMI/AIS, we modeled cause-specific hazards of AMI/AIS. To account for the matched design, Cox models were stratified on matched sets.

Because endocarditis is a common cause of septic emboli to the brain, and sometimes the coronary vessels, we performed a supplementary analysis in which we excluded all CAB patients with endocarditis. Since AMI/AIS might have preceded CAB in some patients despite our sample validation results, we conducted supplementary sensitivity analyses in which we excluded matched groups if the CAB patient had a primary discharge code of AMI/AIS. In regression models we controlled for a priori potential confounders: age, gender, calendar-time, marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular diseases, other comorbid conditions, and use of medications for cardiovascular disease (see **Supplemental Table 1** for further detail).

We further examined AMI/AIS RRs for predefined CAB subgroups (age group, sex, study period, etiologic agent, focus of infection, and levels of inflammatory markers) and in strata of previous cardiovascular disease. Analyses within strata of previous cardiovascular

disease required that we ignored the matching, so we used modified Poisson regression. For 2005-2010 when intensive care unit (ICU) data were available, we did a supplementary subgroup analysis restricted to CAB patients who had an ICU stay, as a proxy for severe sepsis. Stratified and subgroup analyses were controlled for age, gender, calendar-time, and any comorbidity (except when stratified on comorbidity). Next, we included interaction terms in regression models and used the Wald test to assess whether the effect of CAB on AMI/AIS differed by subgroup.

Finally, due to possible residual confounding when comparing hospitalized CAB patients with "healthy" population controls, we performed a sensitivity analysis to estimate how much a potential strong unmeasured confounder might have influenced the observed association (see Supplement).

For Cox models the proportional hazards assumption was checked with log-minus-log plots. Stata 11.2 for Windows (Stata Corp., College Station, TX) was used for all data analyses.

## Results

### Study subject characteristics

The study included 4389 CAB patients, 43 831 matched population controls, and 21 893 matched hospitalized controls. Median study participant age was 73 years (interquartile range, 61-82 years). CAB patients had a substantially higher burden of pre-existing disease and filled drug prescriptions than background population controls, and a burden similar to other hospitalized patients (**Table 1**). Among CAB patients the 30-day mortality was 15.7%, nearly twice that of hospitalized controls (7.9%), and after one year it was 29.7% (vs. 5.8% for population controls and 23.9% for hospitalized controls) (**Supplemental Table 2**).

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**Risk for AMI/AIS**

Within the first 30 days of follow-up, 3.6% of CAB patients suffered an AMI and/or an AIS (vs. 0.2% for population controls and 1.7% for hospitalized controls), 1.7% an AMI (vs. 0.1% for population controls and 0.8% for hospitalized controls) and 2.1% an AIS (vs. 0.1% for population controls and 0.9% for hospitalized control) (**Table 2**). Approximately 80% of these early events among CAB patients occurred during the index admission (57/73 AMI events and 72/91 AIS events).

The adjusted 0-30 day RR of AMI/AIS in CAB patients vs. population controls was 20.86 (95% CI, 15.38-28.29) and vs. population controls 2.18 (95% CI, 1.80-2.65). Similar short-term risk-increases were observed when AMI and AIS was analysed separately, see **Table 2**. An increased hazard rate ratio of AMI/AIS remained for CAB patients compared to population controls during 31-180 days (AMI/AIS, adj. HR, 1.64; 95% CI, 1.18-2.27), with an adj. HR of 1.90 (95% CI, 1.26-2.89) for AIS and 1.42 (95% CI, 0.86-2.34) for AMI. Compared to hospitalized controls, HRs were close to one within 31-180 days. 181-365 days after admission, the adjusted AMI/AIS HRs were close to one both when compared with population and hospital controls (**Table 2**).

**Risk for AMI/AIS in subgroups**

Generally, the finding of an increased risk of AMI and AIS was consistent across subgroups. As expected, CAB patients and controls without previous cardiovascular disease (CVD) had lower absolute risks of AMI and AIS within 0-30 days (**Table 3 and 4**). However, the 30-day AMI and AIS relative risk increase tended to be higher in CAB patients without previous cardiovascular disease, related to a low baseline risk among their controls. In comparison, the absolute risk increase of AMI/AIS tended to be similar in those with and without previous cardiovascular

disease. **Supplemental Table 3** details the 0-30-day AMI/AIS risk by subgroups and strata of prevalent cardiovascular disease, and **Table 4-6** show data on longer-term AMI and AIS risks. Patients with Gram-positive infections were younger than patients with Gram-negative CAB (median age 71.0 vs. 75.9 years) and they had lower prevalence of previous AMI (6.5% vs. 9.1%) and stroke (9.8% vs. 15.7%) (**Supplemental Table 2**). Gram-positive CAB yielded a 1.2% risk for AMI and a 2.5% risk for AIS. For Gram-negative CAB both the AMI and the AIS risk was 1.9%. Of note, *Streptococcus pneumoniae* was a major contributor to the Gram-positive CAB group, as was *Escherichia coli* for the Gram-negative group. Therefore, infection with these pathogens mirrored the findings from the respective Gram-stain groups. Patients with *S aureus* infection had an elevated 30-day risk of AMI and in particular AIS (**Table 3 and 4**), especially if they had endocarditis (4.5% with AMI and 9.1% with AIS) yet also without endocarditis (1.8% with AMI and 3.2% with AIS). The corresponding adjusted HRs for AIS were high with *S aureus* infection, and remained increased during 31-180 days of follow-up when compared to hospitalized controls (HR, 7.12; 95% CI, 1.63-31.03) and to population controls (HR, 7.39; 95% CI, 2.21-24.69) (**Supplemental Table 6**).

Patients who had elevated WBC, increased C-reactive protein levels, or all blood culture bottles positive had high 30-day risk increases for AMI and AIS (**Tables 3 and 4**; also see Supplement).

**Supplementary and sensitivity analyses**

CAB patients who needed ICU treatment had a 6.0% 30-day risk of AMI/AIS (adj. RR vs. hospitalized controls, 4.43; 95% CI, 1.82-10.74, and, vs. population controls, 84.53; 95% CI 10.41-686.60) and those without ICU-stay had a 3.0% risk (adj. RR vs. hospitalized controls, 2.24; 95% CI, 1.59-3.15, and, vs. population controls, 19.39; 95% CI, 11.81-31.81)

Exclusion of 160 patients with endocarditis and their matched controls gave 30-day absolute risk estimates for AMI/AIS of 3.5% for CAB patients vs. 1.7% for hospitalized controls (adj. RR, 2.08; 95% CI, 1.71-2.55) and 0.2% for population controls (adj. RR, 20.08; 95% CI, 14.71-27.43).

Exclusion of 61 matched groups in which the CAB patients had a primary discharge diagnosis of AMI/AIS lowered the adjusted 0-30 day RR of AMI/AIS to 1.36 (95% CI, 1.08-1.72) when compared to hospitalized controls, and to 12.98 (95% CI, 9.33-18.06) when compared to population controls.

We estimated that if a strong unmeasured confounder had a prevalence of 5% among population controls and 50% in CAB, and independently increased the 30-day AMI/AIS risk by a factor of 20, the true risk for AMI/AIS following CAB would still be increased 5.73- fold (5.09-fold for AMI and 6.34-fold for AIS).

## Discussion

This study provides evidence that acute admission with CAB is associated with a transient more than 2-fold increased risk of AMI and AIS when compared to other acutely hospitalized patients and a 20-fold increased risk when compared to the background population. Importantly, a more than 60% increased risk for AMI/AIS persists for 1 to 6 months after CAB hospitalization when compared to population controls. Patients with *S aureus* bacteremia are at particularly increased risk for both early and late AIS. However, all types of CAB increase the short-term risk for cardiovascular events.

To our knowledge, this is the largest cohort study to evaluate the risk of AMI and AIS after microbiologically verified infection. Our 30-day absolute risk estimates for AMI (1.7%)

and AIS (2.1%) are consistent with findings from previous smaller cohort studies. Levine et al. pooled data from three clinical trials in patients with severe sepsis and septic shock and found that 0.5-1.5% had AMI and 1.0-2.7% had ischemic stroke within 28 days.[7] For patients with respiratory tract infection, we observed absolute risks consistent with previous pneumonia studies.[5,8–11] In the largest cohort study conducted to date, Perry et. al evaluated the risk of cardiovascular events among 50 119 patients admitted for pneumonia.[11] Within 30 days following admission, 1.2 % of patients experienced a first-time AMI, and 0.2% a first-time stroke. For endocarditis and meningitis, AMI and AIS risk estimates in our study were particularly high but were less than the ≥ 10% reported in previous studies that included hemorrhagic stroke outcomes.[20,21] Most previous cohort studies on the association between infection and cardiovascular events lacked a comparison group or did not have adequate long-term follow-up. One small cohort study compared 208 patients hospitalized for pneumonia with 395 hospitalized controls and found an 8-fold risk increase for acute coronary syndrome within 15 days,[9] higher than our 2.2-fold increased RR within 30 days.

Case-only study designs have been used to examine short-term risk of acute coronary syndrome and stroke after hospitalization for infection.[6,9,12] Patients were included in these studies if they had both a transient exposure (infection) and an acute outcome of interest (AMI or stroke) during an observation period. The outcome-risk was compared for different time periods with each patient serving as his/her own control. In 32 patients the risk of acute coronary syndrome increased 50-fold within a 15-day period after hospitalization for pneumonia.[9] Likewise, in 42 patients the risk of AMI was 35-fold higher within 2 days after recognition of *S aureus* bacteremia[6], and in 669 patients the risk of stroke was 8-fold higher within 2 weeks after infection.[12] These estimates are comparable to our 20-fold increased RR vs. population controls.

Few data are available on the long-term risks of AMI/AIS following infection. A case-only study by Smeeth et al. found that out-of-hospital respiratory tract or urinary tract infection was associated with a 1.2-fold increased risk of AMI or stroke within 29-91 days after infection.[14] In comparison, we found 1.4 to 1.9-fold increased risks for AMI and stroke, respectively during 31-180 days when CAB patients were compared to population controls. Variations in study populations and the definition and severity of infection, AMI, and stroke make it difficult to directly compare risk estimates from various studies. Nonetheless, infection is associated with 30-day AMI and stroke risk in the present study and in previous studies.

Several mechanisms explain why bacterial infections can trigger cardiovascular events. In theory, any severe infection that causes hypotension may disturb the balance between myocardial or cerebral metabolic supply and demand and trigger an ischemic event.[15] Toxins from Gram-negative and Gram-positive bacteria can impair myocardial function[16] and damage the endothelium.[17] Furthermore, bacteria can provoke inflammation-induced activation of the coagulatory system and directly activate platelets[18], which may lead to thrombosis. Moreover, septic embolism may be important. The markedly increased risk only within the first 30 days after bacteremia supports a pathogenic link between acute inflammation associated with bacterial infection and vascular events. In a previous study, Grau et al. found that an increased neutrophil count heralds a short period at increased risk for recurrent ischemic events.[27] Moreover, previous studies have shown that more severe in-hospital infection is associated with higher risk increases for AMI and AIS than less severe infection treated in primary care.[2,4,13,14] We found that high levels of inflammatory markers such as CRP and WBC, and high bacteremia severity as reflected by multiple culture bottles being positive or need for ICU stay predicted high risk increases for AMI/AIS. However, due to limited precision of estimates we cannot conclude that more severe

inflammation or more severe disease confers a greater risk for AMI/AIS than lower levels of inflammation and severity.

Finally, our findings suggest that patients with *S aureus* infection may have a particularly high propensity for thrombosis.[28]

Strengths of the present study included large sample size, population-based design, and complete follow-up of all study subjects. We had access to high quality microbiological data and captured all diagnosed cases of hospitalized CAB over a 20-year period in the study population.[22] Our data on AMI/AIS had high validity.[29–31] Because all data was prospectively collected in independent databases, recall and investigator bias was negligible.

Our study had some limitations. Heart failure and stroke are known risk factors for infection, with risk of reverse causation bias. To increase the likelihood that infection preceded AMI/AIS we limited our study to patients who had a positive blood culture on the day of admission. Furthermore, our medical record review did not reveal reverse causation bias in any patient, and CAB remained associated with AMI/AIS in various sensitivity analyses.

CAB patients were already receiving medical attention and therefore potentially more likely to be diagnosed with AMI/AIS. However, AMI and AIS are serious acute conditions that usually lead to hospital contact. Out-of-hospital deaths from AMI/AIS may have decreased risk estimates for population controls. On the other hand, severe infection may lead to death before AMI/AIS is diagnosed in hospitalized patients. A third possible limitation is that troponin spill during severe infection may have falsely inflated AMI risk estimates.[32] However, the AMI risk was similar before and after the introduction of troponin assays in clinical practice. Because death was a competing risk in this study, the usual 1-to-1 correspondence between risk and rate was lost.[33] Therefore, hazard ratios of AMI and AIS during 31-180 and 181-365 days should be

interpreted with some caution. Although we were able to adjust for a wide range of confounders, residual and unmeasured confounding may have occurred. For example, we lacked information on smoking status and relied on proxy variables for smoking (e.g., chronic pulmonary disease). However, to nullify our findings, an unmeasured confounder would have to be extremely strong. The fact that there was no adjusted risk increase for AMI/AIS in CAB patients versus both control cohorts after more than 180 days argues against substantial unmeasured confounding factors.

In conclusion, patients admitted with CAB had a transient increased risk of AMI and AIS. The risk of AMI/AIS was greatest during the first 30 days after the infection although a modestly elevated risk in particular for AIS was observed for 6 months post-infection. There is a need for a better understanding of the mechanisms including metabolic supply/demand mismatch and embolic events that may increase the risk for cardiovascular events following severe infection. Improving our understanding of these mechanisms through future experimental and observational studies may lead to more targeted prevention and treatment strategies.

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**Table 1.** Descriptive characteristics of 4389 patients with a first-time diagnosis of community-acquired bacteremia and their age, gender, and calendar-time matched controls, 1992-2010

| | CAB patients (n=4389) | Population controls (n=43 831) | Acutely hospitalized controls (n= 21 893) |
|---|---|---|---|
| Age, yrs | | | |
| 15-64 | 1340 (30.5) | 13 400 (30.6) | 6700 (30.6) |
| 65-79 | 1637 (37.3) | 16 370 (37.3) | 8185 (37.4) |
| ≥80 | 1412 (32.2) | 14 061 (32.1) | 7008 (32.0) |
| Gender | | | |
| Female | 2347 (53.5) | 23 464 (53.5) | 11 717 (53.5) |
| Male | 2042 (46.5) | 20 367 (46.5) | 10 176 (46.5) |
| Marital status | | | |
| Married | 2005 (45.7) | 21 893 (50.0) | 10 345 (47.3) |
| Never married or unknown* | 573 (13.1) | 4960 (11.3) | 2622 (12.0) |
| Divorced or widowed | 1811 (41.3) | 16 978 (38.7) | 8926 (40.8) |
| Medication use | | | |
| Digoxin | 574 (13.1) | 3223 (7.4) | 2542 (11.6) |
| Nitrates | 635 (14.5) | 4354 (9.9) | 3172 (14.5) |
| Diuretics | 2661 (60.6) | 18 725 (42.7) | 12 368 (56.5) |
| Beta-blockers | 1283 (29.2) | 9545 (21.8) | 6184 (28.3) |
| Calcium channel antagonists | 1126 (25.7) | 8404 (19.2) | 5494 (25.1) |
| ACE inhibitors | 1226 (27.9) | 8921 (20.4) | 5725 (26.2) |
| Aspirin | 1106 (25.2) | 7756 (17.7) | 5138 (23.5) |
| Platelet function inhibitors | 128 (2.9) | 780 (1.8) | 593 (2.7) |
| Antidiabetics | 634 (14.5) | 2544 (5.8) | 1484 (6.8) |
| Statins | 492 (11.2) | 3743 (8.5) | 2306 (10.5) |
| Other lipid-lowering drugs | 21 (0.5) | 88 (0.2) | 49 (0.2) |
| Inhaled corticosteroids | 242 (5.5) | 1147 (2.6) | 1444 (6.6) |
| Inhaled drugs for COPD/asthma | 1333 (33.1) | 8977 (20.5) | 14338 (34.5) |
| Disulfiram | 78 (1.8) | 213 (0.5) | 367 (1.7) |
| Hormone replacement therapy | 220 (5.0) | 2028 (4.6) | 497 (2.3) |
| Oral glucocorticoids | 553 (12.6) | 1634 (3.7) | 2476 (11.3) |
| Comorbidity | | | |
| Myocardial infarction | 345 (7.9) | 2326 (5.3) | 1587 (7.3) |
| Cerebrovascular disease | 579 (13.2) | 3656 (8.3) | 2642 (12.1) |
| Angina | 643 (14.7) | 3840 (8.8) | 2903 (13.3) |
| Congestive heart failure | 515 (11.7) | 1965 (4.5) | 1796 (8.2) |
| Hypertension | 740 (16.9) | 4560 (10.4) | 3293 (15.0) |
| Valvular heart disease | 168 (3.8) | 751 (1.7) | 589 (2.7) |
| Atrial fibrillation/flutter | 467 (10.6) | 2517 (5.7) | 1720 (7.9) |
| Peripheral vascular disease | 342 (7.8) | 1533 (3.5) | 1239 (5.7) |
| Hemiplegia | 20 (0.5) | 56 (0.1) | 66 (0.3) |
| Dyslipidaemia | 148 (3.4) | 863 (2.0) | 624 (2.9) |
| Diabetes mellitus | 490 (11.2) | 1702 (3.9) | 1751 (8.0) |

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| | | | |
|---|---|---|---|
| Diabetes, end-organ damage | 241 (5.5) | 643 (1.5) | 816 (3.7) |
| Chronic pulmonary disease | 687 (15.7) | 3032 (6.9) | 3516 (16.1) |
| Any tumor | 583 (13.3) | 3832 (8.7) | 3119 (14.2) |
| Metastatic solid tumor | 84 (1.9) | 213 (0.5) | 395 (1.8) |
| Leukemia | 46 (1.0) | 65 (0.1) | 118 (0.5) |
| Lymphoma | 55 (1.3) | 143 (0.3) | 193 (0.9) |
| Connective tissue disease | 246 (5.6) | 1091 (2.5) | 1002 (4.6) |
| Ulcer disease | 378 (8.6) | 2293 (5.2) | 1797 (8.2) |
| Moderate to severe renal disease | 156 (3.6) | 478 (1.1) | 579 (2.6) |
| Mild liver disease | 103 (2.3) | 204 (0.5) | 292 (1.3) |
| Moderate to severe liver disease | 31 (0.7) | 41 (0.1) | 79 (0.4) |
| Alcohol related diagnosis | 240 (5.5) | 724 (1.7) | 1081 (4.9) |
| Obesity | 243 (5.5) | 824 (1.9) | 820 (3.8) |
| Osteoporosis | 192 (4.4) | 831 (1.9) | 765 (3.5) |
| Dementia | 103 (2.3) | 680 (1.6) | 376 (1.7) |
| AIDS | 5 (0.1) | 4 (0.0) | 6 (0.0) |

Data are given as number (percentage) of study subjects. *Marital status unknown for 0.02%.

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**Table 2.** Risk and relative risk for acute myocardial infarction and acute ischemic stroke among patients with community-acquired bacteremia and their age, gender and calendar-time matched controls, Northern Denmark, 1992-2010.

| | Risk, % (n/N) | | | Relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Hospitalized controls | CAB pts vs. population controls | | CAB pts vs. hospitalized controls | |
| | | | | Crude | Adjusted* | Crude | Adjusted* |
| **AMI/AIS risk** | | | | | | | |
| 0-30 days | 3.6 (160/4389) | 0.2 (72/43 831) | 1.7 (365/21 893) | 22.22 (16.82-29.36) | 20.86 (15.38-28.29) | 2.19 (1.83-2.62) | 2.18 (1.80-2.65) |
| 31-180 days | 1.4 (49/3589) | 0.7 (247/35 676) | 1.2 (201/16187) | 2.06 (1.52-2.81) | 1.64 (1.18-2.27) | 1.03 (0.75-1.41) | 0.95 (0.69-1.32) |
| 181-365 days | 1.2 (38/3188) | 0.9 (277/30 873) | 1.2 (162/13 007) | 1.33 (0.95-1.87) | 0.98 (0.68-1.40) | 0.88 (0.61-1.27) | 0.83 (0.57-1.21) |
| **AMI risk** | | | | | | | |
| 0-30 days | 1.7 (73/4389) | 0.1 (37/43 831) | 0.8 (166/21 893) | 19.73 (13.19-29.51) | 17.70 (11.33-27.64) | 2.20 (1.67-2.89) | 2.32 (1.71-3.13) |
| 31-180 days | 0.2 (20/3645) | 0.3 (126/36 265) | 0.6 (104/16 757) | 1.63 (1.01-2.61) | 1.42 (0.86-2.34) | 0.84 (0.52-1.36) | 0.90 (0.54-1.49) |
| 181-365 days | 0.5 (18/3250) | 0.4 (132/31 570) | 0.6 (77/13 392) | 1.31 (0.80-2.14) | 0.88 (0.52-1.50) | 0.91 (0.54-1.53) | 0.91 (0.52-1.60) |
| **AIS risk** | | | | | | | |
| 0-30 days | 2.1 (91/4389) | 0.1 (37/43 831) | 0.9 (206/21 893) | 26.00 (17.61-38.40) | 25.82 (16.72-39.89) | 2.21 (1.73-2.81) | 2.41 (1.84-3.15) |
| 31-180 days | 0.9 (33/3641) | 0.4 (130/36 218) | 0.6 (107/16 694) | 2.67 (1.81-3.92) | 1.90 (1.26-2.89) | 1.34 (0.90-1.99) | 1.25 (0.82-1.91) |
| 181-365 days | 0.6 (20/3238) | 0.5 (156/31 437) | 0.7 (92/13 301) | 1.27 (0.80-2.03) | 0.97 (0.58-1.59) | 0.81 (0.49-1.34) | 0.71 (0.42-1.20) |

Abbreviations: CAB, community-acquired bacteremia. AMI, acute myocardial infarction. AIS, acute ischemic stroke. CI, confidence interval.
*Relative risk estimates for all CAB patients versus their age-, gender- and calendar-time-matched controls further adjusted for marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular disease, other co-morbidity, and medications for cardiovascular disease.

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**Table 3.** 0-30 day risk and relative risk for acute myocardial infarction among subgroups of patients with community-acquired bacteremia and their age, gender and calendar-time matched controls, Northern Denmark, 1992-2010.

| | 0-30 day AMI risk, % (n/N) | | | 0-30 day AMI relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Hospitalized controls | CAB patients vs. population controls | | CAB patients vs. hospitalized controls | |
| Age, yrs | | | | | | | |
| 15-64 | 0.4 (5/1340) | 0.0 (1/13 400) | 0.3 (19/6700) | 48.26 | (5.51-422.92) | 1.24 | (0.46-3.30) |
| 65-80 | 2.1 (35/1638) | 0.1 (12/16 380) | 1.0 (82/8190) | 28.63 | (14.83-55.29) | 2.13 | (1.44-3.16) |
| 80+ | 2.3 (33/1411) | 0.2 (24/14 051) | 0.9 (65/7003) | 13.61 | (7.88-23.52) | 2.52 | (1.65-3.85) |
| Sex | | | | | | | |
| Female | 1.4 (34/2347) | 0.0 (10/23 464) | 0.6 (73/11 717) | 33.07 | (16.16-67.66) | 2.32 | (1.54-3.49) |
| Male | 1.9 (39/2042) | 0.1 (27/20 367) | 0.9 (93/10 176) | 14.03 | (8.48-23.21) | 2.07 | (1.43-3.01) |
| Previous CVD† | | | | | | | |
| No | 1.1 (33/3040) | 0.1 (20/35 885) | 0.5 (84/16 162) | 20.35 | (11.72-35.36) | 2.11 | (1.41-3.15) |
| Yes | 3.0 (40/1349) | 0.2 (17/7946) | 1.4 (82/5731) | 14.43 | (8.25-25.25) | 2.09 | (1.44-3.02) |
| Previous AMI | | | | | | | |
| No | 1.4 (56/4044) | 0.1 (24/41 505) | 0.5 (108/20 306) | 23.79 | (14.76-38.35) | 2.56 | (1.86-3.52) |
| Yes | 4.9 (17/345) | 0.6 (13/2326) | 3.7 (58/1587) | 9.10 | (4.55-18.19) | 1.34 | (0.79-2.28) |
| Previous stroke | | | | | | | |
| No | 1.4 (53/3810) | 0.1 (29/40 175) | 0.7 (144/19 251) | 19.44 | (12.38-30.51) | 1.86 | (1.36-2.54) |
| Yes | 3.5 (20/579) | 0.2 (8/3656) | 0.8 (22/2642) | 16.05 | (7.10-36.30) | 4.09 | (2.25-7.44) |
| Study period | | | | | | | |
| 1992-2002 | 1.7 (38/2200) | 0.1 (16/21 989) | 0.9 (96/10 982) | 23.03 | (12.67-41.85) | 1.96 | (1.34-2.85) |
| 2003-2010 | 1.6 (35/2154) | 0.1 (21/21 842) | 0.6 (70/10 911) | 16.37 | (9.37-28.60) | 2.49 | (1.66-3.74) |
| Etiologic agent | | | | | | | |
| Gram-positive | 1.2 (23/1872) | 0.1 (13/18 695) | 0.7 (70/9341) | 17.18 | (8.59-34.39) | 1.60 | (1.01-2.55) |
| *S pneumoniae* | 0.8 (8/1018) | 0.0 (4/10 173) | 0.6 (33/5084) | 19.66 | (5.94-65.01) | 1.18 | (0.55-2.52) |
| *S aureus* | 2.2 (7/321) | 0.0 (1/3208) | 0.7 (11/1598) | 67.72 | (8.17-561.43) | 3.14 | (1.30-7.59) |
| Other Gram-positive | 1.5 (8/533) | 0.2 (8/5327) | 1.0 (26/2659) | 9.87 | (3.68-26.50) | 1.49 | (0.67-3.35) |
| Gram-negative | 1.9 (43/2228) | 0.1 (22/22 242) | 0.8 (86/11 113) | 19.03 | (11.17-32.40) | 2.50 | (1.73-3.62) |
| *E coli* | 2.3 (36/1545) | 0.1 (16/15 434) | 0.7 (57/7711) | 22.08 | (12.27-39.71) | 3.15 | (2.08-4.77) |
| Other Gram-negative | 1.0 (7/683) | 0.1 (6/6808) | 0.9 (29/3402) | 11.56 | (3.52-37.91) | 1.22 | (0.52-2.83) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Polymicrobial/fungal | 2.4 (7/289) | 0.1 (2/2881) | 0.7 (10/1439) | 34.04 | (7.16-161.87) | 3.51 | (1.34-9.21) |
| Focus of infection | | | | | | | |
| Respiratory tract | 1.0 (10/963) | 0.0 (3/9619) | 0.7 (36/4805) | 32.09 | (8.77-117.43) | 1.35 | (0.67-2.69) |
| Urinary tract | 2.1 (31/1461) | 0.1 (19/14 583) | 0.8 (56/7287) | 15.79 | (8.78-28.40) | 2.79 | (1.80-4.32) |
| CNS | 0 (0/163) | 0.1 (1/1630) | 0.5 (4/815) | - | - | - | - |
| Endocarditis | 1.3 (2/160) | 0.2 (3/1600) | 0.8 (6/800) | 6.49 | (1.13-37.40) | 1.61 | (0.40-6.41) |
| Miscellaneous foci | 0.9 (6/655) | 0.1 (5/6548) | 0.6 (18/3269) | 11.16 | (3.13-37.56) | 1.61 | (0.64-4.05) |
| Unknown or multiple | 2.4 (24/987) | 0.1 (6/9851) | 0.9 (46/4917) | 39.00 | (15.82-96.16) | 2.58 | (1.56-4.29) |
| Blood culture bottles[‡] | | | | | | | |
| Some positive | 1.3 (24/1843) | 0.0 (8/18 390) | 0.7 (62/9187) | 29.90 | (13.17-67.87) | 1.95 | (1.21-3.14) |
| All positive | 1.8 (34/1898) | 0.1 (25/18 961) | 0.6 (57/9466) | 13.57 | (7.80-23.09) | 2.99 | (1.97-4.55) |
| WBC (×10^9/L)[‡] | | | | | | | |
| <3.5 | 1.0 (1/102) | 0.1 (1/1013) | 1.0 (5/505) | 9.88 | (0.62-158.55) | 0.97 | (0.11-8.47) |
| 3.5-10 | 1.5 (10/661) | 0.1 (9/6604) | 0.5 (15/3298) | 11.06 | (4.30-28.44) | 3.34 | (1.47-7.57) |
| >10 | 1.7 (42/2514) | 0.1 (19/25 094) | 0.7 (83/12534) | 21.70 | (12.33-38.18) | 2.55 | (1.76-3.70) |
| CRP (mg/L)[‡] | | | | | | | |
| <10 | 0.8 (1/133) | 0.2 (3/1324) | 0.8 (5/660) | 3.32 | (0.29-38.04) | 1.01 | (0.12-8.64) |
| 10-100 | 2.1 (20/941) | 0.1 (11/9382) | 0.6 (29/4685) | 17.87 | (8.52-37.45) | 3.46 | (1.95-6.16) |
| >100 | 1.5 (32/2203) | 0.1 (15/22 005) | 0.6 (69/10 992) | 20.93 | (11.21-39.06) | 2.33 | (1.53-3.54) |

Abbreviations: CAB, community-acquired bacteremia. CI, confidence interval. CVD, cardiovascular disease. CNS, central nervous system. WBC, white blood cell count. CRP, C-reactive protein.

[*]Relative risk estimates are controlled for age, gender, calendar-time, and any comorbidity (except where stratified by comorbidity). [†]Previous CVD defined as any previous diagnosis of AMI, heart failure, atrial fibrillation or stroke. [‡]Blood culture bottle data from 1996-2010 and WBC and CRP-data from 1998-2010. Blood culture data on number of bottles was missing for 0.1% of patients (categorized as "Some positive"), WBC data for 0.8% (categorized as normal, i.e. 3.5-10×10^9/L), and CRP data for 1.0% (categorized as normal, i.e. <10 mg/L).

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**Table 4.** 0-30 day risk and relative risk for acute ischemic stroke among subgroups of patients with community-acquired bacteremia and their age, gender and calendar-time matched controls, Northern Denmark, 1992-2010.

| | 0-30 day AIS risk, % (n/N) | | | 0-30 day AIS relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Hospitalized controls | CAB patients vs. population controls | | CAB patients vs. hospitalized controls | |
| Age, yrs | | | | | | | |
| 15-64 | 0.8 (11/1340) | 0.0 (3/13 400) | 0.3 (22/6700) | 35.46 | (9.99-159.20) | 2.40 | (1.13-5.06) |
| 65-80 | 2.7 (45/1638) | 0.0 (7/16 380) | 1.3 (103/8190) | 60.60 | (27.43-133.90) | 2.22 | (1.56-3.14) |
| 80+ | 2.5 (35/1411) | 0.2 (25/14 051) | 1.2 (81/7003) | 13.56 | (8.08-22.76) | 2.13 | (1.44-3.13) |
| Sex | | | | | | | |
| Female | 2.4 (57/2347) | 0.1 (26/23 464) | 0.9 (101/11 717) | 20.70 | (12.98-33.01) | 2.83 | (2.05-3.89) |
| Male | 1.7 (34/2042) | 0.0 (9/20 367) | 1.0 (105/10 176) | 36.50 | (17.44-76.35) | 1.60 | (1.09-2.35) |
| Previous CVD† | | | | | | | |
| No | 1.6 (49/3040) | 0.0 (15/35 885) | 0.5 (87/16 075) | 39.66 | (22.31-70.47) | 3.06 | (2.16-4.34) |
| Yes | 3.1 (42/1349) | 0.3 (20/7946) | 2.1 (119/5731) | 12.86 | (7.43-21.65) | 1.50 | (1.06-2.12) |
| Previous AMI | | | | | | | |
| No | 2.1 (84/4044) | 0.1 (30/41 505) | 0.9 (181/20 306) | 28.64 | (18.89-43.41) | 2.33 | (1.80-3.00) |
| Yes | 2.0 (7/345) | 0.2 (5/2326) | 1.6 (25/1587) | 9.94 | (3.13-31.60) | 1.28 | (0.55-3.00) |
| Previous stroke | | | | | | | |
| No | 1.6 (62/3810) | 0.1 (24/40 175) | 0.6 (108/19 251) | 27.32 | (17.07-43.72) | 2.92 | (2.14-3.99) |
| Yes | 5.0 (29/579) | 0.3 (11/3656) | 3.7 (98/2642) | 16.73 | (8.32-33.66) | 1.35 | (0.90-2.01) |
| Study period | | | | | | | |
| 1992-2002 | 2.4 (52/2200) | 0.1 (21/21 989) | 1.0 (112/10 982) | 23.04 | (13.81-38.45) | 2.30 | (1.66-3.19) |
| 2003-2010 | 1.8 (39/2154) | 0.1 (14/21 842) | 0.9 (94/10 911) | 27.37 | (14.83-50.51) | 2.08 | (1.44-3.00) |
| Etiologic agent | | | | | | | |
| Gram-positive | 2.5 (46/1872) | 0.0 (8/18 695) | 0.9 (82/9341) | 54.56 | (25.81-115.34) | 2.80 | (1.95-4.03) |
| *S pneumoniae* | 2.1 (21/1018) | 0.0 (3/10 173) | 0.8 (41/5084) | 65.42 | (19.90-215.04) | 2.63 | (1.55-4.47) |
| *S aureus* | 4.0 (13/321) | 0 (0/3208) | 1.4 (22/1598) | - | - | 2.85 | (1.47-5.54) |
| Other Gram-positive | 2.3 (12/533) | 0.1 (5/5327) | 1.0 (19/2659) | 23.88 | (8.44-67.56) | 3.11 | (1.48-6.52) |
| Gram-negative | 1.9 (42/2228) | 0.1 (27/22 242) | 0.7 (106/11 113) | 14.78 | (9.06-24.11) | 1.96 | (1.39-2.78) |
| *E coli* | 1.7 (26/1545) | 0.1 (23/15 434) | 0.9 (70/7711) | 10.82 | (6.13-19.09) | 1.86 | (1.20-2.87) |
| Other Gram-negative | 2.3 (16/683) | 0.1 (4/6808) | 1.1 (36/3402) | 38.08 | (12.76-113.60) | 2.17 | (1.22-3.87) |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Polymicrobial/fungal | 1.0 (3/289) | 0 (0/2881) | 1.3 (18/1439) | - | - | 0.84 | (0.24-2.93) |
| Focus of infection | | | | | | | |
| Respiratory tract | 1.0 (10/963) | 0.0 (3/9619) | 0.9 (46/4805) | 32.40 | (8.61-121.92) | 1.24 | (0.61-2.49) |
| Urinary tract | 1.8 (26/1461) | 0.1 (20/14 583) | 0.9 (62/7287) | 12.52 | (6.95-22.57) | 2.11 | (1.35-3.29) |
| CNS | 2.4 (4/163) | 0 (0/1630) | 0.2 (2/815) | - | - | 10.58 | (2.42-46.35) |
| Endocarditis | 6.9 (11/160) | 0.1 (1/1600) | 0.9 (7/800) | 116.70 | (16.50-825.49) | 8.18 | (2.96-22.59) |
| Miscellaneous foci | 1.5 (10/655) | 0.1 (6/6548) | 1.0 (33/3269) | 13.57 | (5.05-36.46) | 1.47 | (0.74-2.94) |
| Unknown or multiple | 3.0 (30/987) | 0.1 (5/9851) | 1.2 (60/4917) | 53.80 | (20.35-142.21) | 2.41 | (1.57-3.71) |
| Blood culture bottles[‡] | | | | | | | |
| Some positive | 1.8 (33/1843) | 0.1 (23/18 390) | 0.8 (73/9187) | 12.62 | (7.40-21.52) | 2.24 | (1.48-3.37) |
| All positive | 2.1 (40/1898) | 0.0 (9/18 961) | 1.0 (95/9466) | 44.86 | (21.77-92.42) | 2.10 | (1.47-3.02) |
| WBC (×10^9/L)[‡] | | | | | | | |
| <3.5 | 0 (0/102) | 0.1 (1/1013) | 1.0 (5/505) | - | - | - | - |
| 3.5-10 | 1.5 (10/661) | 0.1 (4/6604) | 0.9 (30/3298) | 23.80 | (7.47-75.81) | 1.66 | (0.81-3.42) |
| >10 | 2.1 (54/2514) | 0.1 (16/25 094) | 0.9 (112/12534) | 32.43 | (18.50-56.86) | 2.41 | (1.76-3.30) |
| CRP (mg/L)[‡] | | | | | | | |
| <10 | 0 (0/133) | 0.1 (1/1324) | 0.8 (5/660) | - | - | - | - |
| 10-100 | 1.9 (18/941) | 0.1 (8/9382) | 0.9 (44/4685) | 21.50 | (9.33-49.53) | 2.04 | (1.19-3.52) |
| >100 | 2.1 (46/2203) | 0.1 (12/22 005) | 0.9 (69/10 992) | 36.87 | (19.44-69.99) | 2.35 | (1.67-3.30) |

See footnotes to Table 3.

**SUPPLEMENTAL MATERIAL**

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**Table 1:** ICD and ATC codes

| **Outcome: Acute myocardial infarction and stroke** | **ICD codes** |
|---|---|
| Acute myocardial infarction | ICD-8: 410 ; ICD-10: I21 |
| Acute ischemic stroke | ICD-8: 432-434 ; ICD-10: I63-I64 (except I63.6) |
| **Comorbidities (previous)*** | **ICD codes** |
| Myocardial infarction | ICD-8: 410; ICD-10: I21-I23 |
| Cerebrovascular disease | ICD-8: 430-438; ICD-10: I60-I69, G45, G46 |
| Angina | ICD-8: 413; ICD-10: I20, I25.1 |
| Congestive heart failure | ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49, ICD-10: I11.0, I13.0, I13.2, I50 |
| Valvular heart disease | ICD-8: 394-396, 424.00-19, 397.00, 397.01, 424.90-92; ICD-10: I34-37 |
| Atrial fibrillation | ICD-8: 427.93, 427.94; ICD-10: I48 |
| Peripheral vascular disease | ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77 |
| Dyslipidemia | ICD-8: 272.00, 272.01, 279.00, 279.01; ICD-10: E78 |
| Hypertension | ICD-8: 400-404; ICD-10: I10-13 |
| Hemiplegia | ICD-8: 344; ICD-10: G81, G82 |
| Diabetes | ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9 |
| Diabetes with end-organ damage | ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10: E10.2-E10.8, E11.2-E11.8 |
| Chronic pulmonary disease | ICD-8: 490-493, 515-518; ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3 |
| Any tumor | ICD-8: 140-194; ICD-10: C00-C75 |
| Leukemia | ICD-8: 204-207; ICD-10: C91-C95 |
| Lymphoma | ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96 |
| Metastatic solid tumor | ICD-8: 195-199; ICD-10: C76-C80 |
| Connective tissue disease | ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30-M36, D86 |
| Ulcer disease | ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28 |
| Moderate to severe renal disease | ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 |
| Mild liver disease | ICD-8: 571, 573.01, 573.04; ICD-10: B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0 |
| Moderate to severe liver disease | ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 |
| Alcohol-related disease | ICD-8: 291, 303, 979, 980, 577.10; ICD-10: F.10, K29.2, K.86.0, Z72.1, R78.0, T51 |
| Obesity | ICD-8: 277; ICD-10: E65-E68 |
| Osteoporosis | ICD-8: 723.09; ICD-10: M80-M82 |
| Dementia | ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, |

| | |
|---|---|
| | F05.1, G30 |
| AIDS | ICD-8: 079.83; ICD-10: B21-B24 |
| **Co-medications*** | **ATC codes (any previous use if not specified)** |
| Digoxin | C01AA |
| Nitrates | C01DA (if ≥2 prescriptions are registered). |
| Diuretics | C03 |
| Beta-blockers | C07 |
| Calcium-channel antagonists | C08 |
| ACE inhibitors | C09 (C02 before 1 January 1996) |
| Aspirin | B01AC06, N02BA01 (125 days' exposure window) |
| Platelet function inhibitors | B01AC04, B01AC07, B01AC30 (125 days' exposure window) |
| Antidiabetics | A10A, A10B |
| Statins | C10AA, C10B, B04AB (125 days' exposure window) |
| Other lipid-lowering drugs | C10AB, C10AC, C10AD, C10AX (125 days' exposure window) |
| Inhaled corticosteroids | R03BA |
| Inhaled drugs for COPD/asthma | R03 |
| Disulfiram | N07BB01 |
| Hormone replacement therapy | G03C, G03F (125 days' exposure window) |
| Oral glucocorticoids | H02AB (125 days' exposure window) |

*The following covariates, based on ICD and ATC codes, were used in the regression analyses in the main model to adjust for baseline differences between all patients with first-time community-acquired bacteremia and their age, gender, and calendar-time matched controls: Marital status (married/never married or unknown/divorced or widowed), previous acute myocardial infarction (yes/no), previous cerebrovascular disease (yes/no), diabetes (diagnosis of diabetes or use of antidiabetics - yes/no), chronic pulmonary disease (diagnosis of chronic pulmonary disease or use of inhaled drugs for COPD/asthma - yes/no), other cardiovascular disease (hypertension, angina, congestive heart failure, valvular heart disease, atrial fibrillation, peripheral vascular disease, or dyslipidemia - yes/no), other comorbid conditions (any tumor, leukemia, lymphoma, metastatic solid cancer, connective tissue disease, ulcer disease, hemiplegia, moderate to severe renal disease, mild and moderate to severe liver disease, alcoholism-related conditions including use of disulfiram, obesity, osteoporosis, dementia, AIDS, hormone replacement therapy, or oral glucocorticoids - yes/no ), and medications for cardiovascular disease (ACE-inhibitors, beta-blockers, calcium-channel antagonists, diuretics, nitrates, statins, other lipid-lowering drugs, aspirin, or platelet function inhibitors - yes/no).

For analyses stratified by previous cardiovascular disease (yes/no) in which we ignored the matched design we adjusted for age, gender, and calendar-time by regression analyses.

For analyses of CAB subgroups according to age, sex, study period, etiologic agent, focus of infection, levels of inflammatory markers, and ICU stay we calculated relative risk estimates versus age-, gender- and calendar-time-matched controls with further adjustment for any comorbidity (yes/no).

**Table 2.** Baseline characteristics and mortality for patients with community-acquired bacteraemia and their matched controls, Northern Denmark, 1992-2010

| Study group (n=) | Age, median (IQR) | Gender, male (%) | Previous AMI (%) | Previous stroke (%) | 30-day mortality (%) | 180-day mortality (%) | 365-day mortality (%) |
|---|---|---|---|---|---|---|---|
| **CAB patients (4389)** | 73.8 (61.4-82.2) | 46.5 | 7.9 | 13.2 | 15.7 | 24.8 | 29.4 |
| **Hospitalized controls (21 893)** | 73.7 (61.3-82.1) | 46.5 | 7.3 | 12.1 | 7.9 | 18.1 | 23.9 |
| **Population controls (43 831)** | 73.8 (61.3-82.1) | 46.5 | 5.3 | 8.3 | 0.3 | 2.7 | 5.8 |
| **CAB patients by:** | | | | | | | |
| **Age, yrs** | | | | | | | |
| 15-64 (1340) | 53.9 (42.3-59.9) | 47.5 | 3.8 | 4.1 | 9.4 | 14.2 | 16.8 |
| 65-80 (1638) | 73.5 (69.8-77.1) | 46.5 | 9.3 | 15.6 | 15.1 | 24.6 | 29.7 |
| 80+ (1411) | 85.1 (82.5-88.4) | 45.6 | 10.0 | 19.0 | 22.5 | 35.1 | 40.9 |
| **Sex** | | | | | | | |
| Female (2347) | 74.1 (61.8-82.5) | - | 5.5 | 11.6 | 15.0 | 23.4 | 27.1 |
| Male (2042) | 73.4 (60.8-82.0) | - | 10.5 | 11.9 | 16.6 | 26.4 | 31.9 |
| **Previous CVD*** | | | | | | | |
| No (3040) | 70.0 (56.5-80.3) | 43.8 | - | - | 13.9 | 21.7 | 25.5 |
| Yes (1349) | 79.2 (71.9-84.5) | 52.8 | 25.6 | 42.9 | 20.0 | 31.8 | 38.1 |
| **Previous AMI** | | | | | | | |
| No (4044) | 73.3 (60.5-82.1) | 45.2 | - | 12.6 | 15.5 | 24.4 | 28.9 |
| Yes (345) | 78.2 (70.2-82.7) | 62.3 | - | 20.3 | 18.8 | 29.3 | 34.5 |
| **Previous stroke** | | | | | | | |
| No (3810) | 72.6 (59.6-81.6) | 45.5 | 7.2 | - | 14.8 | 23.3 | 27.8 |
| Yes (579) | 79.3 (72.5-84.5) | 53.0 | 12.1 | - | 21.9 | 34.4 | 39.7 |
| **Study period** | | | | | | | |
| 1992-2002 (2200) | 73.6 (60.9-81.7) | 46.5 | 6.9 | 11.4 | 16.4 | 25.5 | 30.1 |
| 2003-2010 (2189) | 74.1 (61.7-82.7) | 46.6 | 8.9 | 15.0 | 15.1 | 24.1 | 28.6 |
| **Etiologic agent** | | | | | | | |
| Gram-positive (1872) | 71.0 (58.4-80.0) | 51.8 | 6.5 | 9.8 | 17.5 | 26.1 | 30.2 |
| *S pneumoniae* (1018) | 68.4 (55.7-78.8) | 47.1 | 5.2 | 8.3 | 15.8 | 21.9 | 24.9 |
| *S aureus* (321) | 73.7 (61.3-82.1) | 58.6 | 8.1 | 10.9 | 30.5 | 42.4 | 47.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Other Gram-positive (533) | 73.1 (61.8-81.6) | 56.9 | 7.9 | 12.2 | 12.8 | 24.4 | 30.2 |
| Gram-negative (2228) | 75.9 (64.2-83.0) | 41.1 | 9.1 | 15.7 | 13.3 | 22.2 | 26.9 |
| *E coli* (1545) | 76.7 (66.4-83.5) | 34.3 | 9.8 | 15.2 | 11.2 | 20.1 | 24.8 |
| Other Gram-negative (683) | 73.6 (57.0-82.1) | 56.4 | 7.5 | 16.8 | 18.0 | 27.1 | 31.8 |
| Polymicrobial/fungal (289) | 78.4 (67.6-84.5) | 54.3 | 7.6 | 15.6 | 23.5 | 36.0 | 42.6 |
| **Focus of infection** | | | | | | | |
| Respiratory tract (963) | 69.1 (56.0-79.2) | 48.5 | 5.6 | 8.4 | 14.6 | 17.4 | 23.7 |
| Urinary tract (1461) | 77.3 (66.6-83.7) | 38.2 | 8.8 | 17.0 | 8.1 | 21.1 | 23.1 |
| CNS (163) | 57.4 (42.5-70.2) | 49.7 | 1.8 | 3.1 | 17.8 | 20.1 | 23.9 |
| Endocarditis (160) | 70.6 (56.7-78.9) | 65.0 | 9.4 | 10.0 | 9.4 | 23.1 | 28.1 |
| Miscellaneous (655) | 72.8 (59.5-81.4) | 49.6 | 9.5 | 11.6 | 13.3 | 24.0 | 28.1 |
| Unknown or >1 (987) | 76.4 (65.7-84.1) | 51.4 | 8.4 | 15.5 | 30.5 | 40.6 | 46.0 |
| **Blood culture bottles**[†] | | | | | | | |
| Some positive (1843) | 73.5 (60.3-81.9) | 45.4 | 8.4 | 15.8 | 11.7 | 20.9 | 25.6 |
| All positive (1898) | 74.7 (63.0-82.9) | 47.5 | 8.3 | 12.2 | 18.2 | 27.3 | 31.9 |
| **WBC (×10^9/L)** [†] | | | | | | | |
| <3.5 (102) | 70.9 (60.9-80.9) | 52.9 | 3.9 | 7.8 | 40.2 | 52.0 | 57.8 |
| 3.5-10 (661) | 73.3 (61.5-82.6) | 50.5 | 8.6 | 14.7 | 15.7 | 24.2 | 27.8 |
| >10 (2514) | 74.6 (62.3-82.6) | 44.6 | 9.0 | 14.6 | 14.2 | 23.4 | 28.1 |
| **C-reactive protein (mg/L)** [†] | | | | | | | |
| <10 (133) | 75.9 (64.9-84.7) | 54.1 | 12.8 | 17.3 | 12.8 | 20.3 | 27.8 |
| 10-100 (941) | 76.3 (64.6-83.4) | 53.4 | 10.3 | 17.1 | 12.5 | 24.1 | 28.8 |
| >100 (2203) | 73.3 (61.0-81.8) | 42.5 | 7.8 | 13.0 | 14.5 | 24.8 | 29.1 |

Abbreviations: WBC, White blood cell count . IQR, inter-quartile range. CNS, central nervous system. [*]Previous CVD defined as any previous diagnosis of AMI, stroke, heart failure or atrial fibrillation. [†]Data available from 1996-2010 (culture bottles) and 1998-2010 (WBC, CRP).

**Table 3.** 0-30 day risk and relative risk for acute myocardial infarction or acute ischemic stroke among subgroups of patients with community-acquired bacteremia and their age, gender and calendar-time matched controls, Northern Denmark, 1992-2010.

| | 0-30 day AMI/AIS risk, % (n/N) | | | 0-30 day AMI/AIS relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Hospitalized controls | CAB patients vs. population controls | | CAB patients vs. hospitalized controls | |
| Age, yrs | | | | | | | |
| 15-64 | 1.2 (16/1340) | 0.0 (4/13 400) | 0.6 (38/6700) | 38.32 | (12.71-115.56) | 2.00 | (1.14-3.51) |
| 65-80 | 4.7 (77/1638) | 0.1 (19/16 380) | 2.2 (182/8190) | 38.94 | (23.73-63.92) | 2.13 | (1.64-2.76) |
| 80+ | 4.7 (67/1411) | 0.3 (49/14 051) | 2.1 (145/7003) | 13.39 | (9.21-19.46) | 2.28 | (1.72-3.03) |
| Sex | | | | | | | |
| Female | 3.7 (88/2347) | 0.2 (36/23 464) | 1.5 (173/11 717) | 23.50 | (15.97-34.59) | 2.56 | (1.98-3.29) |
| Male | 3.5 (72/2042) | 0.2 (36/20 367) | 1.9 (193/10 176) | 19.26 | (12.80-28.96) | 1.84 | (1.42-2.39) |
| Previous CVD† | | | | | | | |
| No | 2.7 (81/3040) | 0.1 (35/35 885) | 1.1 (170/16 162) | 28.34 | (19.13-41.98) | 2.58 | (1.98-3.35) |
| Yes | 5.9 (79/1349) | 0.5 (37/7946) | 3.4 (195/5731) | 13.02 | (8.85-19.15) | 1.73 | (1.34-2.22) |
| Previous AMI | | | | | | | |
| No | 3.4 (137/4044) | 0.1 (54/41 505) | 1.4 (287/20 306) | 25.92 | (18.95-35.47) | 2.30 | (1.85-2.84) |
| Yes | 6.7 (23/345) | 0.8 (18/2326) | 4.9 (78/1587) | 8.98 | (4.94-16.33) | 1.83 | (1.33-2.54) |
| Previous stroke | | | | | | | |
| No | 3.0 (113/3810) | 0.1 (53/40 175) | 1.3 (249/19 251) | 22.61 | (16.34-31.28) | 2.38 | (1.95-2.90) |
| Yes | 8.1 (47/579) | 0.5 (19/3656) | 4.4 (116/2642) | 15.79 | (9.30-26.82) | 1.36 | (0.86-2.14) |
| Study period | | | | | | | |
| 1992-2002 | 4.0 (87/2200) | 0.2 (37/21 989) | 1.9 (204/10 982) | 22.35 | (15.15-32.98) | 2.11 | (1.65-2.69) |
| 2003-2010 | 3.3 (73/2154) | 0.2 (35/21 842) | 1.5 (161/10 911) | 20.37 | (13.56-30.61) | 2.26 | (1.73-2.97) |
| Etiologic agent | | | | | | | |
| Gram-positive | 3.6 (67/1872) | 0.1 (21/18 695) | 1.6 (150/9341) | 30.62 | (18.80-49.88) | 2.20 | (1.67-2.92) |
| *S pneumoniae* | 2.8 (29/1018) | 0.1 (7/10 173) | 1.4 (72/5084) | 39.74 | (17.58-89.86) | 2.02 | (1.34-3.03) |
| *S aureus* | 5.9 (19/321) | 0.0 (1/3208) | 2.1 (33/1598) | 179.60 | (23.96-1346.45) | 2.80 | (1.63-4.84) |
| Other Gram-positive | 3.6 (19/533) | 0.2 (13/5327) | 1.7 (45/2659) | 14.42 | (7.28-28.58) | 2.06 | (1.20-3.53) |
| Gram-negative | 3.8 (84/2228) | 0.2 (49/22 242) | 1.7 (187/11 113) | 16.49 | (11.53-23.60) | 2.24 | (1.74-2.88) |
| *E coli* | 3.9 (61/1545) | 0.3 (39/15 434) | 1.6 (123/7711) | 15.13 | (10.12-22.62) | 2.47 | (1.83-3.33) |
| Other Gram-negative | 3.4 (23/683) | 0.1 (10/6808) | 1.9 (64/3402) | 22.38 | (10.12-49.47) | 1.79 | (1.12-2.86) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Polymicrobial/fungal | 3.1 (9/289) | 0.1 (2/2881) | 1.9 (28/1439) | 43.97 | (9.48-203.86) | 1.62 | (0.77-3.40) |
| Focus of infection | | | | | | | |
| Respiratory tract | 2.1 (20/963) | 0.1 (6/9619) | 1.6 (77/4805) | 32.18 | (12.93-80.11) | 1.29 | (0.81-2.06) |
| Urinary tract | 3.8 (56/1461) | 0.3 (39/14 583) | 1.6 (115/7287) | 13.89 | (9.20-20.97) | 2.45 | (1.79-3.35) |
| CNS | 2.5 (4/163) | 0.1 (1/1630) | 0.6 (5/815) | 39.07 | (4.27-359.51) | 4.61 | (1.76-12.05) |
| Endocarditis | 7.5 (12/160) | 0.3 (4/1600) | 1.6 (13/800) | 30.20 | (9.85-92.56) | 4.63 | (2.10-10.19) |
| Miscellaneous foci | 2.4 (16/655) | 0.2 (11/6548) | 1.5 (50/3269) | 13.63 | (6.45-28.80) | 1.55 | (0.90-2.67) |
| Unknown or multiple | 5.3 (52/987) | 0.1 (11/9851) | 0.9 (46/4917) | 44.94 | (23.18-87.14) | 2.42 | (1.74-3.36) |
| Blood culture bottles‡ | | | | | | | |
| Some positive | 3.1 (57/1843) | 0.2 (31/18 390) | 1.4 (132/9187) | 17.16 | (11.07-26.62) | 2.15 | (1.58-2.94) |
| All positive | 3.8 (72/1898) | 0.2 (34/18 961) | 1.6 (151/9466) | 20.58 | (13.61-31.10) | 2.38 | (1.82-3.12) |
| WBC (×10^9/L) ‡ | | | | | | | |
| <3.5 | 1.0 (1/102) | 0.2 (2/1013) | 2.0 (10/505) | 4.80 | (0.43-53.32) | 0.50 | (0.06-3.91) |
| 3.5-10 | 3.0 (20/661) | 0.2 (13/6604) | 1.4 (45/3298) | 15.09 | (7.46-30.50) | 2.23 | (1.30-3.81) |
| >10 | 3.7 (94/2514) | 0.1 (35/25 094) | 1.5 (191/12534) | 26.03 | (17.52-38.67) | 2.46 | (1.94-3.12) |
| CRP (mg/L) ‡ | | | | | | | |
| <10 | 0.8 (1/133) | 0.3 (4/1324) | 1.5 (10/660) | 2.49 | (0.25-24.56) | 0.50 | (0.06-3.91) |
| 10-100 | 4.0 (38/941) | 0.2 (19/9382) | 0.6 (73/4685) | 19.43 | (11.28-33.46) | 2.61 | (1.78-3.82) |
| >100 | 3.4 (76/2203) | 0.1 (27/22 005) | 1.5 (163/10 992) | 27.35 | (17.52-42.68) | 2.33 | (1.79-3.04) |

Abbreviations: CAB, community-acquired bacteremia. CI, confidence interval. CVD, cardiovascular disease. CNS, central nervous system. WBC, white blood cell count. CRP, C-reactive protein.

*Relative risk estimates are controlled for age, gender, calendar-time, and any comorbidity (except where stratified by comorbidity). †Previous CVD defined as any previous diagnosis of AMI, heart failure, atrial fibrillation or stroke. ‡Blood culture bottle data from 1996-2010 and WBC and CRP-data from 1998-2010. Blood culture data on number of bottles was missing for 0.1% of patients (categorized as "Some positive"), WBC data for 0.8% (categorized as normal, i.e. 3.5-10×10^9/L), and CRP data for 1.0% (categorized as normal, i.e. <10 mg/L).

**Table 4.** 31-180, and 181-365 day risk and relative risk for acute myocardial infarction or acute ischemic stroke among patients with community-acquired bacteremia and their age, gender, and calendar-time matched controls, Northern Denmark, 1992-2010

| | AMI/AIS risk, n/N (%) | | | Relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Acutely hospitalized controls | CAB patients vs. population controls | | CAB patients vs. hospitalized controls | |
| **31-180 day AMI/AIS risk** | | | | | | | |
| All CAB patients | 49/3589 (1.4) | 247/35 676 (0.7) | 201/16 388 (1.2) | 1.64 | (1.18-2.27) | 0.95 | (0.69-1.32) |
| CAB patients by: | | | | | | | |
| Age, yrs | | | | | | | |
| 15-64 | 10/1204 (0.7) | 21/12 031 (0.2) | 18/5849 (0.3) | 3.83 | (1.78-8.25) | 2.75 | (1.24-6.06) |
| 65-80 | 23/1340 (1.7) | 99/13 355 (0.7) | 87/6095 (1.4) | 2.33 | (1.47-3.70) | 1.12 | (0.70-1.79) |
| 80+ | 16/1045 (1.5) | 127/10 290 (1.2) | 96/4444 (2.2) | 1.21 | (0.71-2.03) | 0.66 | (0.39-1.13) |
| Sex | | | | | | | |
| Female | 30/1935 (1.6) | 105/19 258 (0.5) | 30/8888 (1.0) | 2.68 | (1.78-4.04) | 1.36 | (0.89-2.08) |
| Male | 19/1654 (1.1) | 142/16 418 (0.9) | 110/7500 (1.5) | 1.29 | (0.79-2.09) | 0.74 | (0.45-1.21) |
| Previous CVD† | | | | | | | |
| No | 26/2562 (1.0) | 139/29 564 (0.5) | 106/12 445 (0.9) | 2.24 | (1.47-3.42) | 1.17 | (0.76-1.79) |
| Yes | 23/1027 (2.2) | 108/6112 (1.8) | 95/3943 (2.4) | 1.43 | (0.91-2.24) | 0.90 | (0.57-1.42) |
| Previous AMI | | | | | | | |
| No | 43/3323 (1.3) | 201/33 878 (0.6) | 167/15 315 (1.1) | 2.18 | (1.56-3.03) | 1.14 | (0.81-1.59) |
| Yes | 6/266 (2.3) | 46/1798 (2.6) | 34/1073 (3.2) | 0.99 | (0.42-2.32) | 0.68 | (0.28-1.62) |
| Previous stroke | | | | | | | |
| No | 36/3170 (1.1) | 192/32 858 (0.6) | 153/14 563 (1.1) | 1.93 | (1.35-2.73) | 1.04 | (0.72-1.50) |
| Yes | 13/419 (3.1) | 55/2818 (2.0) | 48/1825 (2.6) | 1.87 | (1.02-3.43) | 1.14 | (0.61-2.10) |
| Study period | | | | | | | |
| 1992-2002 | 25/1787 (1.4) | 151/17 782 (0.8) | 113/8139 (1.4) | 1.56 | (1.01-2.39) | 0.91 | (0.58-1.41) |
| 2003-2010 | 24/1802 (1.3) | 96/17 894 (0.5) | 88/8249 (1.1) | 2.42 | (1.54-3.79) | 1.18 | (0.74-1.86) |
| Etiologic agent | | | | | | | |
| Gram-positive | 21/1507 (1.4) | 81/15 007 (0.5) | 80/6959 (1.1) | 2.43 | (1.55-4.12) | 1.18 | (0.72-1.92) |
| *S pneumoniae* | 7/843 (0.8) | 32/8402 (0.4) | 40/3926 (1.0) | 2.13 | (0.93-4.87) | 0.77 | (0.34-1.74) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *S aureus* | 6/211 (2.8) | 18/2101 (0.9) | 11/970 (1.1) | 3.47 | (1.34-8.99) | 2.69 | (0.95-7.66) |
| Other Gram-positive | 8/453 (1.8) | 31/4504 (0.7) | 29/2063 (1.4) | 2.44 | (1.11-5.37) | 1.23 | (0.56-2.70) |
| Gram-negative | 24/1869 (1.3) | 141/18 551 (0.8) | 102/8472 (1.2) | 1.58 | (1.02-2.45) | 0.95 | (0.61-1.50) |
| *E coli* | 14/1322 (1.1) | 99/13 120 (0.8) | 75/5988 (1.3) | 1.30 | (0.74-2.28) | 0.73 | (0.41-1.31) |
| Other Gram-negative | 10/547 (1.8) | 42/5431 (0.8) | 27/2484 (1.1) | 2.30 | (1.14-4.64) | 1.61 | (0.77-3.38) |
| Polymicrobial/fungal | 4/213 (1.9) | 25/2118 (1.2) | 19/957 (1.3) | 1.61 | (0.56-4.67) | 0.80 | (0.27-2.39) |
| Focus of infection | | | | | | | |
| Respiratory tract | 8/810 (1.0) | 36/8077 (0.4) | 38/3747 (1.0) | 2.18 | (1.00-4.77) | 0.89 | (0.41-1.92) |
| Urinary tract | 24/1296 (1.9) | 107/12 858 (0.8) | 82/5863 (1.4) | 2.07 | (1.32-3.24) | 1.19 | (0.75-1.89) |
| CNS | 1/132 (0.8) | 4/1318 (0.3) | 4/640 (0.6) | 2.37 | (0.27-21.36) | 0.71 | (0.08-6.55) |
| Endocarditis | 4/134 (3.0) | 10/1333 (0.8) | 5/616 (0.8) | 4.81 | (1.43-16.12) | 3.54 | (0.93-13.50) |
| Miscellaneous foci | 7/556 (1.3) | 45/5531 (0.8) | 21/2553 (0.8) | 1.51 | (0.67-3.37) | 1.56 | (0.65-3.72) |
| Unknown or multiple | 5/661 (0.8) | 45/6559 (0.4) | 51/2969 (1.7) | 1.04 | (0.41-2.64) | 0.43 | (0.17-1.07) |
| Blood culture bottles‡ | | | | | | | |
| Some positive | 23/1584 (1.5) | 109/15 723 (0.7) | 204/7249 (1.4) | 1.99 | (1.26-3.13) | 0.91 | (0.58-1.44) |
| All positive | 16/1503 (1.1) | 91/14 947 (0.6) | 67/6840 (1.0) | 1.78 | (1.04-3.05) | 0.99 | (0.57-1.72) |
| WBC (×10^9/L) ‡ | | | | | | | |
| <3.5 | 0/60 (0) | 2/595 (0.3) | 4/271 (1.5) | - | - | - | - |
| 3.5-10 | 5/541 (0.9) | 32/5375 (0.6) | 28/2474 (1.1) | 1.39 | (0.54-3.58) | 0.81 | (0.31-2.12) |
| >10 | 29/2091 (1.4) | 133/20 779 (0.6) | 110/9564 (1.2) | 2.11 | (1.40-3.16) | 1.09 | (0.72-1.64) |
| CRP (mg/L) ‡ | | | | | | | |
| <10 | 2/116 (1.7) | 9/1148 (0.8) | 7/523 (1.3) | 2.12 | (0.46-9.83) | 1.44 | (0.28-7.36) |
| 10-100 | 15/796 (1.9) | 54/7899 (0.7) | 45/3585 (1.3) | 2.59 | (1.46-4.62) | 1.42 | (0.78-2.58) |
| >100 | 17/1780 (1.0) | 104/17 702 (0.6) | 90/8201 (1.1) | 1.56 | (0.93-2.62) | 0.78 | (0.46-1.31) |
| **181-365 day AMI/AIS risk** | | | | | | | |
| All CAB patients | 38/3188 (1.2) | 277/30 873 (0.9) | 162/13 007 (1.2) | 0.98 | (0.68-1.40) | 0.83 | (0.57-1.21) |
| CAB patients by: | | | | | | | |
| Age, yrs | | | | | | | |
| 15-64 | 8/1135 (0.7) | 17/11 283 (0.2) | 19/5298 (0.4) | 3.67 | (1.56-8.60) | 1.78 | (0.76-4.13) |
| 65-80 | 15/1177 (1.3) | 110/11 500 (1.0) | 85/4678 (1.8) | 1.18 | (0.68-2.03) | 0.67 | (0.38-1.20) |
| 80+ | 15/876 (1.7) | 150/8090 (1.9) | 58/3031 (1.9) | 0.91 | (0.54-1.56) | 0.85 | (0.48-1.53) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Female | 20/1733 (1.2) | 127/16 854 (0.8) | 74/7191 (1.0) | 1.39 | (0.87-2.24) | 0.95 | (0.57-1.59) |
| Male | 18/1455 (1.2) | 150/14 019 (1.1) | 88/5816 (1.5) | 1.05 | (0.64-1.72) | 0.79 | (0.47-1.33) |
| Previous CVD[†] | | | | | | | |
| No | 14/2318 (0.6) | 161/25 976 (0.6) | 94/10 159 (0.9) | 1.00 | (0.58-1.73) | 0.59 | (0.38-1.04) |
| Yes | 24/870 (2.8) | 116/4897 (2.4) | 68/2848 (2.4) | 1.23 | (0.79-1.91) | 1.17 | (0.73-1.86) |
| Previous AMI | | | | | | | |
| No | 30/2955 (1.0) | 240/29 426 (0.8) | 142/12 237 (1.2) | 1.23 | (0.84-1.79) | 0.80 | (0.54-1.18) |
| Yes | 8/233 (3.4) | 37/1447 (2.6) | 20/770 (2.6) | 1.42 | (0.66-3.06) | 1.40 | (0.62-3.20) |
| Previous stroke | | | | | | | |
| No | 28/2840(1.0) | 212/28 632 (0.7) | 130/11 698 (1.1) | 1.32 | (0.89-1.96) | 0.81 | (0.54-1.22) |
| Yes | 10/348 (2.9) | 65/2241 (2.9) | 32/1309 (2.4) | 1.02 | (0.52-1.99) | 1.19 | (0.58-2.44) |
| Study period | | | | | | | |
| 1992-2002 | 18/1586 (1.1) | 165/15 332 (1.1) | 90/6397 (1.4) | 0.96 | (0.59-1.57) | 0.71 | (0.42-1.21) |
| 2003-2010 | 20/1602 (1.2) | 112/15 541 (0.7) | 72/6610 (1.1) | 1.57 | (0.97-2.53) | 1.06 | (0.64-1.75) |
| Etiologic agent | | | | | | | |
| Gram-positive | 16/1344 (1.2) | 100/13 093 (0.8) | 65/5618 (1.2) | 1.38 | (0.81-2.35) | 1.06 | (0.61-1.86) |
| *S pneumoniae* | 8/780 (1.0) | 54/7633 (0.7) | 42/3326 (1.3) | 1.27 | (0.60-2.70) | 0.79 | (0.37-1.70) |
| *S aureus* | 1/176 (0.6) | 10/1705 (0.6) | 8/726 (1.1) | 0.77 | (0.10-6.01) | 0.76 | (0.09-6.39) |
| Other Gram-positive | 7/388 (1.8) | 36/3755 (1.0) | 15/1566 (1.0) | 1.73 | (0.77-3.90) | 1.94 | (0.77-4.89) |
| Gram-negative | 21/1665 (1.3) | 157/16 071 (1.0) | 84/6701 (1.3) | 1.20 | (0.76-1.89) | 0.82 | (0.50-1.34) |
| *E coli* | 20/1187 (1.7) | 113/11 436 (1.0) | 65/4749 (1.4) | 1.56 | (0.97-2.52) | 1.04 | (0.62-1.76) |
| Other Gram-negative | 1/478 (0.2) | 44/4635 (0.9) | 19/1952 (1.0) | 0.21 | (0.03-1.54) | 0.15 | (0.02-1.16) |
| Polymicrobial/fungal | 1/179 (0.6) | 20/1709 (1.2) | 13/688 (1.9) | 0.44 | (0.06-3.26) | 0.31 | (0.04-2.42) |
| Focus of infection | | | | | | | |
| Respiratory tract | 8/744 (1.1) | 25/7386 (0.3) | 39/3138 (0.5) | 1.36 | (0.64-2.89) | 0.86 | (0.40-1.87) |
| Urinary tract | 14/1155 (1.2) | 105/11 095 (0.9) | 63/4577 (1.4) | 1.19 | (0.68-2.09) | 0.76 | (0.41-1.39) |
| CNS | 0/124 (0) | 3/1228 (0.2) | 9/573 (1.6) | - | - | - | - |
| Endocarditis | 3/113 (2.7) | 11/1098 (1.0) | 6/464 (1.3) | 2.44 | (0.68-8.77) | 2.62 | (0.60-11.43) |
| Miscellaneous foci | 2/485 (0.4) | 48/4696 (1.0) | 15/1990 (0.8) | 0.37 | (0.09-1.51) | 0.41 | (0.09-1.91) |
| Unknown or multiple | 11/567 (1.9) | 58/5472 (1.1) | 30/2265 (1.3) | 1.63 | (0.85-3.11) | 1.34 | (0.66-2.72) |
| Blood culture bottles[‡] | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Some positive | 17/1404 (1.2) | 121/13 618 (0.9) | 81/5727 (1.4) | 1.25 | (0.75-2.08) | 0.74 | (0.43-1.28) |
| All positive | 15/1337 (1.1) | 106/12 946 (0.8) | 58/5464 (1.1) | 1.29 | (0.75-2.23) | 1.05 | (0.58-1.87) |
| WBC (×10^9/L) [‡] | | | | | | | |
| <3.5 | 0/48 (0) | 1/469 (0.2) | 4/189 (2.1) | - | - | - | - |
| 3.5-10 | 4/484 (0.8) | 42/4691 (0.9) | 16/1978 (0.8) | 0.90 | (0.32-2.52) | 1.00 | (0.32-3.11) |
| >10 | 24/1860 (1.3) | 147/18 021 (0.8) | 103/7642 (1.4) | 1.47 | (0.95-2.28) | 0.90 | (0.57-1.41) |
| CRP (mg/L) [‡] | | | | | | | |
| <10 | 0/105 (0) | 4/1007 (0.4) | 7/419 (1.7) | - | - | - | - |
| 10-100 | 11/683 (1.6) | 82/6577 (1.2) | 40/2718 (1.5) | 1.24 | (0.66-2.33) | 1.06 | (0.54-2.09) |
| >100 | 17/1604 (1.1) | 104/15 597 (0.7) | 76/6672 (1.1) | 1.46 | (0.87-2.45) | 0.86 | (0.50-1.47) |

Abbreviations: CAB, community-acquired bacteremia. CI, confidence interval. CNS, central nervous system. WBC, white blood cell count. CRP, C-reactive protein.

[*]Relative risk estimates for all CAB patients versus their matched controls are adjusted for age, gender, calendar-time, marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular disease, other co-morbidity, and medications for cardiovascular disease. Relative risk estimates in stratified analyses and subgroup analyses are controlled for age, gender, calendar-time and any comorbidity (yes/no, except where stratified by comorbid disease). [†]Previous CVD defined as any previous diagnosis of AMI, stroke, heart failure or atrial fibrillation. [‡]Blood culture bottle data from 1996-2010 and WBC and CRP-data from 1998-2010. [§]Not adjusted for comorbidity due to few events.

**Table 5.** 31-180, and 181-365 day risk and relative risk for acute myocardial infarction among patients with community-acquired bacteremia and their age, gender, and calendar-time matched controls, Northern Denmark, 1992-2010

| | AMI risk, n/N (%) | | | Relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Acutely hospitalized controls | CAB patients vs. population controls | | CAB patients vs. hospitalized controls | |
| **31-180 day AMI risk** | | | | | | | |
| All CAB patients | 20/3645 (0.2) | 126/36 265 (0.3) | 104/16 757 (0.6) | 1.42 | (0.86-2.34) | 0.90 | (0.54-1.49) |
| CAB patients by: | | | | | | | |
| Age, yrs | | | | | | | |
| 15-64 | 3/1210 (0.2) | 15/12 094 (0.1) | 11/5893 (0.2) | 1.66 | (0.47-5.82) | 1.52 | (0.41-5.55) |
| 65-80 | 8/1368 (0.6) | 52/13 640 (0.4) | 44/6277 (0.7) | 1.46 | (0.68-3.07) | 0.79 | (0.37-1.70) |
| 80+ | 9/1067 (0.8) | 59/10 531 (0.6) | 49/4587 (1.1) | 1.51 | (0.75-3.07) | 0.77 | (0.38-1.68) |
| Sex | | | | | | | |
| Female | 11/1969 (0.6) | 48/19 619 (0.2) | 49/9105 (0.5) | 2.19 | (1.13-4.25) | 1.01 | (0.52-1.97) |
| Male | 9/1667 (0.5) | 78/16 646 (0.5) | 55/7652 (0.7) | 1.09 | (0.54-2.18) | 0.70 | (0.35-1.43) |
| Previous CVD† | | | | | | | |
| No | 11/2594 (0.4) | 76/30 011 (0.3) | 56/12 674 (0.4) | 1.83 | (0.97-3.45) | 0.93 | (0.49-1.78) |
| Yes | 9/1051 (0.9) | 50/6254 (0.8) | 48/4083 (1.2) | 1.22 | (0.60-2.48) | 0.71 | (0.35-1.44) |
| Previous AMI | | | | | | | |
| No | 15/3361 (0.4) | 92/34 427 (0.3) | 77/15 648 (0.5) | 1.77 | (1.02-3.06) | 0.86 | (0.49-1.49) |
| Yes | 5/269 (1.9) | 34/1838 (1.8) | 27/1109 (2.4) | 1.10 | (0.43-2.83) | 0.76 | (0.29-1.97) |
| Previous stroke | | | | | | | |
| No | 17/3208 (0.5) | 110/33 383 (0.3) | 88/14 848 (0.6) | 1.72 | (1.03-2.86) | 0.86 | (0.51-1.44) |
| Yes | 3/437 (0.7) | 16/2882 (0.6) | 16/1893 (0.8) | 1.49 | (0.43-5.16) | 0.75 | (0.22-2.58) |
| Study period | | | | | | | |
| 1992-2002 | 7/1810 (0.4) | 80/18 099 (0.4) | 54/8335 (0.6) | 0.84 | (0.39-1.83) | 0.55 | (0.25-1.21) |
| 2003-2010 | 13/1828 (0.7) | 46/18 120 (0.3) | 50/8422 (0.6) | 2.67 | (1.40-4.85) | 1.20 | (0.64-2.22) |
| Etiologic agent | | | | | | | |
| Gram-positive | 11/1533 (0.7) | 44/15273 (0.3) | 41/7120 (0.6) | 2.44 | (1.25-4.76) | 1.24 | (0.63-2.44) |
| *S pneumoniae* | 3/852 (0.4) | 17/8494 (0.2) | 23/3987 (0.6) | 1.86 | (0.54-6.41) | 0.57 | (0.17-1.94) |
| *S aureus* | 3/219 (1.4) | 10/2181 (0.5) | 7/1015 (0.7) | 2.88 | (0.78-10.61) | 2.15 | (0.54-8.62) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Other Gram-positive | 5/462 (1.1) | 17/4598 (0.4) | 11/2118 (0.5) | 2.70 | (0.99-7.40) | 2.14 | (0.73-6.31) |
| Gram-negative | 8/1897 (0.4) | 69/18 854 (0.4) | 50/8665 (0.6) | 1.04 | (0.50-2.17) | 0.68 | (0.32-1.45) |
| *E coli* | 4/1342 (0.3) | 48/13 339 (0.4) | 38/6121 (0.6) | 0.72 | (0.26-2.00) | 0.44 | (0.16-1.25) |
| Other Gram-negative | 4/555 (0.7) | 21/5515 (0.4) | 12/2544 (0.5) | 1.87 | (0.63-5.52) | 1.46 | (0.46-4.60) |
| Polymicrobial/fungal | 1/215 (0.5) | 13/2138 (0.6) | 13/972 (1.3) | 0.93 | (0.12-7.23) | 0.33 | (0.04-2.49) |
| Focus of infection | | | | | | | |
| Respiratory tract | 4/816 (0.5) | 18/8139 (0.2) | 23/3794 (0.6) | 2.18 | (0.73-6.50) | 0.70 | (0.24-2.07) |
| Urinary tract | 8/1316 (0.6) | 52/13 075 (0.4) | 40/5994 (0.7) | 1.40 | (0.66-2.94) | 0.85 | (0.40-1.84) |
| CNS | 0/134 (0) | 3/1338 (0.2) | 1/648 (0.2) | - | - | - | - |
| Endocarditis | 2/143 (1.4) | 6/1424 (0.4) | 0/665 (0) | 5.07 | (0.92-27.81) | - | - |
| Miscellaneous foci | 2/563 (0.4) | 20/5605 (0.4) | 11/2605 (0.4) | 0.98 | (0.23-4.23) | 0.95 | (0.21-4.37) |
| Unknown or multiple | 4/673 (0.6) | 27/6684 (0.4) | 29/3051 (1.0) | 1.34 | (0.47-3.84) | 0.64 | (0.22-1.84) |
| Blood culture bottles‡ | | | | | | | |
| Some positive | 11/1607 (0.7) | 51/15 972 (0.3) | 56/7401 (0.8) | 2.10 | (1.08-4.07) | 0.85 | (0.44-1.63) |
| All positive | 6/1528 (0.4) | 43/15 205 (0.3) | 31/7007 (0.4) | 1.34 | (0.57-3.17) | 0.87 | (0.36-2.09) |
| WBC (×10^9/L) ‡ | | | | | | | |
| <3.5 | 0/60 (0) | 2/596 (0.3) | 2/274 (0.7) | - | - | - | - |
| 3.5-10 | 4/548 (0.7) | 15/5447 (0.3) | 15/2526 (0.6) | 2.44 | (0.81-7.37) | 1.25 | (0.41-3.81) |
| >10 | 12/2127 (0.6) | 59/21 153 (0.3) | 55/9794 (0.6) | 2.00 | (1.07-3.76) | 0.96 | (0.51-1.81) |
| CRP (mg/L) ‡ | | | | | | | |
| <10 | 1/116 (0.9) | 6/1149 (0.5) | 4/526 (0.8) | 1.66 | (0.20-13.80) | 1.83 | (0.19-17.85) |
| 10-100 | 7/807 (0.9) | 27/8015 (0.3) | 23/3667 (0.6) | 2.49 | (1.08-5.78) | 1.36 | (0.57-3.24) |
| >100 | 8/1812 (0.4) | 43/18 032 (0.2) | 45/8401 (0.5) | 1.81 | (0.84-3.88) | 0.76 | (0.36-1.63) |
| **181-365 day AMI risk** | | | | | | | |
| All CAB patients | 18/3250 (0.5) | 132/31 570 (0.4) | 77/13 392 (0.6) | 0.88 | (0.52-1.50) | 0.91 | (0.52-1.60) |
| CAB patients by: | | | | | | | |
| Age, yrs | | | | | | | |
| 15-64 | 3/1146 (0.3) | 13/11 400 (0.1) | 6/5367 (0.1) | 1.78 | (0.49-6.38) | 1.95 | (0.48-97.92) |
| 65-80 | 8/1211 (0.7) | 48/11870 (0.4) | 40/4856 (0.8) | 1.34 | (0.63-2.86) | 0.78 | (0.36-1.70) |
| 80+ | 7/893 (0.8) | 71/8300 (0.9) | 31/3129 (1.0) | 0.92 | (0.42-2.01) | 0.78 | (0.34-1.81) |
| Sex | | | | | | | |
| Female | 10/1771 (0.6) | 58/17 278 (0.3) | 34/7408 (0.5) | 1.53 | (0.78-3.01) | 1.05 | (0.51-2.16) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Male | 8/1479 (0.5) | 74/14 292 (0.5) | 43/5984 (0.7) | 0.91 | (0.44-1.90) | 0.72 | (0.33-1.56) |
| Previous CVD[†] | | | | | | | |
| No | 6/2354 (0.2) | 75/26 517 (0.3) | 47/10 416 (0.5) | 0.93 | (0.41-2.14) | 0.51 | (0.22-1.20) |
| Yes | 12/896 (1.3) | 57/5053 (1.1) | 30/2976 (1.0) | 1.25 | (0.67-2.34) | 1.32 | (0.67-2.58) |
| Previous AMI | | | | | | | |
| No | 13/3016 (0.4) | 108/30 083 (0.4) | 62/12 593 (0.5) | 1.19 | (0.67-2.12) | 0.79 | (0.43-1.44) |
| Yes | 5/234 (2.1) | 24/1487 (1.6) | 15/784 (1.9) | 1.40 | (0.53-3.68) | 1.21 | (0.44-3.35) |
| Previous stroke | | | | | | | |
| No | 17/2866 (0.6) | 109/29 246 (0.4) | 67/12 003 (0.6) | 1.58 | (0.95-2.64) | 0.97 | (0.57-1.65) |
| Yes | 1/367 (0.3) | 23/2301 (1.0) | 10/1389 (0.7) | 0.30 | (0.04-2.21) | 0.35 | (0.44-2.74) |
| Study period | | | | | | | |
| 1992-2002 | 8/1618 (0.5) | 84/15 698 (0.5) | 42/6609 (0.6) | 0.83 | (0.40-1.73) | 0.71 | (0.33-1.54) |
| 2003-2010 | 10/1632 (0.6) | 48/15 872 (0.3) | 35/6783 (0.5) | 1.76 | (0.88-3.48) | 1.06 | (0.52-2.16) |
| Etiologic agent | | | | | | | |
| Gram-positive | 5/1370 (0.4) | 48/13 374 (0.4) | 30/5779 (0.5) | 0.85 | (0.33-2.14) | 0.76 | (0.29-2.00) |
| *S pneumoniae* | 1/790 (0.1) | 27/7744 (0.3) | 17/3397 (0.5) | 0.29 | (0.04-2.13) | 0.25 | (0.03-1.87) |
| *S aureus* | 1/183 (0.5) | 8/1778 (0.4) | 6/760 (0.8) | 0.91 | (0.11-7.35) | 0.97 | (0.11-8.49) |
| Other Gram-positive | 3/397 (0.8) | 13/3852 (0.3) | 7/1622 (0.4) | 2.17 | (0.61-7.71) | 2.04 | (0.49-8.43) |
| Gram-negative | 12/1698 (0.7) | 75/16 449 (0.5) | 42/6906 (0.6) | 1.44 | (0.78-2.66) | 0.95 | (0.49-1.84) |
| *E coli* | 11/1207 (0.9) | 51/11 669 (0.4) | 31/4878 (0.6) | 1.87 | (0.97-3.61) | 1.18 | (0.58-2.40) |
| Other Gram-negative | 1/491 (0.2) | 24/4780 (0.5) | 11/2028 (0.5) | 0.41 | (0.06-3.05) | 0.30 | (0.04-2.36) |
| Polymicrobial/fungal | 1/182 (0.5) | 9/1747 (0.5) | 5/707 (0.7) | 0.93 | (0.12-7.39) | 0.71 | (0.08-6.14) |
| Focus of infection | | | | | | | |
| Respiratory tract | 1/753 (0.1) | 25/7386 (0.3) | 16/3201 (0.5) | 0.34 | (0.05-2.50) | 0.26 | (0.03-2.02) |
| Urinary tract | 7/1181 (0.6) | 45/11 396 (0.4) | 34/4730 (0.7) | 1.37 | (0.62-3.06) | 0.74 | (0.33-1.70) |
| CNS | 0/127 (0) | 3/1258 (0.2) | 5/585 (0.9) | - | - | - | - |
| Endocarditis | 2/121 (1.7) | 6/1179 (0.5) | 3/505 (0.6) | 3.23 | (0.64-16.31) | 4.78 | (0.64-35.90) |
| Miscellaneous foci | 1/493 (0.2) | 22/4786 (0.5) | 9/2044 (0.4) | 0.41 | (0.05-3.06) | 0.33 | (0.04-2.82) |
| Unknown or multiple | 7/575 (1.2) | 31/5565 (0.6) | 10/2327 (0.4) | 1.87 | (0.82-4.26) | 2.30 | (0.86-6.18) |
| Blood culture bottles[‡] | | | | | | | |
| Some positive | 5/1434 (0.3) | 63/13 955 (0.5) | 39/5902 (0.7) | 0.67 | (0.27-1.69) | 0.46 | (0.18-1.18) |
| All positive | 7/1361 (0.5) | 38/13 215 (0.3) | 26/5626 (0.5) | 1.73 | (0.76-3.90) | 1.00 | (0.43-2.34) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| WBC (×10^9/L) ‡ | | | | | | | |
| <3.5 | 0/48 (0) | 0/469 (0) | 2/191 (1.0) | - | - | - | - |
| 3.5-10 | 1/491 (0.2) | 19/4771 (0.4) | 4/2024 (0.2) | 0.51 | (0.07-3.81) | 0.88 | (0.10-8.08) |
| >10 | 11/1899 (0.6) | 69/18 460 (0.4) | 48/7876 (0.6) | 1.34 | (0.70-2.55) | 0.86 | (0.44-1.68) |
| CRP (mg/L) ‡ | | | | | | | |
| <10 | 0/105 (0) | 2/1009 (0.2) | 2/420 (0.5) | - | - | - | - |
| 10-100 | 3/695 (0.4) | 34/6717 (0.5) | 20/2797 (0.7) | 0.80 | (0.24-2.62) | 0.51 | (0.15-1.75) |
| >100 | 9/1638 (0.5) | 52/15 974 (0.3) | 32/6874 (0.5) | 1.43 | (0.70-2.94) | 1.11 | (0.53-2.36) |

Abbreviations: CAB, community-acquired bacteremia. CI, confidence interval. CNS, central nervous system. WBC, white blood cell count. CRP, C-reactive protein.

*Relative risk estimates for all CAB patients versus their matched controls are adjusted for age, gender, calendar-time, marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular disease, other co-morbidity, and medications for cardiovascular disease. Relative risk estimates in stratified analyses and subgroup analyses are controlled for age, gender, calendar-time and any comorbidity (yes/no, except where stratified by comorbid disease). †Previous CVD defined as any previous diagnosis of AMI, stroke, heart failure or atrial fibrillation. ‡Blood culture bottle data from 1996-2010 and WBC and CRP-data from 1998-2010. §Not adjusted for comorbidity due to few events.

**Table 6.** 31-180, and 181-365 day risk and relative risk for acute ischemic stroke among patients with community-acquired bacteremia and their age, gender, and calendar-time matched controls, Northern Denmark, 1992-2010

| | AIS risk, n/N (%) | | | Relative risk (95% CI)* | | | |
|---|---|---|---|---|---|---|---|
| | CAB patients | Population controls | Acutely hospitalized controls | CAB patients vs. population controls | | CAB patients vs. hospitalized controls | |
| **31-180 day AIS risk** | | | | | | | |
| All CAB patients | 33/3641 (0.9) | 130/36 218 (0.4) | 107/16 694 (0.6) | 1.90 | (1.26-2.89) | 1.25 | (0.82-1.91) |
| CAB patients by: | | | | | | | |
| Age, yrs | | | | | | | |
| 15-64 | 8/1208 (0.7) | 6/12 072 (0.0) | 9/5875 (0.2) | 10.15 | (3.44-29.90) | 4.48 | (1.65-12.13) |
| 65-80 | 17/1361 (1.2) | 50/13 574 (0.4) | 48/6235 (0.8) | 3.55 | (2.02-6.25) | 1.56 | (0.89-2.74) |
| 80+ | 8/1072 (0.7) | 74/10 572 (0.7) | 50/4584 (1.1) | 1.00 | (0.48-2.08) | 0.62 | (0.29-1.33) |
| Sex | | | | | | | |
| Female | 22/1960 (1.1) | 63/19 513 (0.3) | 47/9036 (0.5) | 3.18 | (1.94-5.20) | 1.90 | (1.13-3.20) |
| Male | 11/1681 (0.7) | 67/16 705 (0.4) | 60/7658 (0.8) | 1.60 | (0.84-3.06) | 0.82 | (0.43-1.57) |
| Previous CVD† | | | | | | | |
| No | 17/2587 (0.7) | 67/29 978 (0.2) | 56/12 638 (0.4) | 3.23 | (1.90-5.50) | 1.47 | (0.85-2.53) |
| Yes | 16/1054 (1.5) | 63/6240 (1.0) | 51/4056 (1.3) | 1.70 | (0.98-2.95) | 1.18 | (0.67-2.08) |
| Previous AMI | | | | | | | |
| No | 31/3364 (0.9) | 115/34 378 (0.3) | 97/15 572 (0.6) | 2.92 | (1.97-4.35) | 1.43 | (0.96-2.15) |
| Yes | 2/277 (0.7) | 15/1840 (0.8) | 10/1122 (0.9) | 1.04 | (0.24-4.59) | 0.75 | (0.16-3.44) |
| Previous stroke | | | | | | | |
| No | 21/3207 (0.7) | 89/33 342 (0.3) | 74/14 824 (0.5) | 2.61 | (1.62-4.19) | 1.27 | (0.78-2.07) |
| Yes | 12/434 (2.8) | 41/2876 (1.4) | 33/1870 (1.8) | 2.25 | (1.18-4.30) | 1.56 | (0.80-3.03) |
| Study period | | | | | | | |
| 1992-2002 | 19/1809 (1.1) | 78/18 011 (0.4) | 65/8282 (0.8) | 2.20 | (1.32-3.67) | 1.26 | (0.75-2.13) |
| 2003-2010 | 14/1832 (0.8) | 52/18 207 (0.3) | 42/8412 (0.5) | 2.71 | (1.49-4.93) | 1.39 | (0.75-2.56) |
| Etiologic agent | | | | | | | |
| Gram-positive | 12/1518 (0.8) | 40/15126 (0.3) | 43/7042 (0.6) | 2.91 | (1.50-5.63) | 1.32 | (0.69-2.53) |
| *S pneumoniae* | 4/848 (0.5) | 17/8454 (0.2) | 19/3944 (0.5) | 2.07 | (0.67-6.35) | 0.98 | (0.33-2.93) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *S aureus* | 5/214 (2.3) | 8/2132 (0.4) | 5/985 (0.5) | 7.39 | (2.21-24.69) | 7.12 | (1.63-31.03) |
| Other Gram-positive | 3/456 (0.7) | 15/4540 (0.3) | 19/2094 (0.9) | 1.99 | (0.57-6.99) | 0.71 | (0.21-2.40) |
| Gram-negative | 18/1904 (0.9) | 78/18 913 (0.4) | 57/8664 (0.7) | 2.18 | (1.30-3.68) | 1.28 | (0.75-2.20) |
| *E coli* | 11/1352 (0.8) | 57/13 429 (0.4) | 40/6146 (0.7) | 1.82 | (0.95-3.49) | 1.09 | (0.55-2.15) |
| Other Gram-negative | 7/552 (1.3) | 21/5484 (0.4) | 17/2518 (0.7) | 3.21 | (1.34-7.68) | 1.75 | (0.71-4.32) |
| Polymicrobial/fungal | 3/219 (1.4) | 12/2179 (0.6) | 7/988 (0.7) | 2.14 | (0.60-7.61) | 1.49 | (0.38-5.82) |
| Focus of infection | | | | | | | |
| Respiratory tract | 4/816 (0.5) | 20/8138 (0.2) | 16/3789 (0.4) | 1.90 | (0.63-5.70) | 1.13 | (0.37-3.44) |
| Urinary tract | 17/1323 (1.3) | 60/13 137 (0.5) | 45/6018 (0.7) | 2.60 | (1.51-4.49) | 1.55 | (0.87-2.73) |
| CNS | 1/132 (0.8) | 1/1319 (0.1) | 4/642 (0.6) | 8.50 | (0.53-136.07) | 0.68 | (0.07-6.34) |
| Endocarditis | 3/135 (2.2) | 4/1346 (0.3) | 5/624 (0.8) | 6.95 | (1.52-31.81) | 2.72 | (0.63-11.78) |
| Miscellaneous foci | 6/561 (1.1) | 25/5585 (0.4) | 11/2582 (0.4) | 2.31 | (0.93-5.75) | 2.69 | (0.97-7.51) |
| Unknown or multiple | 2/674 (0.3) | 20/6693 (0.3) | 26/3039 (0.9) | 0.99 | (0.23-4.28) | 0.34 | (0.08-1.43) |
| Blood culture bottles‡ | | | | | | | |
| Some positive | 14/1604 (0.9) | 61/15 928 (0.4) | 52/7369 (0.7) | 2.09 | (1.16-3.77) | 1.10 | (0.60-2.01) |
| All positive | 12/1527 (0.8) | 52/15 203 (0.3) | 41/6966 (0.6) | 2.42 | (1.27-4.59) | 1.21 | (0.62-2.33) |
| WBC (×10^9/L) ‡ | | | | | | | |
| <3.5 | 0/61 (0) | 0/606 (0) | 2/279 (0.7) | - | - | - | - |
| 3.5-10 | 2/550 (0.4) | 20/6471 (0.4) | 13/2523 (0.5) | 0.87 | (0.20-3.74) | 0.67 | (0.15-3.02) |
| >10 | 20/2121 (0.9) | 75/21 015 (0.4) | 61/9727 (0.6) | 2.57 | (1.56-4.24) | 1.31 | (0.78-2.19) |
| CRP (mg/L) ‡ | | | | | | | |
| <10 | 1/116 (0.9) | 4/1149 (0.3) | 3/528 (0.6) | 2.11 | (0.24-18.92) | 1.08 | (0.11-10.59) |
| 10-100 | 9/813 (1.1) | 27/8076 (0.3) | 23/3674 (0.6) | 3.13 | (1.45-6.72) | 1.74 | (0.79-3.83) |
| >100 | 12/1803 (0.7) | 64/17 942 (0.4) | 50/8327 (0.6) | 1.79 | (0.96-3.34) | 0.94 | (0.50-1.78) |
| **181-365 day AIS risk** | | | | | | | |
| All CAB patients | 20/3238 (0.6) | 156/31 437 (0.5) | 92/13 301 (0.7) | 0.97 | (0.58-1.59) | 0.71 | (0.42-1.20) |
| CAB patients by: | | | | | | | |
| Age, yrs | | | | | | | |
| 15-64 | 5/1139 (0.4) | 4/11 339 (0.0) | 13/5329 (0.2) | 9.38 | (2.49-35.32) | 1.54 | (0.54-4.37) |
| 65-80 | 7/1200 (0.6) | 69/11 765 (0.6) | 47/4822 (1.0) | 0.92 | (0.42-2.01) | 0.55 | (0.23-1.30) |
| 80+ | 8/899 (0.9) | 83/8333 (1.0) | 32/3150 (1.0) | 0.88 | (0.43-1.83) | 0.86 | (0.39-1.90) |
| Sex | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Female | 10/1761 (0.6) | 73/17 149 (0.4) | 45/7345 (0.6) | 1.22 | (0.63-2.38) | 0.81 | (0.39-1.66) |
| Male | 10/1477 (0.6) | 83/14 288 (0.6) | 47/5956 (0.8) | 1.09 | (0.56-2.11) | 0.81 | (0.40-1.63) |
| Previous CVD[†] | | | | | | | |
| No | 8/2345 (0.3) | 89/26 417 (0.3) | 51/10 338 (0.5) | 1.04 | (0.51-2.15) | 0.64 | (0.30-1.35) |
| Yes | 12/893 (1.3) | 67/5020 (1.3) | 41/2963 (1.4) | 1.05 | (0.57-1.95) | 0.99 | (0.52-1.88) |
| Previous AMI | | | | | | | |
| No | 17/2995 (0.6) | 141/29 941 (0.5) | 87/12 479 (0.7) | 1.19 | (0.72-1.97) | 0.75 | (0.44-1.26) |
| Yes | 3/243 (1.2) | 15/1496 (1.0) | 5/822 (0.6) | 1.29 | (0.37-4.47) | 2.10 | (0.50-8.83) |
| Previous stroke | | | | | | | |
| No | 11/2877 (0.4) | 108/29 138 (0.3) | 69/11 948 (0.6) | 1.02 | (0.55-1.89) | 0.60 | (0.32-1.14) |
| Yes | 9/361 (2.5) | 28/2299 (2.1) | 23/1353 (1.7) | 1.21 | (0.59-2.46) | 1.52 | (0.70-3.31) |
| Study period | | | | | | | |
| 1992-2002 | 10/1607 (0.6) | 86/15582 (0.6) | 51/6535 (0.8) | 1.04 | (0.53-2.01) | 0.66 | (0.32-1.36) |
| 2003-2010 | 10/1631 (0.6) | 70/15 585 (0.4) | 41/6766 (0.6) | 1.29 | (0.66-2.52) | 1.00 | (0.50-2.01) |
| Etiologic agent | | | | | | | |
| Gram-positive | 11/1356 (0.8) | 56/13 244 (0.4) | 37/5705 (0.6) | 1.78 | (0.93-3.43) | 1.19 | (0.60-2.37) |
| *S pneumoniae* | 7/785 (0.9) | 30/7697 (0.4) | 25/3364 (0.7) | 2.18 | (0.94-5.04) | 1.12 | (0.48-2.61) |
| *S aureus* | 0/177 (0) | 2/1722 (0.1) | 3/733 (0.4) | - | - | - | - |
| Other Gram-positive | 4/394 (1.0) | 24/3825 (0.6) | 9/1608 (0.6) | 1.48 | (0.51-4.28) | 1.68 | (0.51-5.52) |
| Gram-negative | 9/1700 (0.5) | 88/16447 (0.5) | 46/6888 (80.7) | 0.91 | (0.46-1.82) | 0.65 | (0.30-1.39) |
| *E coli* | 9/1215 (0.7) | 67/11 731 (0.6) | 37/4892 (0.8) | 1.20 | (0.60-2.42) | 0.87 | (0.40-1.90) |
| Other Gram-negative | 0/485 (0) | 21/4716 (0.4) | 9/1996 (0.5) | - | - | - | - |
| Polymicrobial/fungal | 0/182 (0) | 12/1746 (0.7) | 9/708 (1.3) | - | - | - | - |
| Focus of infection | | | | | | | |
| Respiratory tract | 7/751 (0.9) | 31/7368 (0.4) | 23/3184 (0.7) | 2.09 | (0.91-4.81) | 1.22 | (0.52-2.89) |
| Urinary tract | 7/1181 (0.6) | 64/11 373 (0.6) | 34/4719 (0.7) | 0.99 | (0.45-2.17) | 0.71 | (0.30-1.71) |
| CNS | 0/124 (0) | 0/1232 (0) | 4/575 (0.7) | - | - | - | - |
| Endocarditis | 1/114 (0.9) | 5/112 (0.4) | 4/471 (0.8) | 1.71 | (0.20-14.64) | 0.99 | (0.11-9.13) |
| Miscellaneous foci | 1/490 (0.2) | 26/4757 (0.5) | 7/2017 (0.3) | 0.33 | (0.05-2.46) | 0.46 | (0.05-4.07) |
| Unknown or multiple | 4/578 (0.7) | 30/5595 (0.5) | 20/2335 (0.9) | 1.20 | (0.42-3.41) | 0.78 | (0.26-2.33) |
| Blood culture bottles[‡] | | | | | | | |
| Some positive | 12/1427 (0.8) | 63/13 870 (0.5) | 45/5860 (0.8) | 1.75 | (0.93-3.26) | 0.92 | (0.47-1.79) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| All positive | 8/1355 (0.6) | 73/13 153 (0.6) | 35/5563 (0.6) | 1.01 | (0.48-2.10) | 1.05 | (0.48-2.32) |
| WBC (×10^9/L) [‡] | | | | | | | |
| <3.5 | 0/92 (0) | 1/943 (0.1) | 2/383 (0.5) | - | - | - | - |
| 3.5-10 | 3/494 (0.6) | 27/4796 (0.6) | 12/2029 (0.6) | 1.06 | (0.32-3.51) | 1.13 | (0.30-4.23) |
| >10 | 13/1886 (0.7) | 84/18 316 (0.5) | 61/7787 (0.8) | 1.47 | (0.81-2.65) | 0.85 | (0.46-1.55) |
| CRP (mg/L) [‡] | | | | | | | |
| <10 | 0/106 (0) | 2/1019 (0.2) | 5/425 (1.2) | - | - | - | - |
| 10-100 | 8/702 (1.1) | 53/6778 (0.8) | 22/2805 (0.8) | 1.43 | (0.68-3.02) | 1.57 | (0.68-3.61) |
| >100 | 8/1621 (0.5) | 57/15 795 (0.4) | 48/6783 (0.7) | 1.32 | (0.63-2.78) | 0.65 | (0.30-1.39) |

Abbreviations: CAB, community-acquired bacteremia. CI, confidence interval. CNS, central nervous system. WBC, white blood cell count. CRP, C-reactive protein.

[*]Relative risk estimates for all CAB patients versus their matched controls are adjusted for age, gender, calendar-time, marital status, previous AMI, previous cerebrovascular disease, diabetes, chronic pulmonary disease, other cardiovascular disease, other co-morbidity, and medications for cardiovascular disease. Relative risk estimates in stratified analyses and subgroup analyses are controlled for age, gender, calendar-time and any comorbidity (yes/no, except where stratified by comorbid disease). [†]Previous CVD defined as any previous diagnosis of AMI, stroke, heart failure or atrial fibrillation. [‡]Blood culture bottle data from 1996-2010 and WBC and CRP-data from 1998-2010. [§]Not adjusted for comorbidity due to few events.

**Sensitivity analysis.**

We used *episensi* in Stata to perform a deterministic sensitivity analysis and estimate how much a potential strong unmeasured confounder might influence the observed association between community-acquired bacteremia (CAB) and acute myocardial infarction (AMI) / acute ischemic stroke (AIS) when compared to population controls. We assumed the following worst-case scenario: 1) a relative AMI and AIS risk of 20 associated with the unmeasured confounder, 2) a confounder prevalence of 5% among population controls, and 3) a 10 times higher prevalence of the confounder in patients with CAB.

We estimated that if an unmeasured confounder was strongly associated with CAB (odds ratio of 10), and independently increased the 30-day AMI/AIS risk by a factor of 20, the true risk for AMI/AIS following CAB would still be increased 5.73-fold (5.06-fold for AMI, 6.34-fold for AIS) when compared with population controls.

# Study II

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PLOS ONE

# Venous Thromboembolism after Community-Acquired Bacteraemia: A 20-year Danish Cohort Study

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## Abstract

***Background:*** Infections may increase the risk for venous thromboembolism (VTE), but little is known about VTE risk associated with community-acquired bacteraemia (CAB). We examined the risk for VTE within one year of CAB in comparison to that in matched controls.

***Methods:*** We conducted a population-based cohort study in North Denmark 1992–2011, using data from high-quality health-care databases. We included 4,213 adult CAB patients who had positive blood cultures drawn on the day of hospital admission, 20,084 matched hospitalised controls admitted for other acute medical illness, and 41,121 matched controls from the general population. We computed 0–90 and 91–365 day absolute risks for hospital-diagnosed VTE and used regression analyses with adjustment for confounding factors to compare the risk for VTE in bacteraemia patients and controls.

***Results:*** Among CAB patients, 1.1% experienced VTE within 90 days of admission and 0.5% during 91–365 days after admission. The adjusted 90-day odds ratio (OR) for VTE was 1.9 (95% CI 1.4–2.7) compared with hospitalised controls, and 23.4 (95% CI 12.9–42.6) compared with population controls. During 91–365 days after CAB admission, the VTE risk remained moderately increased (adjusted hazard ratio vs. hospitalised controls, 1.4; 95% CI 0.8–2.5, and vs. population controls, 1.9; 95% CI 1.0–3.3). Compared to hospitalised controls, the 90-day VTE risk increase was greater for Gram-positive infection (adjusted OR 2.5; 95% CI 1.6–4.1) than for Gram-negative infection (adjusted OR, 1.2; 95% CI 0.7–2.1), partly due to a high risk after *Staphylococcus aureus* infection (3.6%).

***Conclusion:*** The risk for VTE is substantially increased within 90 days after community-acquired bacteraemia when compared to hospitalised controls and population controls. However, the absolute risk of VTE following CAB is low.

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## Introduction

Hospitalisations for community-acquired bacteraemia (CAB) have increased by 50% in recent years [1]. Venous thromboembolism (VTE) is a potentially life-threatening complication in hospitalised medical patients, and any association between CAB and VTE is therefore clinically important. The extent to which infections may cause VTE is debated. Previous observational studies have found 28-day or in-hospital risks of 0.5–1.5% for symptomatic VTE in patients hospitalised for sepsis or severe sepsis [2,3] and a 1-year risk of 1.9% after hospitalisation for sepsis [2]. In acutely hospitalised medical patients, two studies have identified infection as an independent risk factor for VTE (odds ratio 1.27 and 1.74, vs. patients hospitalised for other disease) [4,5]. Also, a recent case-control study found that patients hospitalised with infection had a 5- to 12-fold increased risk for VTE within 2 weeks after infection compared to population controls, and that this risk increase waned over time but remained significantly elevated for up to 1 year [6]. Cohort studies with long-term follow-up of VTE-risk after infection are sparse [2,7], and none has included a comparison group. Previous studies have also lacked microbiological confirmation of infection, which may lead to a falsely inflated association due to possible misdiagnosis of VTE as skin infection or pneumonia.

We aimed to assess the short- and longer-term risks of symptomatic VTE in a cohort of hospitalised medical patients with microbiologically confirmed CAB compared with acutely hospitalised controls and with the background population.

## Materials and Methods

### Ethics Statement

This study was approved by the Danish Data Protection Agency (2011-41-5864). In accordance with Danish law, informed consent was not required for this study because it was entirely register-based.

### Design

We conducted this population-based cohort study in the North Denmark Healthcare Region, where all ~500,000 inhabitants are provided with free tax-supported health care. All blood culture analyses in the Region are performed at the region's referral hospital, Aalborg University Hospital, which provides inpatient care along with a dwindling number of district hospitals (from nine to five).

In Denmark, all residents are assigned a unique Civil Registration System (CRS) number which is registered in the CRS and in all medical registries. The CRS also stores information on date of birth, residency status, dates of immigration/emigration and death, updated daily. We used concatenated data from the CRS, the North Denmark Bacteraemia Database [8], the regional Hospital Discharge Registry (HDR) [9], and the Aarhus University Prescription Database [10].

For this study, we defined CAB as the presence of viable bacteria or fungi in the bloodstream isolated from blood cultures taken on the day of hospital admission, among patients who had not been admitted to hospital within the previous 30 days. The North Denmark Bacteraemia Database, which is described in detail elsewhere [8], was used for information on clinically relevant bacteraemia episodes, including date of blood culture draw, infectious agent, and focus of infection.

The HDR contains International Classification of Disease diagnosis code data (ICD, versions 8 and 10) on hospital discharges since 1977 and outpatient contacts since 1995 [9]. It allows for one primary diagnosis code (condition that prompted patient admission and the main condition responsible for the completed diagnosis and treatment course) and up to twenty secondary codes with no information as to which disease occurred first. We considered primary and secondary VTE codes from inpatient stays and hospital outpatient clinic visits as outcome events during 1992–2011. We specifically did not include VTE-diagnoses from emergency room visits because these codes may have a positive predictive value of only 31% [11]. The prescription registry details Anatomical Therapeutic Chemical Classification (ATC) codes on reimbursed prescriptions in the North Denmark region since 1989. We used the HDR and the prescription database for information on risk factors for VTE: cancer, cardiovascular disease, diabetes, obesity, chronic obstructive pulmonary disease, renal disease, recent hospital admission, recent surgery or trauma, and pregnancy [12]. The corresponding ICD and ATC codes can be found in Supplementary Table S1.

### Study Subjects

Eligibility criteria for all CAB patients and controls were age ≥15 years, residence in the study area for ≥1 year, no hospital stay in the previous 30 days, no history of bacteraemia, and no previous hospital contact with a VTE diagnosis.

We identified all eligible acutely ill medical (non-surgical) patients who had positive blood cultures taken on the day of admission during 1992–2010. To be confident that CAB preceded VTE in these cases, we first identified the patients (n = 26) who had been given a VTE code at discharge from a CAB hospitalisation since 1992. We then examined a convenience sample of cases with available medical files and discharge files, i.e. all cases since 1994 (n = 22, 85%). We found no indication of reverse causation in any patient. Seventeen patients developed VTE during their hospitalisation with CAB, and another five patients had had symptoms of infection for two to seven days before being diagnosed with both CAB and VTE on the day of admission.

Next, we identified two separate comparison cohorts. Because subsequent VTE risk may be related to acute medical hospital stay rather than to infection *per se*, we assembled a matched hospitalised comparison cohort of up to five acutely hospitalised patients for each CAB patient. As the CAB patients, hospitalised controls were admitted to medical departments, i.e. non-surgical and non-psychiatric departments. We excluded controls who were hospitalised because of VTE, i.e., who had a primary diagnosis of VTE from their index admission. The matching factors were sex, exact year of birth, and exact calendar year of hospital admission. Furthermore, for each CAB patient, we chose up to 10 eligible population controls, who were alive on the index date (= date of hospital admission of the CAB patient), matched on sex and exact year of birth.

### Statistics

We followed all study subjects from the index date until first hospital encounter for VTE, death, emigration out of Denmark, or January 1st 2012, whichever came first. We first computed absolute risks for VTE within 0–90 days and 91–365 days after the index date. Next, we used conditional logistic regression to compute odds ratios (ORs) with 95% confidence intervals (CIs) of VTE within 0–90 days and Cox proportional hazards models (stratified on matched groups) to compute hazard ratios (HRs) with 95% CIs of VTE during 91–365 days after the index date. Because VTE events were uncommon in CAB patients and controls during 0–90 days, odds ratios approximate relative risks and may be interpreted as such [13]. ORs and HRs for all CAB patients vs. matched controls were controlled for matching factors (age, gender, calendar-time) and further adjusted for cancer (yes/no), cardiovascular disease (yes/no), other comorbidity (diabetes, obesity, COPD, or renal disease - yes/no), and recent hospital contact (yes/no). Subgroup analyses were performed according to age group, gender, time period, causative pathogen(s), and focus of infection. These were controlled for matching factors and further adjusted for any comorbidity (cancer, cardiovascular disease, diabetes, obesity, COPD, or renal disease - yes/no).

Because the risk of VTE in the 90 days after CAB may be influenced more by the hospitalisation itself than by the CAB, in comparisons with the general population we also computed adjusted ORs of VTE during the CAB index admission vs. matched population controls experiencing VTE during 0–90 days (no population controls experienced VTE during the index admission of the matched CAB patient).

In supplementary analyses we first excluded the eight CAB patients (0.19%) who had a primary VTE diagnosis in the index admission, and their matched control groups. To examine the 90-day risk of VTE occurring clearly after admission/hospitalisation, we subsequently excluded CAB patients and hospitalised controls with any VTE code in the index admission. Finally, we computed the VTE risk after restriction to study subjects without recent surgery/trauma (previous 90 days) or hospital admission (previous 180 days), cancer history or new cancer in the following 365 days, or pregnancy in the 365 days surrounding the index date (here, termed "classic" risk factors for VTE).

The proportional hazards assumption was checked graphically by visual inspection of log- log plots. We used Stata 11.2 (Stata Corp., College Station, TX) for all analyses.

## Results

### Study Subject Characteristics

We identified 4,389 individuals with a first diagnosis of CAB, 21,626 matched acutely hospitalised controls, and 43,831 matched population controls. Among them, 176 CAB patients (4.0%), 709 hospitalised controls (3.3%), and 1,009 population controls (2.3%) had a previous diagnosis of VTE and were excluded. Table 1 shows baseline characteristics of the remaining 4,213 CAB patients and the matched hospitalised and population controls. The majority of study participants were women (53.5%) and the median age was 73 years (IQR 61–82). CAB patients and hospitalised controls had a similar burden of pre-existing disease (Supplementary Table S2). During the index hospitalisation, 10.9% of CAB patients had an intensive care unit stay as did 7.3% of hospitalised controls. Of note, mortality after CAB was 20.5% within 90 days and 29.3% within one year, whereas mortality was lower in both control groups (Table 1).

### VTE Risk

For CAB patients, the 90-day absolute risk of VTE was 1.1% (Table 2), and the 91–365 day risk 0.5% (Table 3). Compared to hospitalised controls, CAB patients had a moderately increased risk of VTE during 0–90 days of follow-up (adjusted OR, 1.9; 95% CI 1.4–2.7; Table 2) and during 91–365 days (adjusted HR 1.4; 95% CI 0.8–2.5; Table 3). Compared to population controls, hospitalisation with CAB was associated with a greatly increased risk for VTE within 90 days (adjusted OR, 23.4; 95% CI 12.9–42.6; Table 2). Throughout the follow-up period most VTE events were diagnosed during a hospital stay (96.7% of events for CAB patients, 92.6% for hospitalised controls, and 86.7% for population controls).

Twenty-six CAB patients (0.6%) experienced VTE during the index admission. No population controls had a VTE diagnosis during the hospitalisation of the corresponding matched cases, but

**Table 1.** Baseline characteristics, 90-day and 365-day mortality for study subjects, Northern Denmark, 1992–2010.

| | Age, median (IQR) | Male (%) | Previous Cancer (%) | 90-day mortality (%) | 365-day mortality (%) |
|---|---|---|---|---|---|
| **All CAB patients (4,213)** | 73.6 (61.2–82.2) | 46.5 | 16.0 | 20.5 | 29.3 |
| **All hospital controls (20,084)** | 73.5 (60.9–82.1) | 46.4 | 14.8 | 12.5 | 21.6 |
| **All population controls (41,121)** | 73.4 (60.9–82.0) | 46.4 | 9.7 | 1.2 | 5.6 |
| **CAB patients according to:** | | | | | |
| **Age, yrs** | | | | | |
| 15–64 (1,306) | 53.9 (42.2–59.9) | 47.5 | 9.7 | 11.7 | 16.6 |
| 65–79 (1,568) | 73.5 (69.8–77.1) | 46.5 | 19.9 | 20.8 | 30.1 |
| ≥80 (1,339) | 85.2 (82.5–88.5) | 45.3 | 17.6 | 28.8 | 40.7 |
| **Sex** | | | | | |
| Female (2,255) | 73.8 (61.6–82.5) | - | 15.8 | 19.6 | 27.1 |
| Male (1,958) | 73.3 (60.4–81.9) | - | 16.2 | 21.6 | 31.8 |
| **Study period** | | | | | |
| 1992–2002 (2,134) | 73.4 (60.7–81.7) | 46.3 | 15.1 | 21.7 | 29.9 |
| 2003–2010 (2,079) | 73.8 (61.4–82.7) | 46.7 | 16.9 | 19.4 | 28.6 |
| **Causative pathogen** | | | | | |
| Gram-positive (1,817) | 70.8 (58.3–80.2) | 51.9 | 15.2 | 22.0 | 30.1 |
| *S. aureus* (302) | 73.2 (61.7–81.3) | 58.9 | 13.6 | 37.4 | 47.1 |
| *S. pneumoniae* (994) | 68.5 (55.8–78.9) | 46.7 | 12.9 | 18.9 | 24.9 |
| Other Gram-positive (521) | 73.1 (61.5–81.6) | 57.2 | 19.6 | 19.0 | 30.3 |
| Gram-negative (2,120) | 75.5 (63.7–83.0) | 40.8 | 16.5 | 17.8 | 26.8 |
| *E. coli* (1,468) | 76.6 (66.3–83.6) | 39.1 | 15.7 | 15.7 | 24.7 |
| Other Gram-negative (652) | 73.3 (56.8–81.7) | 53.9 | 18.3 | 22.7 | 31.4 |
| Polymicrobial/fungal (276) | 78.4 (67.6–84.6) | 54.4 | 17.8 | 31.5 | 43.1 |
| **Focus of infection** | | | | | |
| Respiratory tract (939) | 69.1 (55.9–79.2) | 48.6 | 14.6 | 18.0 | 23.8 |
| Urinary tract (1,382) | 77.1 (66.4–83.7) | 37.8 | 15.1 | 12.3 | 23.0 |
| Skin, bone, or joint (253) | 71.3 (60.6–79.2) | 56.1 | 14.2 | 17.0 | 27.7 |
| Miscellaneous (655) | 69.7 (53.8–79.3) | 51.1 | 14.4 | 20.9 | 27.5 |
| Unknown or multiple (986) | 76.4 (65.6–84.2) | 51.1 | 20.4 | 35.8 | 45.8 |

Abbreviations: IQR, inter-quartile range.

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**Table 2.** 0–90 day risk of a first VTE among patients with first hospital admission for CAB and matched hospitalised controls and population controls, Northern Denmark, 1992–2010.

| | | Risk, n/N (%) | | Odds ratio (95% CI)[1] | Odds ratio (95% CI)[1] |
|---|---|---|---|---|---|
| | CAB patients | Hospitalised controls | Population controls | CAB vs. hospitalised controls | CAB vs. population controls |
| **All study subjects** | 45/4,213 (1.1) | 112/20,084 (0.6) | 18/41,121 (0.0) | 1.9 (1.4–2.7) | 23.4 (12.9–42.6) |
| **Age group, years** | | | | | |
| 15–64 | 15/1,306 (1.2) | 27/6,307 (0.4) | 2/12,936 (0.0) | 2.7 (1.4–5.0) | 102.0 (14.7–710.4) |
| 65–79 | 25/1,568 (1.6) | 47/7,460 (0.6) | 8/15,305 (0.1) | 2.6 (1.6–4.2) | 29.7 (13.1–67.3) |
| ≥80 | 5/1,339 (0.4) | 38/6,317 (0.6) | 8/12,880 (0.1) | 0.7 (0.3–1.7) | 6.3 (2.0–19.7) |
| **Sex** | | | | | |
| Male | 26/1,958 (1.3) | 45/9,322 (0.5) | 11/19,073 (0.1) | 2.8 (1.7–4.6) | 21.5 (10.5–43.7) |
| Female | 19/2,255 (0.8) | 67/10,762 (0.6) | 7/22,041 (0.0) | 1.4 (0.8–2.3) | 27.6 (11.3–67.4) |
| **Study period** | | | | | |
| 1992–2002 | 23/2,134 (1.1) | 43/10,260 (0.4) | 7/20,905 (0.0) | 2.6 (1.6–4.4) | 29.3 (12.5–68.9) |
| 2003–2010 | 22/2,079 (1.1) | 69/9,824 (0.7) | 11/20,216 (0.1) | 1.5 (0.9–2.4) | 19.7 (9.5–41.0) |
| **Causative pathogen** | | | | | |
| Gram positive | 26/1,817 (1.3) | 49/8,651 (0.6) | 3/17,781 (0.0) | 2.5 (1.6–4.1) | 77.0 (23.2–255.8) |
| *S. aureus* | 11/302 (3.6) | 8/1,426 (0.6) | 2/2,947 (0.1) | 7.2 (2.7–19.2) | 51.3 (11.3–232.3) |
| *S. pneumoniae* | 7/994 (0.7) | 30/4,751 (0.6) | 0/9,738 (0) | 1.1 (0.5–2.5) | - |
| Other Gram-positive | 8/521 (1.5) | 11/2,474 (0.4) | 1/5,096 (0) | 3.4 (1.4–8.4) | 80.0[2] (10.0–639.2) |
| Gram negative | 14/2,120 (0.7) | 58/10,115 (0.6) | 14/20,653 (0.1) | 1.2 (0.7–2.1) | 9.8 (4.6–20.6) |
| *E. coli* | 8/1,468 (0.5) | 36/6,992 (0.5) | 11/14,389 (0.1) | 1.1 (0.5–2.3) | 6.9 (2.8–17.4) |
| Other Gram-negative | 6/652 (0.9) | 22/3,123 (0.7) | 3/6,364 (0) | 1.4 (0.5–3.5) | 20.0[2] (5.0–80.0) |
| Polymicrobial and yeasts | 5/276 (1.8) | 5/1,318 (0.4) | 1/2,687 (0) | 5.0 (1.4–17.9) | 49.2[2] (5.7–421.1) |
| **Focus of infection** | | | | | |
| Urinary tract | 7/1,382 (0.7) | 33/6,582 (0.5) | 12/13,431 (0.1) | 1.3 (0.6–2.8) | 7.4 (3.1–17.7) |
| Respiratory tract | 5/939 (0.5) | 28/4,491 (0.6) | 0/9,180 (0) | 0.8 (0.3–2.2) | - |
| Skin, bone or joint | 13/253 (5.1) | 8/1,197 (0.7) | 1/2,491 (0.0) | 8.8 (3.4–22.6) | 124.3 (16.2–953.0) |
| Miscellaneous | 7/695 (1.0) | 16/3,341 (0.5) | 1/6,929 (0.0) | 2.1 (0.9–5.3) | 69.1[2] (8.5–561.4) |
| Unknown or multiple | 11/944 (1.2) | 27/4,473 (0.6) | 3/9,313 (0.0) | 1.8 (0.9–3.7) | 17.7 (5.6–56.1) |

Abbreviations: CI, confidence interval.

[1]Computed by conditional logistic regression. Controls matched for age, sex and calendar time act as reference group. All odds ratio estimates are controlled for matching factors. Estimates for "All study subjects" are adjusted for cancer, cardiovascular disease, other comorbidity, and recent hospital contact. Subgroup analyses are adjusted for any comorbidity.

[2]Not adjusted for comorbidity due to few events. A (−) denotes that the odds ratio could not be calculated because no events occurred among population controls.

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18 (<0.1%) had a VTE during 0–90 days of follow-up, which corresponded to an adjusted OR of 13.9 (95% CI 7.2–26.8).

The VTE relative risk was especially elevated among young study subjects, both within 90 days and during 91 to 365 days after admission (vs. hospitalised controls, adjusted OR 2.7; 95% CI 1.4–5.0, and adjusted HR, 3.4; 95% CI 1.2–9.9) (Table 2 and Table 3).

Gram-positive CAB was associated with a higher relative risk for VTE vs. hospitalised controls within 0–90 days (adjusted OR, 2.5; 95% CI 1.6–4.1) than Gram-negative CAB (adjusted OR, 1.2; 95% CI 0.7–2.1) (Table 2). During 91–365 days of follow-up, Gram-positive CAB remained a high-risk infection (adjusted HR vs. hospitalised controls, 2.0; 95% CI 0.8–4.7; Table 3). Of note, patients with Gram-positive bacteraemia were ~5 years younger than patients with Gram-negative bacteraemia (Table 1) but had a higher absolute 90-day risk of VTE (Table 2). In patients with Gram-positive CAB, a particularly high 90-day risk of VTE was found among patients with *S. aureus* infection (11/302, 3.6%), while the risk was lower in patients with *S. pneumonia* infection (7/994, 0.7%). Skin or bone/joint infection was also a high-risk infection for VTE (0–90 day risk for VTE of 5.1%, 13/253), and in this group the two most common infectious agents where *S. aureus* (0–90 day risk for VTE of 7.2%, 6/83) and β-hemolytic streptococci (0–90 day risk for VTE of 0.8%, 1/121).

After excluding CAB patients with a primary diagnosis of VTE at the index admission, CAB remained associated with an increased 90-day risk for VTE (OR vs. hospitalised controls, 1.6; 95% CI 1.1–2.3), see Supplementary Table S3. When examining the 90-day risk for VTE after index admission, CAB was associated with a 1.5-fold increased risk (OR) of VTE within 90 days when compared to hospitalised controls and a 9.2-fold increased risk (OR) when compared to population controls (Supplementary Table S3). In patients with no "classic" risk factors for VTE, CAB was associated with a 90-day OR of 2.8 when compared to hospitalised controls (95% CI 1.6–4.8; Supplementary Table S3).

**Table 3.** 91–365 day risk of first VTE diagnosis among patients with first hospital admission for CAB and matched hospitalised controls and population controls, Northern Denmark, 1992–2010.

| | Risk, n/N (%) | | | HR (95% CI)[1] | HR (95% CI)[1] |
|---|---|---|---|---|---|
| | CAB patients | Hospitalised controls | Population controls | CAB vs. hospitalised controls | CAB vs. population controls |
| **All study subjects** | 15/3,316 (0.5) | 45/13,920 (0.3) | 72/32,022 (0.2) | 1.4 (0.8–2.5) | 1.9 (1.0–3.3) |
| **Age group, years** | | | | | |
| 15–64 | 7/1,140 (0.6) | 10/5,294 (0.2) | 6/11,274 (0.1) | 3.4 (1.2–9.9) | 10.5 (3.4–32.6) |
| 65–79 | 4/1,226 (0.3) | 21/5,105 (0.4) | 36/11,872 (0.3) | 0.8 (0.3–2.4) | 1.0 (0.4–2.9) |
| ≥80 | 4/950 (0.4) | 14/3,521 (0.4) | 30/8,876 (0.3) | 1.1 (0.4–3.6) | 1.2 (0.4–3.3) |
| **Sex** | | | | | |
| Male | 7/1,1519 (0.5) | 21/6,313 (0.3) | 30/14,628 (0.2) | 1.5 (0.6–3.6) | 2.0 (0.9–4.7) |
| Female | 8/1,797 (0.4) | 24/7,607 (0.3) | 42/17,394 (0.2) | 1.3 (0.6–3.0) | 1.7 (0.8–3.8) |
| **Study period** | | | | | |
| 1992–2002 | 4/1,658 (0.2) | 15/6,929 (0.2) | 27/16,066 (0.2) | 1.1 (0.4–3.5) | 1.2 (0.4–3.6) |
| 2003–2010 | 11/1,658 (0.7) | 30/6,991 (0.4) | 45/15,956 (0.3) | 1.5 (0.7–3.1) | 2.3 (1.2–4.4) |
| **Causative pathogen** | | | | | |
| Gram positive | 8/1,397 (0.6) | 19/5,982 (0.3) | 23/13,556 (0.2) | 2.0 (0.8–4.7) | 3.3 (1.5–7.5) |
| *S. aureus* | 1/180 (0.6) | 5/762 (0.7) | 4/1,741 (0.2) | 0.9[2] (0.1–7.5) | 2.4[2] (0.3–21.9) |
| *S. pneumoniae* | 4/802 (0.5) | 7/3,489 (0.2) | 9/7,798 (0.1) | 2.8 (0.7–10.2) | 4.2 (1.3–13.8) |
| Other Gram-positive | 3/415 (0.7) | 7/1,731 (0.4) | 10/4,017 (0.2) | 2.6 (0.6–11.7) | 3.3 (0.8–12.8) |
| Gram negative | 7/1,726 (0.4) | 25/7,198 (0.3) | 49/16,634 (0.3) | 1.0 (0.4–2.5) | 1.1 (0.5–2.5) |
| *E. coli* | 5/1,233 (0.4) | 16/5,066 (0.3) | 34/11,828 (0.3) | 1.3 (0.4–3.5) | 1.2 (0.5–3.1) |
| Other Gram-negative | 2/500 (0.4) | 9/2,132 (0.4) | 15/4,855 (0.3) | 0.7 (0.1–3.4) | 1.0 (0.2–4.4) |
| Polymicrobial and yeasts | 0/186 (0) | 1/740 (0.1) | 0/1,783 (0) | - | - |
| **Focus of infection** | | | | | |
| Urinary tract | 4/1,206 (0.3) | 14/4,942 (0.3) | 31/11,556 (0.3) | 1.2 (0.4–3.8) | 1.1 (0.4–3.1) |
| Respiratory tract | 3/767 (0.4) | 5/3,335 (0.1) | 10/7,451 (0.1) | 2.4 (0.5–10.6) | 2.8 (0.8–10.4) |
| Skin, bone or joint | 0/198 (0) | 5/819 (0.6) | 4/1,921 (0.2) | - | - |
| Miscellaneous | 1/545 (0.2) | 9/2,356 (0.4) | 8/5,309 (0.2) | 0.3 (0.0–2.6) | 1.2 (0.1–10.3) |
| Unknown or multiple | 7/600 (1.2) | 12/2,468 (0.5) | 19/5,785 (0.3) | 2.6 (0.9–7.0) | 3.1 (1.3–7.4) |

Abbreviations: HR, Hazard Ratio. CI, confidence interval.
[1]Computed by Cox regression stratified on matched groups. All hazard ratio estimates are controlled for matching factors (age, sex, calendar time). Estimates for "All study subjects" are adjusted for cancer, cardiovascular disease, other comorbidity, and recent hospital contact. Subgroup analyses are adjusted for any comorbidity.
[2]Not adjusted for comorbidity due to few events. A (−) denotes that the hazard ratio could not be calculated.
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## Discussion

In this population-based cohort study, we found that CAB was associated with a 1.1% risk of VTE within 90 days, nearly a doubling of the risk compared to other acutely hospitalised medical patients. Patients with gram positive bacteraemia, especially *S. aureus* bacteraemia, had a particularly high risk for VTE. When compared to matched hospitalised controls, *S. aureus* infection increased the 90-day risk for VTE by 600%.

This is the first study to examine the risk of VTE after microbiologically verified infection. It is also the largest cohort study to date to examine infection-related VTE risks. A few previous studies have detailed the absolute risk for VTE after infectious disease. In a cohort study of 1,080 hospitalised patients with presumed sepsis, 0.6% had VTE on admission, 1.3% developed in-hospital VTE and 0.6% suffered VTE between discharge and 1 year post-admission [2]. Similarly, pooled data on adverse events from three clinical trials showed a 0.5–0.9% 28-day risk for VTE in patients with severe sepsis [3]. Some clinical trials that specifically addressed the impact of heparin prophylaxis reported short-term absolute risk estimates for VTE ranging from 5 to 15% in medical patients hospitalised for acute infectious disease [5,14]. The reason for this discrepancy is mainly that asymptomatic deep venous thromboses accounted for the majority of events in the trials.

Data on the relative risk increase for VTE conferred by infectious disease are sparse. In a Spanish registry-based study involving more than 1.5 million medical department discharges, acute infectious disease was associated with 1.27-fold increased risk for in-hospital VTE when compared to other diseases [4]. Using data from the MEDENOX trial, Alikhan et al. found that infectious disease was the only acute illness associated with a significantly increased risk for VTE in hospitalised medical patients (OR = 1.74 within 14 days, compared with other medical illness) [5]. To our knowledge only one previous study has examined how the risk for VTE after hospitalisation for infections varies according to the focus of the infection. In a case-control study, Schmidt et al. found an up to 12-fold increased risk for VTE within 2 weeks after hospitalisation for infections (vs.

population controls), with the highest increase after skin infections [6]. Similarly, we found that microbiologically verified skin, bone and joint infections were high-risk infections for VTE, particularly if caused by *S. aureus*. That *S. aureus* skin and osteoarticular infection may be associated with a high risk for VTE has previously been suggested in case reports and smaller case series [15–17].

In a recent clinical guideline on the use of VTE prophylaxis in hospitalised medical patients, the American College of Physicians stated that a decision to initiate prophylactic heparin therapy should be based on an individualized assessment of the risk for VTE and bleeding, and that current evidence does not support the use of any specific VTE risk assessment tool [18]. Others have advocated the use of large observational datasets to identify inpatients who may benefit from VTE prophylaxis [19]. Our data indicate that it might be advantageous to include CAB and/or *S. aureus* infection in any future VTE risk assessment tool for use in medical inpatients.

Infections may induce thromboembolism by a number of mechanisms [20]. During systemic inflammatory activity, endothelial cell apoptosis, tissue-factor expression, thrombin generation and fibrin deposition is increased, while anticoagulatory pathways and fibrinolysis are impaired [20,21]. Gram-positive bacteria, including *S. aureus*, may have an exceptionally high propensity for inducing thrombosis [17,22]. Immobilization is a risk factor for VTE [12] and is pronounced during severe infection, especially infection causing bone and joint pain [23].

Strengths of the present study include the large sample size and microbiological verification of infection. We used computerized medical databases of high quality and validated VTE codes [8,11]. Furthermore, we had complete and long follow-up.

However, this study also has limitations. The predictive value of a VTE discharge code (from wards including outpatient clinics) in the Danish registries approaches only 75% [11], which would bias our estimates towards the null if misclassification was similar in CAB patients and controls. The 90-day mortality among CAB patients was 20.5% in our study, and it could be argued that some patients may have died from an unidentified pulmonary embolism, which may have led to an underestimation of the true pulmonary embolism risk after CAB. Surveillance bias is possible, particularly for infections that clinically mimic VTE. However, pneumonia and skin infections caused by β-hemolytic streptococci were associated with a relatively low absolute risk of VTE, indicating that this bias is likely to be small if present at all. There is a risk that VTE may have preceded CAB in some patients. To decrease the risk for reverse causation, we restricted the study to patients who had positive blood cultures on the day of admission. A further argument against reverse causation is that our review of a sample of medical records did not reveal instances in which the VTE preceded the CAB. Another issue that should be taken into consideration is the lack of data on in-hospital medication use. For instance, anticoagulant use could have lowered the risk of VTE and we may therefore have underestimated the VTE risk increase associated with bacteremia in the absence of this treatment, particularly versus population controls. We used information from health-care databases to adjust for important risk factors for VTE, but residual and unmeasured confounding remain possible, for example thrombophilia.

We conclude that CAB is associated with a substantially increased short-term risk for VTE. However, with the possible exception of *S. aureus* infection, the absolute risk for VTE after CAB is low.

## Supporting Information

**Table S1 ICD and ATC codes.**
(DOCX)

**Table S2 Descriptive characteristics of 4,213 patients admitted with a first diagnosis of community-acquired bacteraemia and their matched controls, 1992–2010.**
(DOCX)

**Table S3 Risk of VTE in CAB patients and controls when restricting analysis to patients with no VTE diagnosis during index admission and to patients with no "classic" risk factor for VTE.**
(DOCX)

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## Author Contributions

Conceived and designed the experiments: MDP MS HCS RWT JAB HN. Performed the experiments: MDP MS HCS RWT JAB HN. Analyzed the data: MDP. Contributed reagents/materials/analysis tools: MDP MS HCS RWT JAB HN. Wrote the paper: MDP. Critical revision of the manuscript: MDP MS HCS RWT JAB HN. Final approval of the manuscript: MDP MS HCS RWT JAB HN.

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**Table S1. ICD and ATC codes.**

| **Outcome** | **ICD codes** |
|---|---|
| **Deep venous thrombosis** | ICD-8: 451.00, 451.08, 451.09, 451.90, 451.92, 451.99, 452-453, ICD-10: I80.1-9, I81-82 |
| **Pulmonary embolism** | ICD-8: 450.99, ICD-10: I26 |
| **Comorbidities (previous) and pregnancy** | **ICD and ATC codes**[1] |
| **Cardiovascular disease** | |
| Myocardial infarction | ICD-8: 410; ICD-10: I21-I23 |
| Cerebrovascular disease | ICD-8: 430-438; ICD-10: I60-I69, G45-G46 |
| Congestive heart failure | ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49, ICD-10: I11.0, I13.0, I13.2, I50 |
| Peripheral vascular disease | ICD-8: 440-445; ICD-10: I70- I74, I77 |
| ACE inhibitors | ATC: C09 (C02 before 1 January 1996) |
| Beta blockers | ATC: C07 |
| Calcium channel blockers | ATC: C08 |
| Diuretics | ATC: C03 |
| Nitrates | ATC: C01DA (if ≥2 prescriptions are registered) |
| Aspirin | ATC: B01AC06, N02BA01 (in previous 125 days) |
| **Diabetes** | ICD-8: 249, 250; ICD-10: E10-E11; ATC: A10 |
| **Chronic pulmonary disease** | ICD-8: 490-493, 515-518; ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3; ATC: R03 |
| **Renal disease** | ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 |
| **Cancer** | ICD-8: 140-209; ICD-10: C00-C97 |
| **Obesity** | ICD-8: 277; ICD-10: E65-E68 |
| **Trauma** | ICD-8: 800.09-959.99; ICD-10: S00-T14 |
| **Pregnancy** | ICD-8: 630-680; ICD-10: O00-O99 |

[1]Drugs are any previous use, unless otherwise specified.

**Table S2. Descriptive characteristics of 4,213 patients admitted with a first diagnosis of community-acquired bacteraemia and their matched controls, 1992–2010.**

| | Community-acq. bacteraemia patients (n=4,213) | Acutely hospitalised controls (n=20,084) | General population controls (n=41,121) |
|---|---|---|---|
| **Age, yrs** | | | |
| 15-64 | 1,306 (31.0) | 6,307 (31.4) | 12,936 (31.5) |
| 65-79 | 1,568 (37.2) | 7,460 (37.1) | 15,305 (37.2) |
| ≥80 | 1,339 (31.8) | 6,317 (31.5) | 12,880 (31.3) |
| **Sex** | | | |
| Female | 2,255 (53.5) | 10,762 (53.6) | 22,048 (53.6) |
| Male | 1,958 (46.5) | 9,322 (46.4) | 19,073 (46.4) |
| **Comorbidity** | | | |
| Cancer | 674 (16.0) | 2,980 (14.8) | 3,988 (9.7) |
| Cardiovascular disease[1] | 3,041 (72.2) | 13,044 (65.0) | 23,005 (55.9) |
| Chronic pulmonary disease[1] | 1,457 (34.6) | 6,226 (31.0) | 8,903 (21.7) |
| Diabetes mellitus[1] | 645 (11.1) | 2,023 (10.1) | 2,594 (6.3) |
| Obesity | 222 (5.3) | 705 (3.5) | 730 (1.8) |
| Renal disease | 142 (3.4) | 476 (2.4) | 430 (1.1) |
| **Recent hospital contact** | | | |
| Inpatient admission[2] | 946 (22.5) | 2,643 (13.2) | 3,136 (7.6) |
| Surgery[3] | 542 (12.9) | 2,842 (14.2) | 1,654 (4.0) |
| Trauma[3] | 174 (4.1) | 947 (4.7) | 580 (1.4) |
| Pregnancy[4] | 5 (0.1) | 79 (0.4) | 148 (0.4) |

Data are no. (%) of patients.
[1]Includes previous use of drugs for cardiovascular disease, chronic pulmonary disease and diabetes, respectively. [2]Inpatient hospital admission within 180 days before the index date. [3]Any surgery or trauma within 90 days before the index date. [4]Pregnancy within 365 days of the index date.

**Table S3. Risk of VTE in CAB patients and controls when restricting analysis to patients with no VTE diagnosis during index admission and to patients with no ‘‘classic’’ risk factor for VTE.**

| | **0-90 day risk in patients with no primary diagnosis of VTE from index admission[2]** | **0-90 day risk in patients with no diagnosis of VTE from index admission** | **0-90 day risk in patients with no “classic” risk factor[1]** | **91-365 day risk in patients with no “classic” risk factor[1]** |
|---|---|---|---|---|
| **Absolute risk, n/N (%)** | | | | |
| CAB patients | 37/4,205 (0.9) | 19/4,187 (0.5) | 26/2,426 (1.1) | 9/2,008 (0.4) |
| Hospitalised controls | 112/20,046 (0.6) | 62/19,908 (0.3) | 28/7,274 (0.4) | 14/5,575 (0.3) |
| Population controls | 18/41,041 (0.0) | 18/40,867 (0.0) | 9/19,251 (0.0) | 26/15,920 (0.2) |
| **Adjusted relative risk (95% CI)[3]** | | | | |
| CAB patients vs. hospitalised controls | 1.6 (1.1-2.3) | 1.5 (0.9-2.5) | 2.8 (1.6-4.8) | 1.7 (0.7-4.0) |
| CAB patients vs. population controls | 18.0 (9.7-33.4) | 9.2 (4.5-18.5) | 21.9 (10.1-47.6) | 2.2 (1.0-4.8) |

Abbreviations: CAB, community-acquired bacteremia. CI, confidence interval. [1]No recent surgery/trauma (previous 90 days) or hospital admission (previous 180 days), cancer history or new cancer in the following 365 days, or pregnancy in the 365 days surrounding the index date. [2]Secondary VTE diagnoses are included. [3]Odds ratio computed using conditional logistic regression (0-90 day risk) and hazard ratio using Cox regression (91-365 day risk), controlled for age, sex, calendar-time, and further adjusted for cardiovascular disease, and other comorbidity (diabetes, obesity, COPD, renal disease). Analyses in patients with no diagnosis of VTE from index admission are also adjusted for cancer and recent surgery/trauma/admission.

# Study III

BMJ Open

# The effect of community-acquired bacteraemia on return to workforce, risk of sick leave, permanent disability pension and death: a Danish population-based cohort study

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## ABSTRACT

**Objectives:** Little is known about the prognosis of community-acquired bacteraemia (CAB) in workforce adults. We assessed return to workforce, risk for sick leave, disability pension and mortality within 1 year after CAB in workforce adults compared with blood culture-negative controls and population controls.

**Design:** Population-based cohort study.

**Setting:** North Denmark, 1996–2011.

**Participants:** We used population-based healthcare registries to identify all patients aged 20–58 years who had first-time blood cultures obtained within 48 h of medical hospital admission, and who were part of the workforce (450 bacteraemia exposed patients and 6936 culture-negative control patients). For each bacteraemia patient, we included up to 10 matched population controls.

**Primary and secondary outcome measures:** Return to workforce, risk of sick leave, permanent disability pension and mortality within 1 year after bacteraemia. Regression analyses were used to compute adjusted relative risks (RRs) with 95% CIs.

**Results:** One year after admission, 78% of patients with CAB, 85.7% of culture-negative controls and 96.8% of population controls were alive and in the workforce, and free from sick leave or disability pension. Compared with culture-negative controls, bacteraemia was associated with an increased risk for long-term sick leave (4-week duration, 40.2% vs 23.9%, adjusted RR, 1.51; CI 1.34 to 1.70) and an increased risk for mortality (30-day mortality, 4% vs 1.4%, adjusted RR, 2.34, CI 1.22 to 4.50; 1-year mortality, 8% vs 3.9%, adjusted RR, 1.73; CI 1.18 to 2.55). Bacteraemia patients had a risk for disability pension similar to culture-negative controls (2.7% vs 2.6%, adjusted RR, 0.99, CI 0.48 to 2.02) but greater than population controls (adjusted RR, 5.20; 95% CI 2.16 to 12.50).

**Conclusions:** CAB is associated with long duration of sick leave and considerable mortality in working-age adults when compared with blood culture-negative controls, and an increased 1-year risk for disability pension when compared with population controls.

## Strengths and limitations of this study

- To our knowledge, this is the first study to examine duration of sick leave and risk for permanent disability pension after community-acquired bacteraemia.
- Strengths include the population-based design and the use of highly valid prospectively collected data on bacteraemia, comorbidity and workforce affiliation.
- When comparing patients with community-acquired bacteraemia and controls, residual and unmeasured confounding may account for some of the increased risk for sick leave, disability pension and death.

## INTRODUCTION

Hospitalisation for community-acquired bacteraemia (CAB) has increased markedly in recent decades, and more than 30% of hospitalisations for CAB are in working-age adults.[1]

Overall, CAB is associated with a 30-day mortality of 13–20% and a 1-year mortality of 25–45%,[2–6] with a lower mortality in working-age adults, for example, a 30-day mortality of 11–16% in 15–64-year-old patients.[4–7] Apart from mortality, information is sparse on outcomes of bacteraemia in working-age adults. Only a few small cohort studies in hospitalised patients with infection have secondarily detailed the proportion of patients who returned to work, with conflicting results: 68% of patients with pneumonia may return to work within 30 days,[8] 43% of survivors of septic shock within 1 year[9] and 93% of survivors of severe sepsis within 3.5 years.[10] None of these studies focused specifically on working-age patients, assessed risk for long-term sick leave or disability pension, accounted for retirement or

included a comparison group. To our knowledge, no study has examined the prognosis after CAB in working-age adults who are part of the workforce and no study has examined return to work after CAB. Because CAB is increasingly common in working-age adults, it is important for patients, families and the society to have detailed knowledge on the prognosis in this age group.

We conducted a 15-year population-based cohort study among 20–58-year-old Danes who were part of the workforce, to examine return to work and risk for sick leave, permanent disability pension and mortality after medical hospitalisation with CAB in comparison with blood culture-negative controls and matched population controls.

## MATERIALS AND METHODS

### Setting

The study was conducted in healthcare region of North Denmark from 1996 to 2011. This area had a stable urban/rural catchment population of approximately 500 000 inhabitants who received universal tax-financed primary and secondary care, free at the point of delivery. Throughout the study period, Aalborg University Hospital was the only referral hospital and all regional hospitals relied on its department of clinical microbiology for blood culture analyses.

For this study, we used prospectively collected data from seven Danish population-based registries. The Civil Registration System (CRS),[11] which is updated daily, was used for personal data, including date of birth and death, place of residence and marital status. Unique CRS numbers, which are recorded for all healthcare contacts, and in administrative databases, facilitated linkage between registries. We further used data from the North Denmark Bacteraemia Research Database,[12] the regional microbiology information system (ADBact; Autonik, Sköldinge, Sweden),[4] the DREAM register on social transfer payments,[13] the Aarhus University Prescription database[14] and the regional Hospital Discharge Registry (HDR).[15] Because data were acquired from registries which are generally available to Danish researchers, no informed consent was needed for this study.

### Data on blood cultures

The bacteraemia database has registered all bacteraemia cases in the study area since 1981, prospectively since 1992.[12] The microbiology information system has been used since 1995 and contains basic information on all blood cultures examined in the region.[4] We used these databases for information on date of blood culture sampling, and also for information on infectious agent(s) and focus of infection in case of positive cultures. Throughout the study period, the blood culture system (BacT/Alert, bioMérieux, Marcy l'Etoil, France) was unchanged and is described in detail elsewhere.[4 12]

### Data on social transfers

The DREAM database contains weekly information on social transfer benefits for all residents in Denmark who have received any such benefit, however, briefly, since 1991.[13 16] In Denmark, people who are part of the workforce (employed or unemployed) can receive sickness absence benefits (paid sick leave) during temporary illness. Paid sick leave is possible for a maximum of 52 weeks (with the possibility for extension) within an 18-month period. People whose illness causes a lasting reduced ability to work can receive permanent disability pension. During the study period, people who were in the workforce could go on early voluntary retirement when they turned 60 and optional retirement with public pension was possible from age 67 (1996–1999) or age 65 (2000–2011). For the present study, DREAM codes were categorised as work-ready codes (employed and unemployed), sick leave codes and permanent disability pension codes. DREAM codes are further detailed in online supplementary table S1. There is no universal definition of long-term sick leave; for this study and elsewhere, it is defined as a disease lasting at least four consecutive weeks.[17]

### Data on hospital admissions and comorbidity

We used the HDR for data on hospital admissions and comorbidity. The HDR has recorded complete diagnosis codes from all inpatient hospitalisations in Denmark since 1977, and from outpatient clinic contacts since 1995. Diagnoses were coded by physicians according to the WHO's International Classification of Diseases (ICD)-8 until 1993 and ICD-10 thereafter).

We recorded the 19 disease categories in the Charlson Comorbidity Index (CCI) and alcohol-related disorders which we considered to be risk factors for death, sick leave and disability pension.[18 19] The comorbidity level was categorised as low (CCI=0), medium (CCI=1–2) or high (CCI>2).

The Aarhus University Prescription database was used for information on preadmission medication use including disulfiram, antidiabetics, drugs for cardiovascular and pulmonary disease and systemic antibiotics.[14] It contains Anatomical Therapeutic Chemical (ATC) classification code data on all reimbursed prescriptions since 1991. ICD and ATC codes used in this study are detailed in online supplementary table S2.

### Study subjects

We included study participants who were 20–58 years of age and were part of the workforce in the 4 weeks prior to admission, that is, did not receive permanent disability benefits, were not retired or on long-term sick leave (ie, received sickness absence benefits for a maximum of 3 weeks within 4 weeks prior to admission). Further eligibility criteria were no record of recent hospitalisation (previous 30 days), no previous blood culture draw (since 1995) or bacteraemia (since 1981) and residence within the study area for ≥1 year.

We identified all inpatients who had a first-time blood culture taken within 48 h of admission during 1996–2010. We defined CAB as the presence of viable bacteria or fungi in the bloodstream, determined by blood cultures performed within 48 h of admission, among patients who were not admitted to the hospital within the previous 30 days. Study participants were categorised as patients with CAB or as blood culture-negative controls. Furthermore, for each patient with CAB, we sampled 10 eligible population controls, who were alive on the date of hospital admission of the patient with CAB and with no recent hospitalisation, matched on sex and year of birth.

### Statistics

We followed all study participants from the date of blood culture draw until death, emigration from Denmark or completion of 1 year of follow-up, whichever occurred first. We first computed the median number and IQR of weeks that patients were on paid sick leave during the year before and after blood culture draw. We then computed the risk of being on sick leave (receiving sickness absence benefits) for at least 4 and for 52 consecutive weeks, respectively, beginning in the week of blood culture draw. Log-binomial regression[20 21] was used to compute the risk difference (RD) and relative risk (RR) with 95% CI of 4-week and 52-week sick leave for patients with CAB versus culture-negative controls. In time-to-event analyses, we first constructed cumulative incidence curves for permanent disability pension and Kaplan-Meier curves for mortality. We used regression analyses based on pseudo-observations[22] to compute RDs and RRs of permanent disability pension and mortality with 95% CIs for patients with CAB versus culture-negative controls and population controls. We considered death as a competing risk for permanent disability pension in all time-to-event analyses. In regression analyses, we adjusted for potential risk factors for sick leave, disability pension and death: age, gender, CCI score, alcoholism-related disease (including disulfiram use), medication use (antidiabetics, drugs for cardiovascular disease and pulmonary disease), civil status and immigrant status.[3 18 19 23–25] Because of few events among population controls, analyses concerning patients with CAB versus population controls were only adjusted for age and gender. In subgroup analyses, we examined the risk for long-term sick leave, disability pension and mortality according to etiological infectious agent and focus of infection. We also stratified analyses by gender, age group and employment status in the 4 weeks prior to admission. Because the management of CAB may have changed throughout the study period, we conducted up-to-date supplementary analyses pertaining to the latter half of the study period (2003–2011). Because previous antibiotic use could bias the risk estimates in our study when comparing patients with CAB and culture-negative controls, we conducted supplementary analyses in which we restricted to patients who had blood culture draw performed on admission and no recent out-of-hospital antibiotic use.

Stata V.11.2 for Windows (Stata Corp, College Station, Texas, USA) was used for all data analyses.

## RESULTS

### Baseline characteristics

We included 7386 acutely hospitalised patients who were part of the workforce immediately before hospitalisation and had a first-time blood culture drawn within 48 h of admission, 450 patients with CAB and 6936 controls with negative blood cultures. Patients with CAB were matched to 4500 population controls, of whom 3765 were included in the study (see flow diagram in the online supplement). Baseline characteristics for study participants can be found in table 1. Patients with CAB were older than culture-negative controls (median age in years 47.7 vs 41.4, p<0.001) but the burden of pre-existing disease was similar and relatively low in both groups. Still, the disease burden was even lower among population controls. In the year before blood culture draw, study participants were on sick leave for a median of 0 weeks (IQR 0–1 week for patients with CAB and culture-negative controls, and 0–0 for population controls).

### Return to work, duration of sickness leave and disability pension

Exactly 1 year after blood culture draw 350 patients with CAB (78.0%), 5944 culture-negative controls (85.7%) and 3644 population controls (96.8%) were alive and part of the workforce, and thus free from sick leave and disability pension (figure 1). In the year after blood culture draw, 50% of patients with CAB were on sick leave for at least 4 weeks (median 4, IQR 0–14 weeks) and 50% of culture-negative controls were on sick leave for 0 weeks (median 0, IQR 0–7 weeks). When compared with blood culture-negative controls, CAB was associated with an increased risk of sick leave for ≥4 consecutive weeks (40.2% vs 23.9%, adjusted RR, 1.51; 95% CI 1.34 to 1.70) and ≥52 weeks (5.8% vs 2.6%, adjusted RR, 1.96; 95% CI 1.31 to 2.93; table 2). However, the 1-year risk for disability pension was similar in the two groups, 2.7% for patients with CAB and 2.6% for culture-negative controls (adjusted RR, 0.99; 95% CI 0.48 to 2.02), see table 2 and figure 2. When compared with population controls, CAB was associated with an increased risk for 1-year disability pension (2.7% vs 0.6%, adjusted RR, 5.20; 95% CI 2.16 to 12.50).

### Mortality

Mortality rose sharply to 4% for patients with CAB within the first 30 days (see online supplementary figure S2), 1.4% for culture-negative controls (adjusted RR, 1.87; 95% CI 1.03 to 3.40; table 2) and 0 for population controls. Within 1 year the mortality was 8.0% for patients with CAB, 3.9% for culture-negative controls (adjusted

**Table 1** Descriptive characteristics of workforce community-acquired bacteraemia patients and blood culture-negative controls, North Denmark, 1996–2010

| | Patients with CAB (n=450) | Blood culture-negative patients (n=6936) | Population controls (n=3765) |
|---|---|---|---|
| Age, years | | | |
| 20–34 | 85 (18.9) | 2338 (33.7) | 767 (20.4) |
| 35–49 | 178 (39.6) | 2676 (38.6) | 1554 (41.3) |
| 50–58 | 187 (41.6) | 2693 (27.7) | 1444 (38.3) |
| Gender | | | |
| Female | 224 (49.8) | 3100 (44.7) | 1851 (49.2) |
| Male | 226 (50.2) | 3836 (55.3) | 1914 (50.8) |
| Marital status | | | |
| Married | 261 (58.0) | 3592 (51.8) | 2311 (61.4) |
| Never married or unknown* | 129 (28.7) | 2521 (36.3) | 982 (26.1) |
| Divorced or widowed | 60 (13.3) | 823 (11.9) | 472 (12.5) |
| Immigrant status | | | |
| Native Dane† | 429 (95.3) | 6520 (94.0) | 3536 (93.9) |
| Immigrant | 21 (4.7) | 416 (6.0) | 229 (6.1) |
| Comorbidity, any previous‡ | | | |
| Myocardial infarction | 4 (0.9) | 76 (1.1) | 19 (0.5) |
| Congestive heart failure | 1 (0.2) | 22 (0.3) | 3 (0.1) |
| Peripheral vascular disease | 5 (1.1) | 55 (0.8) | 18 (0.5) |
| Cerebrovascular disease | 8 (1.8) | 85 (1.2) | 29 (0.8) |
| Hemiplegia | 0 (0) | 6 (0.1) | 2 (0.1) |
| Chronic pulmonary disease | 24 (5.3) | 523 (7.5) | 102 (2.7) |
| Diabetes mellitus | 26 (5.8) | 276 (4.0) | 36 (1.0) |
| Diabetes with end-organ damage | 10 (2.2) | 133 (1.9) | 7 (0.2) |
| Connective tissue disease | 9 (2.0) | 118 (1.7) | 29 (0.8) |
| Moderate to severe renal disease | 3 (0.7) | 93 (1.3) | 15 (0.4) |
| Peptic ulcer disease | 8 (1.8) | 122 (1.8) | 48 (1.3) |
| Mild liver disease | 6 (1.3) | 80 (1.2) | 10 (0.3) |
| Moderate to severe liver disease | 4 (0.9) | 17 (0.3) | 3 (0.1) |
| Any tumour | 15 (3.3) | 193 (2.8) | 65 (1.7) |
| Leukaemia | 1 (0.2) | 25 (0.4) | 3 (0.1) |
| Lymphoma | 0 (0) | 24 (0.4) | 1 (0.0) |
| Metastatic solid tumour | 2 (0.4) | 19 (0.3) | 6 (0.2) |
| Dementia | 0 (0) | 1 (0.0) | 0 (0) |
| HIV/AIDS | 3 (0.7) | 11 (0.2) | 1 (0.0) |
| Alcoholism-related disease | 33 (7.3) | 428 (6.2) | 95 (2.5) |
| Medication use, any previous | | | |
| Drugs for cardiovascular disease | 120 (26.7) | 1741 (25.1) | 579 (15.4) |
| Inhalers for pulmonary disease | 119 (26.4) | 2104 (30.3) | 1159 (30.8) |
| Antidiabetics | 35 (7.8) | 375 (5.4) | 51 (1.4) |
| Disulfiram | 19 (4.2) | 202 (2.9) | 25 (0.7) |
| Antibiotics (past 4 weeks) | 74 (16.4) | 2031 (29.3) | 83 (2.2) |
| Charlson Comorbidity Index‡ | | | |
| 0 | 357 (79.3) | 5468 (78.8) | 3414 (90.7) |
| 1–2 | 87 (19.3) | 1403 (20.2) | 347 (9.2) |
| >2 | 6 (1.3) | 65 (0.9) | 4 (0.1) |
| Employment status | | | |
| Employed, past 4 weeks§ | 281 (62.4) | 4624 (66.7) | 3166 (84.1) |
| Unemployed, past 4 weeks¶ | 107 (23.8) | 1384 (20.0) | 538 (13.8) |
| Sick leave, past 4 weeks** | 62 (13.8) | 928 (13.4) | 61 (1.6) |
| 1 week | 43 (9.6) | 605 (8.7) | 35 (0.9) |
| 2 weeks | 11 (2.4) | 231 (3.3) | 17 (0.5) |
| 3 weeks | 8 (1.8) | 92 (1.3) | 9 (0.2) |

*Unknown for 0.7%.
†Includes 0.18% children of first-generation immigrants.
‡Based on ICD-codes that are detailed in the online supplement.
§Participants who were registered as employed and actively working during all 4 weeks before admission.
¶Participants who spent all 4 weeks as unemployed and participants who were employed/unemployed.
**Participants who were on sick leave for a maximum of 3 weeks in the previous 4 weeks, and otherwise employed or unemployed.
CAB, community-acquired bacteraemia; ICD, International Classification of Diseases.

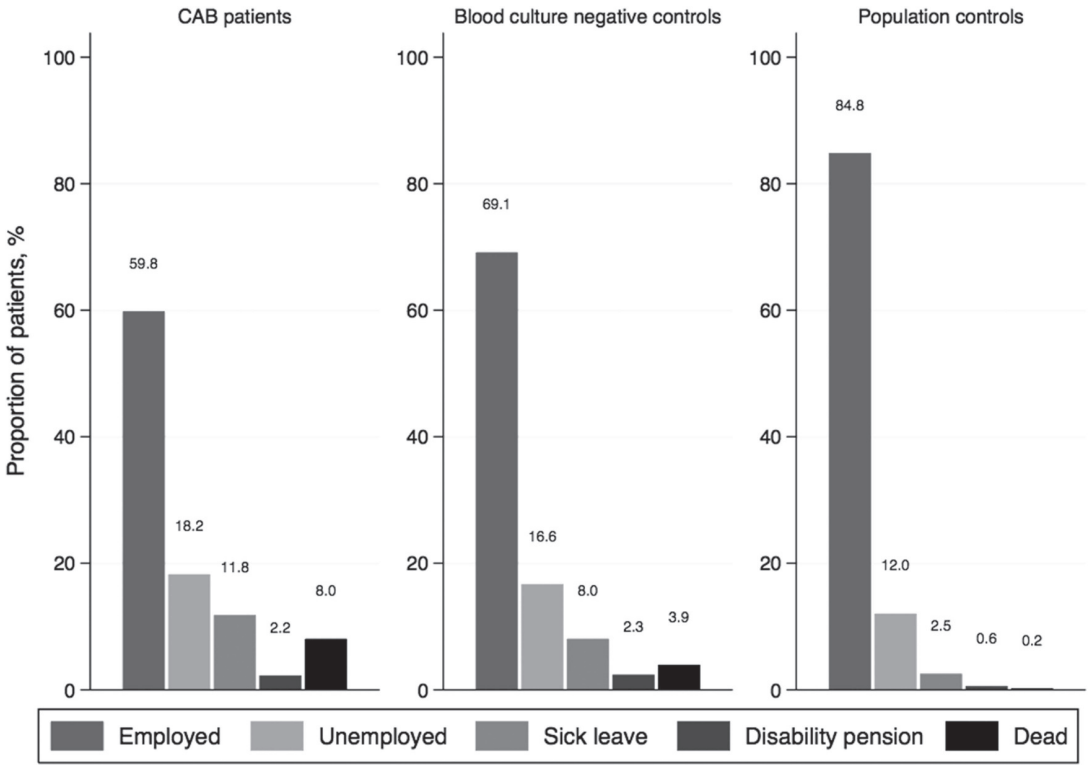


**Figure 1** Employment status and mortality at 1 year after blood culture draw. Note, the cumulative incidence of sick leave and disability pension within 1 year is higher than the proportion of patients that received either benefit at 1 year after blood culture draw (eg, some patients went on sick leave or became disability pensioners and later died during 1 year of follow-up).

RR, 1.52; 95% CI 1.10 to 2.10; table 2) and 0.2% for population controls (adjusted RR, 37.83; 95% CI 15.67 to 91.29).

### Subgroup and stratified analyses

Subgroups of patients with pneumococcal or other Gram-positive infection had a higher risk for 4-week sick leave, 52-week sick leave and 1-year disability pension after CAB than patients with *Escherichia coli* infection or other Gram-negative infection (table 3). Of note, pneumococcal infection was associated with the lowest level of comorbidity (85% with CCI score of 0), the lowest 30-day (1.7%) and 1-year mortality (4.5%) and the highest 1-year risk for permanent disability pension

**Table 2** Sick leave, disability pension and mortality among patients with CAB (N=450) and blood culture-negative controls (N=6936)

| | | Risk number of events (% of N) | | Risk difference, % (95% CI) | | Relative risk (95% CI) | |
|---|---|---|---|---|---|---|---|
| | | patients with CAB | Controls | Crude | Adjusted | Crude | Adjusted |
| Sick leave* | ≥4 weeks | 181 (40.2) | 1658 (23.9) | 16.3 (11.7 to 21.0) | 14.1 (9.5 to 18.7) | 1.68 (1.49 to 1.90) | 1.51 (1.34 to 1.70) |
| | ≥52 weeks | 26 (5.8) | 181 (2.6) | 3.2 (1.0 to 5.4) | 3.0 (0.8 to 5.2) | 2.21 (1.48 to 3.30) | 1.96 (1.31 to 2.93) |
| Disability pension | 1 year | 12 (2.7) | 183 (2.6) | 0.0 (−1.5 to 1.6) | −0.5 (−2.1 to 1.0) | 1.01 (0.57 to 1.80) | 0.99 (0.48 to 2.02) |
| Mortality | 30 days | 18 (4.0) | 99 (1.4) | 2.6 (0.7 to 4.4) | 2.2 (0.4 to 4.0) | 2.80 (1.71 to 4.59) | 2.34 (1.22 to 4.50) |
| | 1 year | 36 (8.0) | 271 (3.9) | 4.1 (1.5 to 6.6) | 3.1 (0.6 to 5.6) | 2.05 (1.47 to 2.86) | 1.73 (1.18 to 2.55) |

*Sick leave for ≥4 and ≥52 consecutive weeks after blood culture draw.
Relative risk and risk difference computed by log-binomial regression (sick leave analyses) and regression analyses based on pseudo-observations (disability pension and mortality analyses). Estimates are adjusted for age, gender, Charlson comorbidity score, alcoholism-related disease, medication use, marital and immigrant status. Because of few events, 30-day mortality estimates were not adjusted for medication use, marital and immigrant status. Because of failure to converge, risk difference estimates for sick leave were not adjusted for immigrant status.
CAB, community-acquired bacteraemia.

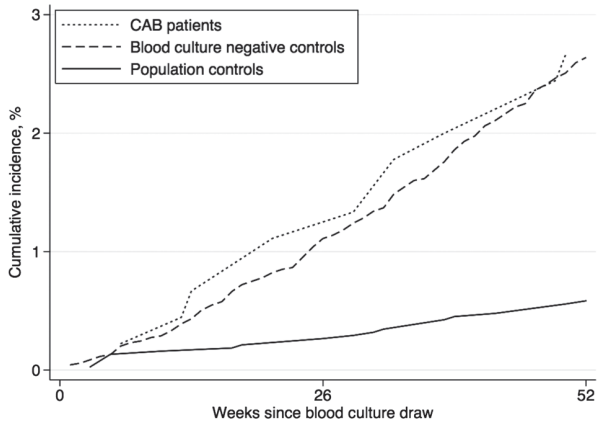


**Figure 2** Cumulative incidence of permanent disability pension in workforce patients with community-acquired bacteraemia (CAB), blood culture-negative controls, and population controls in North Denmark, 1996–2011.

(3.4%; table 3). Patients with *Staphylococcus aureus* bacteraemia and polymicrobial bacteraemia had the highest levels of comorbidity (71% with CCI score of 0 in both groups) and also had the highest 30-day mortality (*S aureus*, 3/31, 9.7% and polymicrobial CAB, 3/14, 21.4%) and 1-year mortality (*S aureus*, 5/31, 16.1% and polymicrobial CAB, 4/14, 28.6%). In these small subgroups with high mortality, a high proportion of patients were on sick leave for a long time after infection (eg, 6/31, 19.4% of patients with *S aureus* infection were on sick leave for 52 consecutive weeks) but the 1-year risk for disability pension was 0. Irrespective of type of focus, CAB was associated with an increased risk for long-term sick leave when compared with culture-negative controls (eg, 40.2% of patients with CAB with respiratory tract infection were on sick leave for at least 4 weeks, adjusted RR, 1.51; 95% CI 1.26 to 1.83). Mortality was particularly high among patients with an unknown focus or more than one focus of infection (30-day mortality of 14.3%), see online supplementary table S3.

When stratifying analyses according to age group and employment status, older age and unemployment were associated with the highest absolute risks for disability pension and mortality (see online supplementary table S4). When comparing patients with CAB to blood culture-negative controls in stratified analyses, CAB was consistently associated with an increased risk for 4-week sick leave, 52-week sick leave and for 30-day and 1-year mortality, table 4 in supplementary S4.

During 2003 to 2011, the association between CAB and study outcomes remained essentially unchanged when compared with culture-negative controls (4-week sick leave 37.7% vs 23.6%, adjusted RR, 1.40; 95% CI 1.18 to 1.66; 1-year disability pension 3.4% vs 2.4%, adjusted RR, 1.58; 95% CI 0.54 to 4.59; 30-day mortality 3.0% vs 1.1%, adjusted RR, 2.09; 95% CI 0.76 to 5.70 and 1-year mortality 7.6% vs 3.3%, adjusted RR, 2.14; 95% CI 1.29 to 3.52).

Analyses restricted to 352 patients with CAB and 4078 culture-negative controls who had no previous antibiotic therapy (blood culture draw performed on admission and no recent out-of-hospital antibiotic use) did not materially influence the association between CAB and 4-week sick leave (adjusted RR, 1.71; 95% CI 1.48 to 1.97), 1-year disability pension (adjusted RR, 1.00; 95% CI 0.06 to 16.82), 30-day mortality (adjusted RR, 1.73; 95% CI 0.68 to 4.41) or 1-year mortality (adjusted RR, 1.70; 95% CI 1.02 to 2.84).

## DISCUSSION

In this large population-based cohort study of adults in the Danish workforce, we found that CAB was associated with a 40% risk for sick leave of at least 4 weeks duration and a nearly 6% risk for 52 weeks of sick leave. Compared with blood culture-negative controls, CAB increased the risk for long-term sick leave by 50–100% but the risk for permanent disability pension within 1 year was similar (~2.7%). Compared with population controls, CAB was associated with a fivefold increased risk for disability pension. While CAB more than doubled the 30-day risk for death and remained associated with a 70% increased risk for death within 1 year when compared with culture-negative controls, the absolute mortality was low after CAB in this study (4% within 30 days and 8% within 1 year). One year after the blood culture draw, nearly 80% of patients with CAB were back in the workforce.

We are not aware of any study that has examined duration of sick leave and risk for permanent disability pension after CAB. Very few previous studies have examined return to work after severe bacterial infection, and in most of these studies this outcome has been a secondary focus and examined in small subgroups of included patients. Poulsen *et al*[9] conducted a study of 172 Danish intensive care unit (ICU) patients with septic shock, and examined physical outcomes in a subgroup of 70 of 80 1-year survivors. At 1-year follow-up, 43% (10/23) of previously employed patients had returned to work, which is considerably fewer than the approximately 80% of patients with CAB who were in the workforce after 1 year in our study. The discrepancy may relate to ICU patients with septic shock being more critically ill than average patients with CAB and it may be related to older study participants in the ICU-based study who may have had the possibility of public retirement pension during the follow-up. In a study from Scotland, Cuthbertson *et al*[10] followed 439 ICU patients with sepsis and asked employment-related questions to survivors at 3.5 and 5 years. At 3.5 years, 93% (53/62 respondents) of previously employed patients had returned to work, and at 5 years the proportion was 75% (46/58 respondents) with some reduction in employment due to retirement.

Return to work after community-acquired pneumonia has been described by Fine *et al*[8] who followed 2287 patients for 30 days, including 539 previously employed

**Table 3** Risk for sick leave, permanent disability pension and mortality in CAB by aetiological agent compared with blood culture-negative controls

| | *Streptococcus pneumoniae* (N=177) | Other Gram-positive (N=78) | *Escherichia coli* (N=103) | Other Gram-negative (N=78) | Polymicrobial (N=14) |
|---|---|---|---|---|---|
| Sick leave, ≥4 weeks | | | | | |
| Risk, n (% of N) | 75 (42.4) | 44 (56.4) | 30 (29.1) | 30 (38.5) | 2 (14.3) |
| Adj. RD % (95% CI)* | 15.3 (8.0 to 22.6) | 30.1 (19.2 to 41.1) | 3.5 (−5.2 to 12.2) | 12.8 (2.1 to 23.5) | −6.4 (−24.3 to 11.5) |
| Adj. RR (95% CI)* | 1.57 (1.32 to 1.87) | 2.03 (1.66 to 2.49) | 1.14 (0.84 to 1.54) | 1.46 (1.10 to 1.93) | 0.55 (0.15 to 2.03) |
| Sick leave, ≥52 weeks | | | | | |
| Risk, n (% of N) | 9 (5.1) | 11 (14.1) | 2 (1.9) | 3 (3.8) | 1 (7.1) |
| Adj. RD % (95% CI)* | 1.9 (−1.3 to 5.0) | 11.5 (3.7 to 19.3) | −1.2 (−1.8 to −0.1) | 1.3 (−3.0 to 5.6) | 5.9 (−8.7 to 20.4) |
| Adj. RR (95% CI)* | 1.73 (0.90 to 3.33) | 4.65 (2.62 to 8.24) | 0.64 (0.16 to 2.56) | 1.33 (0.44 to 4.07) | 2.49 (0.36 to 17.29) |
| Disability pension, 1 year | | | | | |
| Risk, n (% of N) | 6 (3.4) | 2 (2.6) | 2 (1.9) | 2 (2.6) | 0 (0) |
| Adj. RD % (95% CI)* | 0.5 (−2.2 to 3.1) | −0.8 (−4.3 to 2.6) | −1.7 (4.5 to 1.0) | −0.5 (−3.9 to 2.9) | −3.1 (−4.7 to −1.5) |
| Adj. RR (95% CI)* | 1.63 (0.66 to 4.05) | 0.79 (0.18 to 3.54) | 0.35 (0.07 to 4.75) | 1.19 (0.30 to 4.75) | – |
| Mortality, 30 days | | | | | |
| Risk, n (% of N) | 3 (1.7) | 5 (6.4) | 5 (4.9) | 2 (2.6) | 3 (21.4) |
| Adj. RD % (95% CI)* | −0.1 (−2.1 to 1.8) | 4.6 (−0.8 to 10.0) | 3.0 (−1.2 to 7.2) | 0.8 (−2.6 to 4.3) | 20.0 (−1.5 to 41.5) |
| Adj. RR (95% CI)* | 1.05 (0.30 to 3.67) | 3.82 (1.49 to 9.81) | 1.90 (0.55 to 6.61) | 1.81 (0.45 to 7.34) | 13.97 (3.26 to 59.86) |
| Mortality, 1 year | | | | | |
| Risk, n (% of N) | 8 (4.5) | 12 (15.4) | 9 (8.7) | 3 (3.8) | 4 (28.6) |
| Adj. RD % (95% CI)* | −0.1 (−3.2 to 3.0) | 10.1 (2.4 to 17.8) | 3.6 (−1.6 to 8.7) | −0.8 (−5.0 to 3.5) | 23.8 (−0.4 to 48.0) |
| Adj. RR (95% CI)* | 0.81 (0.36 to 1.81) | 3.46 (2.22 to 5.38) | 1.97 (1.04 to 3.73) | 0.67 (0.19 to 2.35) | 3.55 (0.78 to 16.10) |

*Risk difference and relative risk pertaining to patients with CAB versus blood culture-negative controls (absolute risk estimates for controls can be found in table 2). Risk difference and relative risk computed by log-binomial regression (sick leave analyses) and regression analyses based on pseudo-observations (disability pension and mortality analyses). Estimates are Adj for age, gender, Charlson comorbidity score and alcoholism-related disease (due to few events, 30-day mortality estimates are Adj for age and gender only).
Adj, adjusted; CAB, community-acquired bacteraemia.

outpatients and 218 previously employed inpatients. Among less sick outpatients, nearly all (95.3%) of the previously employed had returned to work at day 30. In contrast, 68.1% of previously employed inpatients had returned to work at day 30 and the median time to return to work was 22 days, which is comparable with our findings of a median of 4 weeks on sick leave after CAB.

This is also the first study to examine the mortality after CAB in relatively healthy adults who belong to the workforce immediately before onset of CAB. Some previous cohort studies have examined mortality after CAB according to age group. Søgaard *et al*[3] found a 30-day mortality of 11% in 15–64-year-old patients with CAB, and Leibovici *et al*[5] found a 1-year mortality of 29% after bacteraemia in patients with 18–60 years of age. In a Danish population-based cohort study of 8653 bacteraemia patients aged 30–65 years, Koch *et al*[7] examined mortality according to socioeconomic status and found the highest 30-day mortality (19.7%) in the subgroup with most disability pensioners (the lowest income group). As we excluded nearly 30% of 20–58-year-old patients with CAB because of disability pension or sick leave, the higher short-term and long-term mortality described in previous studies is likely due to the inclusion of multimorbid patients outside the workforce. Our study supports previous studies that have examined the economic costs of sepsis and bacteraemia and found that the indirect costs (productivity loss due to mortality, temporary and permanent morbidity) may outweigh the direct costs (eg, medical expenses associated with hospitalisation) by as much as twofold, and that these severe infections place a high economic burden on individuals, families and the society.[26 27]

Physical and psychological stress is put on hospitalised patients with CAB, and may endure beyond the duration of hospitalisation. In surviving working-age patients, this may lead to prolonged sick leave or permanent disability. During hospitalisation, patients with severe infections are at risk for complications, including some that may be long-lasting/permanent (eg, renal impairment and cardiovascular disease).[28 29] Patients with severe infections may occasionally have abnormal vital signs and ongoing inflammatory activity at discharge.[30] After discharge, they remain at high risk for mortality and for other diseases such as cardiovascular events, and may experience worsened cognitive status and quality of life.[29 31–33]

This study has several strengths. It is large, including more than 10 000 study participants, and it has complete and long follow-up of all study participants. Moreover, data were obtained from high-quality databases, in which they were prospectively recorded, which limits recall bias.

However, this study also has limitations. Sick leave of short duration is under-reported to the social services in

Denmark and we may, therefore, underestimate the true duration of sick leave in hospitalised participants, especially the lower quartile values of sick leave (0 weeks in both groups). However, data on sick leave of at least 15 days duration have been found to be highly valid.[34] Another limitation is that Danes in their late 50s who have declining health may wait for voluntary early retirement instead of applying for disability pension.[35] Since patients with CAB were older than controls, this could lead to falsely increased risk estimates for long-term sick leave and falsely decreased risk estimates for disability pension. In analyses of mortality by focus of infection, immortal-time bias may have prompted falsely low risks of death in patients with an identified focus of infection (and a high risk of death in patients with an unknown focus). Moreover, although we adjusted for many potential confounders, residual and unmeasured confounding is a possibility. Finally, findings from the present study may not directly apply to other countries with dissimilar laws and regulations regarding the job market and social benefits.

In conclusion, our study highlights that CAB is a debilitating condition in adults who are part of the workforce. CAB is associated with long duration of sick leave, but in this relatively healthy population, a low risk for permanent disability and death.

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**Contributors** MD-P, KK, RWT, HCS and HN made substantial contributions to study conception and design, interpreted the data and critically revised the manuscript. MDP, RWT and HCS were responsible for acquisition of data. MDP analysed the data and drafted the manuscript. All authors approved the final version of the manuscript.

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**Competing interests** None.

**Ethics approval** The study was approved by the Danish Data Protection Agency (2011-41-5864).

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**Data sharing statement** No additional data are available.



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Supplement to:

**The effect of community-acquired bacteraemia on return to workforce, risk of sick leave, permanent disability pension and death: A Danish population-based cohort study**

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**Supplement, Table 1.** DREAM codes (version 28) used in the study.

**Supplement, Table 2.** ICD and ATC codes used in the study.

**Supplement, Table 3.** Bacteremia patients' risk for sick leave, permanent disability pension, and mortality by focus of infection compared to blood culture negative controls.

**Supplement, Table 4**. Risk for sick leave, disability pension, and mortality by age, gender, and employment status.

**Supplement, Figure 1.** Flow chart of hospitalised medical study subjects with first-time blood cultures, North Denmark, 1996-2010.

**Supplement, Figure 2.** Cumulative mortality in workforce CAB patients, blood culture negative controls, and population controls, North Denmark, 1996-2011.

**Supplement, Table 1.** DREAM codes (version 28) used in the study.

| DREAM category | Subcategory | Transfer payment, examples | DREAM codes |
|---|---|---|---|
| Work-ready | Employed | No transfer payment, leave, apprentice (adult), student support, maternity leave payment | No code if no transfer payment, 121-126, 412-413, 511-522, 611, 651-661, 881 |
| | Unemployed | Unemployment benefit, vocational pre-rehabilitation and rehabilitation benefit | 111-113, 130-138, 211-299, 730-738, 750,752-758, 760, 762-768 |
| Sick leave | | Sickness absence benefit | 890, 892-899 |
| Permanent disability pension | | ”Flex-job” payment | 740-748, 771-774 |
| | | Disability pension | 781-783 |

During the study period, Danes who were ≥60 years of age could go on voluntary early retirement pension (“efterløn”), and those who were ≥65 years of age could go on public retirement pension. Since we studied subjects 20-58 years of age, retirement codes are not detailed here. All DREAM codes are detailed elsewhere (http://www.dst.dk/da/TilSalg/Forskningsservice/Data/Andre_Styrelser.aspx)

**Supplement, Table 2.** ICD and ATC codes used in the study

| **Comorbidities (previous)** | **ICD codes** |
|---|---|
| Myocardial infarction | ICD-8: 410; ICD-10: I21-I23 |
| Cerebrovascular disease | ICD-8: 430-438; ICD-10: I60-I69, G45, G46 |
| Congestive heart failure | ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49, ICD-10: I11.0, I13.0, I13.2, I50 |
| Peripheral vascular disease | ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77 |
| Hemiplegia | ICD-8: 344; ICD-10: G81, G82 |
| Diabetes | ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9; ATC: A10A, A10B |
| Diabetes with end-organ damage | ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10: E10.2-E10.8, E11.2-E11.8 |
| Chronic pulmonary disease | ICD-8: 490-493, 515-518; ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3; ATC: R03 |
| Any tumor | ICD-8: 140-194; ICD-10: C00-C75 |
| Leukemia | ICD-8: 204-207; ICD-10: C91-C95 |
| Lymphoma | ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96 |
| Metastatic solid tumor | ICD-8: 195-199; ICD-10: C76-C80 |
| Connective tissue disease | ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30-M36, D86 |
| Ulcer disease | ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28 |
| Moderate to severe renal disease | ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 |
| Mild liver disease | ICD-8: 571, 573.01, 573.04; ICD-10: B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0 |
| Moderate to severe liver disease | ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 |

| | |
|---|---|
| Alcoholism-related disease | ICD-8: 291, 303, 979, 980, 577.10; ICD-10: F.10, K29.2, K.86.0, Z72.1, R78.0, T51; ATC: N07BB01 |
| Dementia | ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30 |
| AIDS | ICD-8: 079.83; ICD-10: B21-B24 |
| **Medication use** | **ATC codes (any previous use unless specified)** |
| Drugs for cardiovascular disease | |
| Nitrates | C01DA (if ≥2 prescriptions are registered). |
| Diuretics | C03 |
| Beta-blockers | C07 |
| Calcium-channel antagonists | C08 |
| ACE inhibitors | C09 (C02 before 1 January 1996) |
| Aspirin | B01AC06, N02BA01 (previous 125 days) |
| Antidiabetics | A10A, A10B |
| Inhaled drugs for pulmonary disease | R03 |
| Disulfiram | N07BB01 |
| Systemic antibiotics | J01 (past 4 weeks) |

**Supplement, Table 3.** Bacteremia patients' risk for sick leave, permanent disability pension, and mortality by focus of infection compared to blood culture negative controls.

| | Respiratory tract infection (N=164) | Urinary tract infection (N=93) | Miscellaneous (N=144) | Unknown or multiple (N=49) |
|---|---|---|---|---|
| Sick leave, ≥4 weeks | | | | |
| Risk, n (% of N) | 66 (40.2) | 26 (28.0) | 72 (50.0) | 17 (34.7) |
| Adj. RD % (95% CI)[a] | 13.6 (6.2-21.2) | 2.1 (-7.0-11.2) | 24.1 (15.9-32.2) | 7.9 (-5.3-21.0) |
| Adj. RR (95% CI)[a] | 1.51 (1.26-1.83) | 1.05 (0.76-1.46) | 1.87 (1.58-2.21) | 1.32 (0.90-1.92) |
| Sick leave, ≥52 weeks | | | | |
| Risk, n (% of N) | 7 (4.3) | 1 (1.1) | 16 (11.1) | 2 (7.1) |
| Adj. RD % (95% CI)[a] | 1.1 (-1.8-4.1) | -2.0 (-2.4--1.6) | 8.3 (3.1-13.4) | 1.2 (-4.4-6.7) |
| Adj. RR (95% CI)[a] | 1.73 (0.90-3.33) | 4.65 (2.62-8.24) | 1.33 (0.44-4.07) | 2.49 (0.36-17.29) |
| Disability pension, 1-year | | | | |
| Risk, n (% of N) | 6 (3.7) | 2 (2.2) | 2 (1.4) | 2 (4.1) |
| Adj. RD % (95% CI)[a] | 0.7 (-2.2-3.5) | -1.2 (-4.2-1.8) | -1.6 (-3.5-3.4) | -0.2 (-5.6-5.2) |
| Adj. RR (95% CI)[a] | 1.40 (0.52-3.77) | 0.52 (0.11-2.52) | 0.63 (0.15-2.70) | 1.18 (0.29-4.85) |
| Mortality, 30-day | | | | |
| Risk, n (% of N) | 3 (1.8) | 0 (0) | 8 (5.6) | 7 (14.3) |
| Adj. RD % (95% CI)[a] | 0.1 (-2.0-2.2) | -1.9 (-2.3--1.4) | 3.8 (0.1-7.5) | 12.4 (2.6-22.2) |
| Adj. RR (95% CI)[a] | 0.47 (0.09-2.35) | - | 3.39 (1.55-7.42) | 10.14 (3.82-26.89) |
| Mortality, 1-year | | | | |
| Risk, n (% of N) | 8 (4.9) | 2 (2.2) | 15 (10.4) | 11 (22.5) |
| Adj. RD % (95% CI)[a] | -0.1 (-3.2-3.0) | -2.6 (-5.4-3.2) | 5.8 (0.9-10.7) | 16.0 (4.6-27.5) |
| Adj. RR (95% CI)[a] | 1.26 (0.65-2.44) | 0.68 (0.17-2.83) | 2.46 (1.53-3.97) | 3.66 (1.76-7.64) |

Abbreviations: CAB, community-acquired bacteraemia. Adj., adjusted. [a]Risk difference and relative risk pertains to CAB patients versus blood culture negative controls (absolute risk estimates for controls can be found in main manuscript, Table 2). Risk difference and relative risk computed by log-binomial regression (sick leave analyses) and regression analyses based on pseudo-observations (disability pension and mortality analyses). Estimates are adjusted for age, gender, Charlson comorbidity score, and alcoholism-related disease (due to few events, 30 day mortality estimates are adjusted for age and gender only).

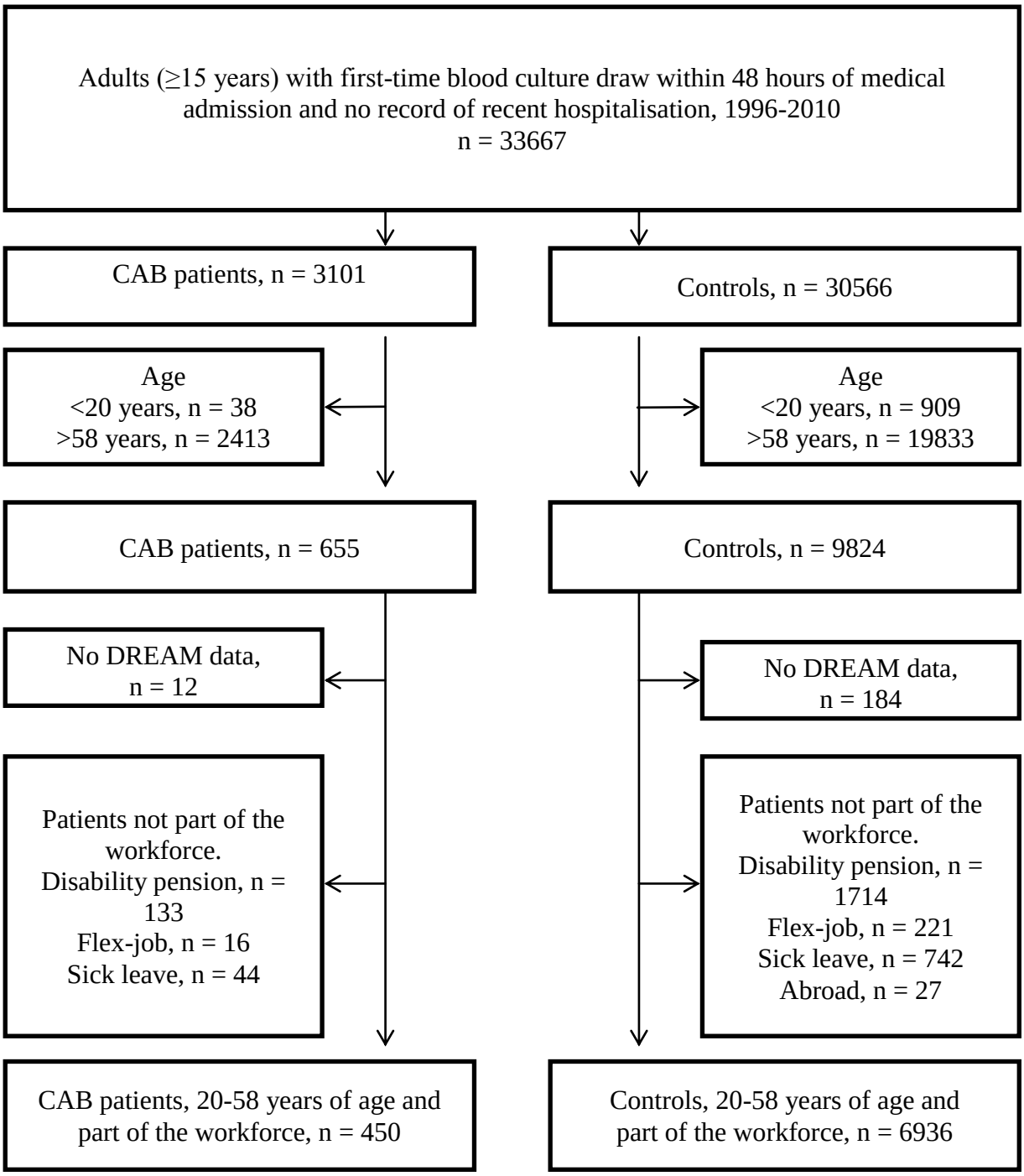
**Supplement, Table 4**. Risk for sick leave, disability pension, and mortality by age, gender, and employment status for community-acquired bacteraemia patients and blood culture negative controls.

| | Age group, years | | | Gender | | Employment status, 4 weeks before blood culture draw | | |
|---|---|---|---|---|---|---|---|---|
| | 20-34 | 35-49 | 50-58 | Female | Male | Employed[a] | Unemployed[b] | Sick leave[c] |
| Sick leave ≥4 weeks | | | | | | | | |
| Risk, CAB pts. | 28/85 (32.9) | 67/178 (37.6) | 86/187 (46.0) | 79/224 (35.3) | 102/226 (45.1) | 98/281 (34.9) | 28/107 (26.2) | 55/62 (88.7) |
| Risk, Controls | 335/2338 (14.3) | 721/2676 (26.9) | 602/1922 (31.3) | 707/3100 (22.8) | 951/3836 (24.8) | 843/4624 (18.2) | 200/1384 (14.5) | 615/928 (66.3) |
| Adj. RR (CI)[d] | 2.29 (1.68-3.13) | 1.39 (1.14-1.70) | 1.47 (1.24-1.74) | 1.33 (1.11-1.61) | 1.66 (1.42-1.93) | 1.71 (1.44-2.03) | 1.81 (1.37-2.40) | 1.23 (1.12-1.36) |
| Sick leave ≥52 weeks | | | | | | | | |
| Risk, CAB pts. | 6/85 (7.1) | 5/178 (2.8) | 15/187 (8.0) | 11/224 (4.9) | 15/226 (6.6) | 11/281 (3.9) | 6/107 (5.6) | 9/62 (14.5) |
| Risk, Controls | 29/2338 (1.2) | 80/2676 (3.0) | 72/1922 (3.8) | 77/3100 (2.5) | 104/3836 (2.7) | 78/4624 (1.7) | 29/1384 (2.1) | 74/928 (8.0) |
| Adj. RR (CI)[d] | 5.69 (2.43-3.34) | 0.94 (0.38-2.28) | 2.16 (1.27-3.70) | 1.76 (0.95-3.27) | 2.17 (1.28-2.67) | 1.97 (1.06-3.68) | 2.33 (0.99-5.49) | 1.74 (0.91-3.32) |
| 1-year disability pension | | | | | | | | |
| Risk, CAB pts. | 0/85 (0) | 5/178 (2.8) | 7/187 (3.7) | 4/224 (1.8) | 8/226 (3.5) | 6/281 (2.1) | 5/107 (4.7) | 1/62 (1.6) |
| Risk, Controls | 20/2338 (0.9) | 69/2676 (2.6) | 94/1922 (4.9) | 81/3100 (2.6) | 102/3836 (2.7) | 69/4624 (1.5) | 102/1384 (7.4) | 12/928 (1.3) |
| Adj. RR (CI)[d] | - | 0.85 (0.22-3.34) | 0.97 (0.42-2.23) | 0.44 (0.13-1.51) | 1.45 (0.65-3.21) | 1.52 (0.52-4.35) | 0.54 (0.17-1.74) | 1.25[e] (0.16-9.45) |
| 30-day mortality | | | | | | | | |
| Risk, CAB pts. | 1/85 (1.2) | 7/178 (3.9) | 10/187 (5.4) | 8/224 (3.6) | 10/226 (4.4) | 10/281 (3.6) | 7/107 (6.5) | 1/62 (1.6) |
| Risk, Controls | 9/2338 | 36/2676 | 54/1922 | 44/3100 | 55/3836 | 55/4624 | 30/1384 | 14/928 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (0.4) | (1.4) | (2.8) | (1.4) | (1.4) | (1.2) | (2.2) | (1.5) |
| Adj. RR (CI)[d] | 3.01[e] (0.39-23.9) | 2.36 (0.82-6.81) | 1.87 (0.88-4.03) | 1.82 (0.61-5.40) | 2.53 (1.00-6.43) | 1.95 (0.89-4.28) | 2.63 (1.09-6.36) | 1.07[e] (0.14-8.00) |
| 1-year mortality | | | | | | | | |
| Risk, CAB pts. | 2/85 (2.4) | 11/178 (6.2) | 23/187 (12.3) | 16/224 (7.1) | 20/226 (8.8) | 19/281 (6.8) | 12/107 (11.2) | 5/62 (8.1) |
| Risk, Controls | 25/2338 (1.1) | 100/2676 (3.7) | 146/1922 (7.6) | 99/3100 (3.2) | 172/3836 (4.5) | 139/4624 (3.0) | 76/1384 (5.5) | 56/928 (6.0) |
| Adj. RR (CI)[d] | 2.19[e] (0.53-9.1) | 1.66 (0.86-3.20) | 1.59 (1.03-2.46) | 1.52 (0.93-2.49) | 1.73 (0.99-3.02) | 1.81 (1.06-3.08) | 1.59 (0.86-2.93) | 1.12 (0.42-3.00) |

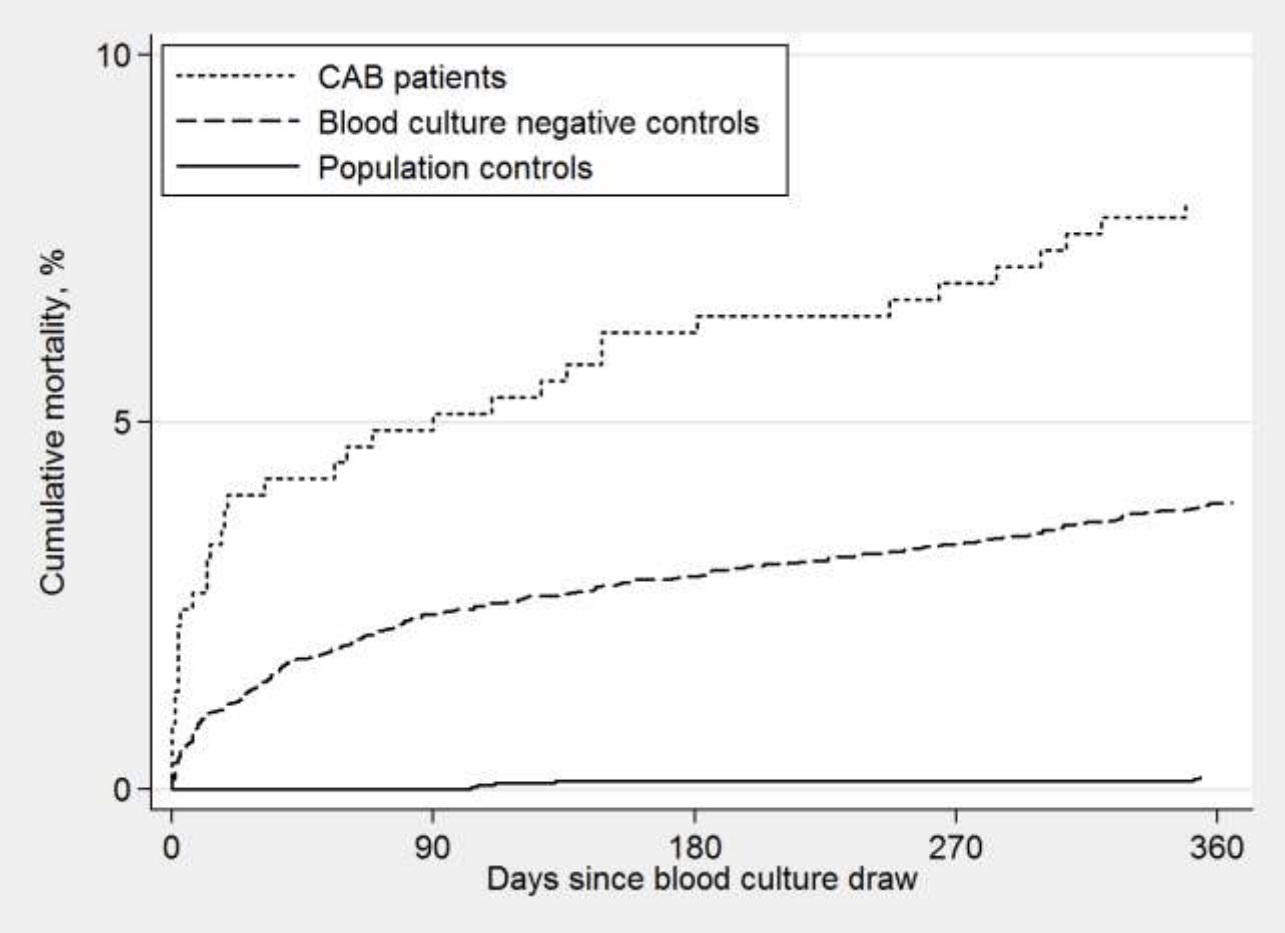
Abbreviations: Adj., adjusted. RR, relative risk. CI, confidence interval. [a]Subjects who were registered as employed and actively working during all 4 weeks before admission. [b]Subjects who spent all 4 weeks as unemployed (84.7%) and subjects who were employed/unemployed (15.3%). [c]Subjects who were on sick leave for a maximum of 3 weeks in the previous 4 weeks, and otherwise employed or unemployed. Absolute risk estimates "Risk" are n/N (%). [d]Relative risk estimates with 95% confidence intervals pertain to CAB patients versus blood culture negative controls, and are adjusted for age, gender, and Charlson comorbidity score. [e]Unadjusted estimates presented due to few events.

**Supplement, Figure 1.** Flow chart of hospitalised medical study subjects with first-time blood cultures, North Denmark, 1996-2010.




Abbreviations: CAB, community-acquired bacteraemia. Each CAB patient was matched to 10 population controls who had no recent hospital admission (previous 30 days) on year of birth, gender, and calendar-time (population controls had to be alive on the date of blood culture draw). Of these 4500 population controls some were excluded because of previous blood culture draw (n=132), age of 59 years (n=35), no DREAM data (n=99), or for not being part of the workforce in the previous four weeks (disability pension [n=336], long-term sick leave [88], abroad [55]) which left 3765 population controls for analysis.

**Supplement, Figure 2.** Cumulative mortality in workforce CAB patients, blood culture negative controls, and population controls, North Denmark, 1996-2011.



# Study IV

# Functional status and quality of life after community-acquired bacteraemia: A matched cohort study

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Key words: Sepsis, infection, quality of life, functional status, activities of daily living, epidemiology

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**Abstract.**

Objectives: Severe bacterial infections may have a prolonged negative effect on subsequent functional status and health-related quality of life (HRQOL). We studied patients for changes in functional status and HRQOL within 3 months of community-acquired bacteraemia (CAB) in comparison to blood culture negative controls.

Methods: Prospective matched cohort study at Aalborg University Hospital, North Denmark. We included clinically stabilized medical patients with first-time CAB and no recent cancer during June 2011 to June 2013. For each CAB patient, we included one acutely admitted blood culture-negative control patient, matched on age, gender, and duration of admission. Functional status and HRQOL before and after 3 months was assessed by Barthel-20 and EuroQol-5D (EQ-5D) questionnaires, respectively. We computed the risk for any deterioration in Barthel-20 score and EQ-5D index score and for ≥10 point deterioration in EQ-5D visual analogue scale (VAS) score. Regression analyses were used to assess adjusted relative risks (RR) with 95% confidence intervals (CIs).

Results: We included 71 CAB patients and 71 controls. After 3 months, 5 CAB patients (7%) and 3 controls (4%) had died while 98% of the remaining patients responded to follow-up questionnaires. Compared with controls, CAB was associated with an increased risk for deterioration in functional status from baseline to 3 months as assessed by Barthel-20 score (14% vs. 3%, adjusted RR, 5.1; CI, 1.2-22.3). HRQOL had become worse in 37% of CAB patients and 28% of controls by EQ-5D index score (adjusted RR, 1.3; CI, 0.8-2.1) and in 39 % of CAB patients and 27 % of controls by VAS (adjusted RR, 1.4; CI, 0.9-2.3).

Conclusion: CAB is associated with increased risk of reduced functional status 3 months post-admission when compared to blood culture negative controls, as well as a high risk for deterioration in HRQOL.

**Introduction.**

Hospitalisation for community-acquired bacteraemia (CAB) has increased by 50% since the mid 1990's [1]. Mortality after CAB is well-studied and has remained high [1,2] but less is known about non-death outcomes after CAB. Functional status and health-related quality of life (HRQOL) are important components of individual's overall health and well-being and therefore of import to patients, next of kin, and health care providers. Functional status and HRQOL has been found to be low at various time points from 3 months to 6 years after hospitalisation for suspected Gram-negative bacteraemia, sepsis, and septic shock when compared to general population norms [3–6]. Studies from the US have found that functional status may deteriorate from before to after hospitalisation for severe sepsis and pneumonia [7, 8]. Only a few longitudinal studies have examined whether severe sepsis and septic shock treated in medical and surgical ICU's affect any change in HRQOL (pre-admission to post-discharge) and they have found conflicting results [9–11]. Most previous studies have lacked information on preadmission functional status and HRQOL which impedes any assessment of a cause-and-effect relationship between severe acute infection and functional status/HRQOL. Moreover, because most previous studies have included subjects with nosocomial infection and lacked a hospitalised comparison group, low functional status/HRQOL after infection in these studies could just as well be attributed to non-infectious disease processes prompting hospital admission or the hospitalisation *per se*. To our knowledge, no study has examined whether CAB in medical patients has any effect on functional status and HRQOL. Our aim was to examine changes in functional status and HRQOL from pre-admission to 3-month follow-up in patients hospitalised with first-time CAB in comparison with hospitalised patients with negative blood cultures.

**Materials and Methods.**

We designed a prospectively conducted matched cohort study at Aalborg University Hospital which is an 800-bed community hospital for the surrounding area and the one referral hospital in North Denmark. Study subjects were included from subspecialty wards under the hospitals Department of Medicine (152 beds) that directly partakes in acute medical admissions (Infectious Diseases, Haematology, Pulmonology, Nephrology, Gastroenterology, and Endocrinology) from June 1 2011 to June 30 2013 and were followed for 3 months. Throughout the study period, the hospitals Department of Clinical Microbiology performed all blood culture analyses in the region using the automated BacT/Alert® system (bioMérieux, Marcy l'Etoile, France) [12]. Its regional microbiological information system (ADBakt, Sköldinge, Sweden) was used for information on ongoing blood cultures, including basic information on potential study subjects (patient age, gender, ward, and date of blood culture draw). For the present study we defined community-acquired bacteraemia as the presence of viable bacteria or fungi in the bloodstream, evidenced by blood cultures performed within 48 hours of admission, among patients who had not been admitted to a hospital within the previous 30 days. In the daily clinical setting, the diagnosis of bacteraemia was based on joint clinical and microbiological assessment, and required that contamination had been effectively ruled out [13].

This study was approved by the Science Ethical Committee (N-20100102) and the Danish Data Protection Agency (2011-41-5864).

Study subjects and follow-up.

Eligibility criteria for study inclusion were age ≥18 years, medical hospitalisation, no hospital stay within the previous 30 days, no history of bacteraemia, no cancer within the last 10 years, and blood culture draw within 48 hours of admission. Moreover, patients had to be clinically stable (not

destined to die during the hospitalisation as judged by treating physicians) and included within 7 days of blood culture draw. We first included CAB patients. Because pre-existing disease and acute hospitalisation in itself may affect functional status and HRQOL, we then used the microbiological information system to randomly select one blood culture-negative control patient matched for each CAB patient. Patients with CAB and controls were matched on age (18-59, 60-79, 80+ years), gender, and time since blood culture draw (+/- 2 days). The microbiological information system was used to screen for potential CAB and control subjects and for information on age, gender, type of hospitalisation (medical/surgical), and date of blood culture draw. Next, we used the electronic patient files to further assess whether potential study subjects satisfied eligibility criteria. Eligible patients were contacted by one of the authors (MDP) for study inclusion if alive and not discharged from the Department of Medicine. For patients who were unable to sign consent forms and answer questionnaires, we contacted next of kin (for consent and proxy responses) and the patients' general practitioner (for consent). At baseline, we interviewed each study subject and used questionnaires to assess pre-admission HRQOL and functional status. We also registered information on the infectious agent(s), focus of the infection, pre-existing disease, medication and alcohol use, smoking history, vital signs on day of blood culture draw, weight, height, and findings from diagnostic tests (microbiology, biochemistry, and radiology). Study subjects were contacted by telephone (by MDP) 3 months after blood culture draw for renewed questionnaire assessment of functional status and HRQOL. Questionnaires were mailed to those who could not be reached by phone.

Questionnaires.

We used a questionnaire-version of the Barthel-20 index for information on functional status [14–16] and the European Quality of Life measure 3 level version questionnaire (EQ-5D) for

information on HRQOL [15, 17, 18]. The Barthel-20 index of activities of daily living (ADL) is widely used as a measure of functional status. It includes 10 items (bowel control, bladder control, grooming, toileting, bathing, dressing, feeding, walking on level surface, walking on stairs, and moving from bed to chair) each of which is scored. These scores are then added to give a total Barthel-20 score (20 = fully independent, 0 = fully dependent on help from others). The EQ-5D questionnaire is a generic measure of HRQOL which consists of a descriptive system and a visual analogue scale (VAS). The first part of the EQ-5D questionnaire, the descriptive system, comprises five different dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each divided into three levels (1 = no problems, 2 = some problems, and 3 = severe problems). Hence, 243 health states exists (= $5^3$), each of which may be converted into a single summary EQ-5D index score by applying preference weights derived from the background population [19]. In Denmark, the EQ-5D index score ranges from +1 ("no problems" in all dimensions) to -0.624 ("severe problems" in all dimensions) [19]. The second part of the questionnaire, the VAS, depicts a 20 cm vertical line which ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Barthel-20 and EQ-5D have previously been translated into Danish and are recommended for assessment of functional status and HRQOL in Denmark [16, 19, 20]. Baseline questionnaires encouraged study subjects to recall their health/functional status as it were 1 month prior to hospitalization. In contrast, at 3 months of follow-up, questionnaires pertained to the day that contact was made. At follow-up, study subjects were asked if their functional status and health status was unchanged, worse, or better compared with baseline (here called "Patient's report"). Before initiating the study, we performed a pilot study (N = 5) which indicated that a personal bedside interview with each patient was the best way to attain responses from hospitalised and bedridden acutely ill patients. Therefore, we used the reliable telephone interview script version of EQ-5D for personal interviews at baseline and during follow-up [18, 21].

Statistics.

EpiData Entry 3.1 (The EpiData Assoc., Odense, Denmark) was used for data entry and Stata 11.2 (Stata Corp., College Station, TX) was used for all data analyses. We used the "eq5d" command in Sata to compute EQ-5D index scores [22]. Next, we computed the absolute risk of deterioration in functional status as assessed by Barthel-20 (a lower Barthel-20 index score) and HRQOL as assessed by EQ-5D (a lower EQ-5D index score, a drop ≥10 in EQ-5D VAS score) at 3 months compared with baseline. We also computed the risk of a worse functional status and HRQOL at follow-up compared with baseline according to the patients report. Subjects who were lost to follow-up (1 in each group) were assumed to have unchanged functional status and HRQOL. Next, we used log-binomial regression [23] to compute risk difference and relative risk of deterioration in functional status and HRQOL for CAB patients vs. controls with 95% confidence intervals (95% CIs). Thus, risk comparisons were between groups and not between individual matched pairs. Regression models were adjusted (adj.) for age, gender, and any comorbidity (yes/no). Among study subjects who responded to questionnaires at baseline and at follow-up (i.e. those not dead or lost to follow-up), we used Spearman's rank correlation coefficient to examine the association between deterioration in Barthel-20/EQ-5D scores and patient's report of a worse functional status/HRQOL at follow-up compared with baseline. For CAB patients and controls, we computed the median and inter-quartile range (IQR) of EQ-5D index score, EQ-5D VAS score, and Barthel-20 index score at baseline and at follow-up. Box plots were used to depict the distributions (median, IQR, and range) of EQ-VAS scores and EQ-5D index scores at baseline and at follow-up for patients with CAB and controls who responded to baseline and follow-up questionnaires. The Wilcoxon signed rank test was used for within group comparisons of baseline and follow-up scores (Barthel-20, EQ-5D index, EQ-5D VAS). Finally, for each group we used the McNemar test to examine whether the proportion of subjects who needed any help in Barthel-20 items and had any

problems in EQ-5D dimensions was greater at follow-up than at baseline (presented as ratios of proportions with 95% CIs).

## RESULTS

In this study we included 71 CAB patients and 71 matched culture-negative controls, see Figure 1. Among CAB patients, the most common aetiological agents were *Escherichia coli* (33%), *Streptococcus pneumoniae* (27%), beta-haemolytic streptococci (11%), and *Staphylococcus aureus* (10%) and the most common confirmed infectious foci were in the urinary tract (40%), lungs (27%), and skin/soft tissue, bone or joint (11%). In both groups the median time from admission to study inclusion and time from blood culture draw to inclusion was 4 days (IQR 3-5). CAB patients and controls were of similar age (63 vs. 64 years) and had a similar functional status as assessed by Barthel-20 score before hospitalisation (median Barthel-20 index score of 20 [range 1-20] for CAB patients and median score 20 [range 2-20] for controls), see Table 1. Still, the burden of pre-existing disease was lower among CAB patients and more CAB patients than controls were previously healthy (23% vs. 10%) and employed before admission (38% vs. 24%). Moreover, fewer patients with CAB lived in retirement homes or nursing homes than controls (6% vs. 8%). Few baseline questionnaires (2%) were completed by proxies. At 3 month follow-up, 1 patient in each group did not respond to telephone calls and mailed questionnaires and 7% (5/71) of patients with CAB and 4% (3/71) of controls had died (Figure 1).

### Functional status

At 3-month follow-up, functional status (Barthel-20 score) had deteriorated in 14% of CAB patients vs. 3% of controls (adj. RR, 5.1; 95% CI 1.2-22.3; Table 2). According to patients' reports, 9% of CAB patients and 3% of controls had a worse functional status at follow-up compared with baseline (Table 2). Deterioration in Barthel-20 score was associated with patient's report of deterioration in functional status (Spearman's rho = 0.58; $p < 0.0001$). For the 65 CAB patients and 67 controls who responded to questionnaires at baseline and at 3 months, functional status as assessed by Barthel-20

score was similar at baseline and at follow-up (patients with CAB, median score at baseline, 20 [range 7-20] vs. median at follow-up, 20 [range 0-20]; p=0.10, and controls, median score at baseline, 20 [range 2-20] vs. median at follow-up, 20 [range 3-20]; p=0.09). Still, for all Barthel-20 items, except walking on stairs, the proportion of CAB patients who needed assistance was greater at follow-up than at baseline (Table 3) and for most items the proportion was >2-fold greater, e.g. 2.3-fold more CAB patients needed help with bathing at follow-up compared with baseline (95% CI 1.1-4.7). In contrast, the proportion of controls who needed help with Barthel-20 items was similar at baseline and at follow-up (Table 3).

**HRQOL**

The 3-month risk for deterioration of EQ-5D index and VAS score (≥10 point reduction) was higher among CAB patients, 37% and 39%, than among controls, 28% and 27%, although the difference was not statistically significant, see Table 2. At follow-up, 32 % of patients with CAB and 18 % of controls reported that their HRQOL had deteriorated compared with baseline (see estimates pertaining to "Patient's report" in Table 2). Patient's report of deterioration in health status was associated with deterioration in EQ-5D scores (EQ-5D index score, Spearman's rho = 0.27, p = 0.002, and ≥10 points in EQ-5D VAS score, Spearman's rho = 0.18, p = 0.03).

EQ-5D index score and EQ-5D VAS score medians and IQRs for patients with CAB and controls who responded to baseline and follow-up questionnaires appear in Figure 2. Both EQ-5D index and EQ-5D VAS scores were lower at follow-up compared with baseline for the 65 CAB patients (EQ-5D index score, p = 0.01, and, EQ-5D VAS score, p = 0.07). In contrast, for the 67 controls the EQ-5D index score had improved at follow-up (p = 0.04) and the EQ-5D VAS score was similar at baseline and follow-up (p = 0.77), see Figure 2. At follow-up, the proportion of patients with CAB with HRQOL problems was increased in all five EQ-5D dimensions compared with baseline (Table

3) and significantly so for usual activities and pain/discomfort (ratio of 2.3, 95% CI 1.4-3.6, and, ratio of 1.7, 95% CI 1.2-2.5). For controls a similar proportion of subjects had problems in EQ-5D dimensions at baseline and at follow-up (Table 3).

**Discussion.**

In this prospectively conducted cohort study we found that first-time community-acquired bacteraemia was associated with a 14% risk for deterioration in functional status (assessed by Barthel-20) and a nearly 40% risk for deterioration in HRQOL (assessed by EQ-5D) from pre-admission to 3 month follow-up. Moreover, the risk for deterioration in functional status was 5-fold higher in patients with CAB than among matched blood culture-negative controls. Among patients with CAB, the proportion of patients who needed help with activities of daily living and who had problems with performing usual activities had approximately doubled at follow-up compared with baseline. In addition, the proportion of CAB patients with pain/discomfort had increased by 70% from baseline to follow-up.

To our knowledge, this is the first prospectively conducted cohort study to assess changes in functional status and HRQOL after microbiologically verified community-acquired infection. Previous literature on the subject is mostly confined to studies on patients with non-microbiologically verified sepsis treated in an ICU setting. In 1995, Perl et al. reported on long-term survival and function in 101 patients with suspected Gram-negative bacteraemia of whom 66% had positive blood cultures. Functional status and HRQOL was assessed in 38 of 40 survivors who were contacted from approximately 2 to 6 years after infection [3]. Survivors had a low functional status as assessed by Barthel-100 at time of interview. Moreover, compared to population norms, survivors reported lower perceived HRQOL, especially with regard to general health, physical dysfunction, and problems with work as assessed by the Short Form 36 questionnaire (SF-36) [3]. Other studies have also found a low HRQOL in survivors of severe infection when compared to population norms [4, 5]. However, more recent studies have shown that sepsis patients already have a lower HRQOL before onset of infection when compared to population norms [9–11].

Two US studies utilising register data from the Health and Retirement study and Medicare report findings that are partly corroborated by our study [7, 8]. Iwashyna et al. found that survivors of severe sepsis hospitalisation acquired significantly more new functional limitations than survivors of non-sepsis hospitalisation [7]. Similarly, Davydow et al. showed that hospitalisation for pneumonia was associated with new limitations in activities and instrumental activities of daily living [8]. In the subgroup of patients with no baseline functional limitations, pneumonia patients suffered significantly more new limitations than patients hospitalised for acute myocardial infarction (difference = 0.61) and fewer than patients hospitalised for stroke (difference = -1.05) [8]. Few longitudinal studies have examined changes in HRQOL from before ICU admission with severe sepsis to various time points after hospitalisation. Hofhuis et al. used the SF-36 among severe sepsis survivors and found a lower HRQOL at 6 month follow-up compared with pre-admission (especially in physical functioning, role physical, and general health dimensions) [9]. In a study from Finland with high loss to follow-up, Karlsson et al. used the EQ-5D questionnaire and found that 98 severe sepsis survivors reported similar EQ-5D VAS before and 17 months (range 12 to 20 months) after infection, while the index score was lower after infection [10]. In contrast, in a small study from France, Nesseler et al. found that in 23 patients with septic shock, for whom SF-36 data was obtained at baseline and at 6 month follow-up, HRQOL improved in bodily pain and vitality dimensions [11].

CAB is a severe acute disease which may entail devastating physical and psychological stress on the afflicted patients. During the acute infection, patients may experience disseminated intravascular coagulation, renal injury, acute cardiovascular events and other complications which can have a lasting effect on individuals' health [24–27]. Moreover, patients with severe infection may experience myopathy and muscle atrophy with prolonged limb and respiratory muscle weakness [28]. Patients hospitalised for infection who survive until discharge may still have

abnormal vital signs and ongoing inflammatory activity upon discharge from hospital [29]. Thus, patients with severe infection such as CAB may experience only partial recovery which could explain the high risk for deterioration in functional status and HRQOL detailed in this study.

Strengths of the present study include microbiological verification of community-acquired infection, the use of a matched control group of hospitalised patients with negative blood cultures, the use of validated instruments to assess functional status and HRQOL pre-admission and at follow-up, and a high degree of follow-up.

This study also has limitations. Our study was selective for patients with no recent cancer or previous bacteremia and it was conducted at one referral university hospital in North Denmark. Hence, our results may not be fully generalisable to patients with CAB with recent cancer or patients with CAB in other settings. Although this is matched cohort study in which we adjusted for confounders, the sample size of the present study prevented comprehensive multivariate analyses. Residual and unmeasured confounding may therefore account for some of the increased risk of deterioration in functional status when we compared patients with CAB with culture-negative controls. When interpreting the results of this study it should be kept in mind that patients who survive a debilitating disease can become accustomed to new health states (a response shift) [30]. Because our study subjects may have adapted to new health states, our estimates of risk of subjective HRQOL deterioration may not comply with more objective observations of changes in health status. As an example, one previously healthy CAB patient went through nearly 3 months of continuous hospitalisation and was practically immobile in an ICU at follow-up. At follow-up, this patient had a Barthel-20 score of 0 (needed help with all items in the Barthel index, vs. 20 or no

need for help at baseline), reported few problems in EQ-5D and responded to EQ-5D with a VAS score identical to baseline.

In conclusion, we have detailed that patients with CAB have a high risk for deterioration in functional status (14 %) and HRQOL (approximately 40%) from pre-admission to 3 months after the date of blood culture draw. Furthermore, patients with CAB have an increased risk for deterioration in functional status when compared to culture-negative controls. Prevention and improved therapy of severe community-acquired bacteremia may have an impact on the population health status at the community level.

**Competing interests.**

There are no financial or non-financial competing interests for this study.

**Authors' contributions.**

MDP, RWT, HN, and HCS participated in the design of the study and in the interpretation of data. MDP collected data and conducted statistical analyses. All authors participated in the writing of the manuscript and approve the final version.

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**Figure 1.** Flow chart of patients screened and included in the study.

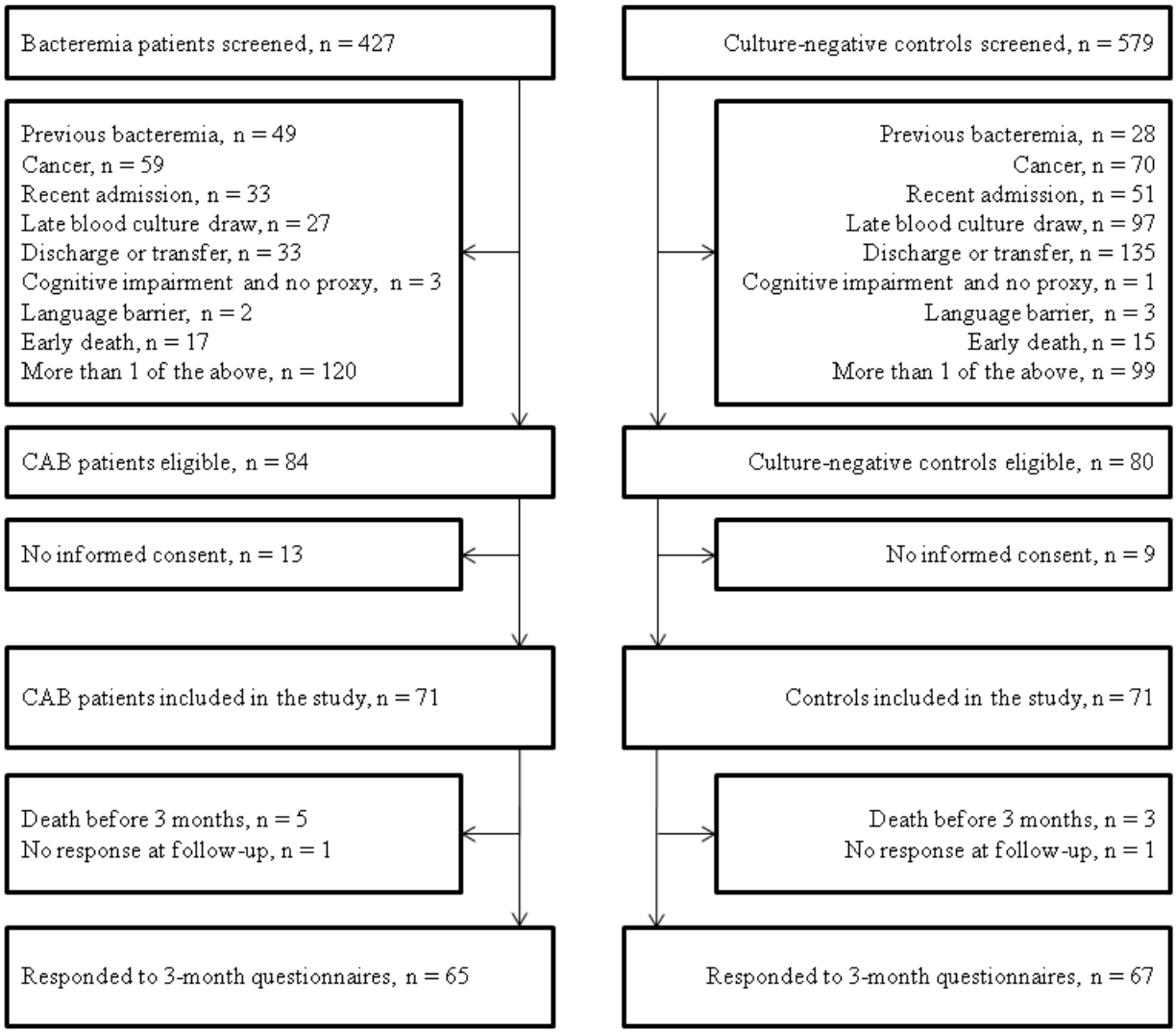


**Table 1.** Baseline characteristics of community-acquired bacteraemia patients and culture-negative controls, North Denmark, 2011-2013.

| | CAB patients (n=71) | Blood culture-negative patients (n=71) |
|---|---|---|
| Age in years, median (IQR) | 63 (52-75) | 64 (51-73) |
| Male sex, n (%) | 38 (54) | 38 (54) |
| Barthel 20-score, median (IQR) | 20 (20-20) | 20 (20-20) |
| EQ-5D index score, median (IQR) | 1 (0.776-1) | 0.771 (0.442-1) |
| EQ-5D VAS score, median (IQR) | 80 (50-100) | 60 (50-80) |
| Never smoker, n (%) | 34 (49) | 30 (42) |
| Pre-existing disease, n (%) | | |
| No pre-existing disease | 16 (23) | 7 (10) |
| Chronic pulmonary disease | 10 (14) | 25 (35) |
| Ischemic heart disease | 4 (6) | 8 (11) |
| Congestive heart failure | 4 (4) | 5 (7) |
| Cerebrovascular disease | 8 (11) | 8 (11) |
| Diabetes mellitus | 17 (24) | 18 (25) |
| Chronic renal disease | 3 (4) | 5 (7) |
| Chronic liver disease | 1 (1) | 0 (0) |
| Connective tissue disease | 4 (6) | 6 (8) |
| Other comorbidity | 47 (66) | 52 (73) |
| Medication use, n (%) | | |
| Antibiotic use, past week | 6 (8) | 18 (25) |
| Glucocorticoids, past 2 months | 6 (8) | 15 (21) |
| Other immunosuppressants, past 2 months | 5 (7) | 4 (6) |
| Clinical characteristics, n (%) | | |
| Temperature >38.0ºC | 54 (76) | 31 (44) |
| Heart rate >90 beats per minute | 44 (63) | 41 (58) |
| Hypotension* | 20 (28) | 10 (14) |
| Respiratory rate > 20 breaths per minute | 29 (41) | 29 (28) |
| Mental status changes | 9 (13) | 6 (8) |
| Laboratory findings, median (IQR) | | |
| C-reactive protein, mg/L | 147 (62-282) | 64 (34-164) |
| White blood cell count ×10^9/L | 16 (11-20) | 13 (10-18) |
| Platelets ×10^9/L | 209 (160-276) | 293 (214-364) |
| Creatinine, mmol/L | 94 (75-128) | 93 (71-113) |
| Blood urea nitrogen, mmol/L | 7 (5-11) | 6 (5-9) |
| Acute renal failure on admission, n (%)† | 4 (6) | 1 (1) |
| CURB-65 >=2 on admission, n (%) | 32 (45) | 23 (32) |
| Intensive care unit stay, n (%) | 6 (8) | 7 (10) |
| Length of stay in days, median (IQR) | 9 (6-17) | 7 (6-12) |

*Systolic blood pressure<90 mmHg or diastolic<60mmHg. †Defined as >2 hours of oliguria or a serum creatinine >2 times greater than the upper limit of normal.

**Table 2.** Risk for deterioration in functional status and HRQOL among patients with CAB and culture-negative controls.

| | Risk for deterioration, % (n/N) | | Risk difference[*] (95% CI) | | Risk ratio[*] (95% CI) | |
|---|---|---|---|---|---|---|
| Deterioration in | CAB patients | Controls | Crude | Adjusted[†] | Crude | Adjusted[†] |
| Functional status | | | | | | |
| Barthel-20 score | 14 (10/71) | 3 (2/71) | 11 (2-20) | 11 (3-19) | 5.0 (1.1-22.0) | 5.1 (1.2-22.3) |
| Patient's report[‡] | 9 (6/71) | 3 (2/71) | 5 (-2-13) | - | 3.0 (0.6-14.4) | 2.9 (0.6-13.3) |
| HRQOL | | | | | | |
| EQ-5D index score | 37 (26/71) | 28 (20/71) | 9 (-7-24) | 10 (-5-25) | 1.3 (0.8-2.1) | 1.3 (0.8-2.1) |
| EQ-5D VAS[§] | 39 (28/71) | 27 (19/71) | 13 (-3-28) | 12 (-3-28) | 1.5 (0.9-2.4) | 1.4 (0.9-2.3) |
| Patient's report[‡] | 32 (23/71) | 18 (13/71) | 14 (0-28) | 15 (1-28) | 1.8 (1.0-3.2) | 1.9 (1.0-3.4) |

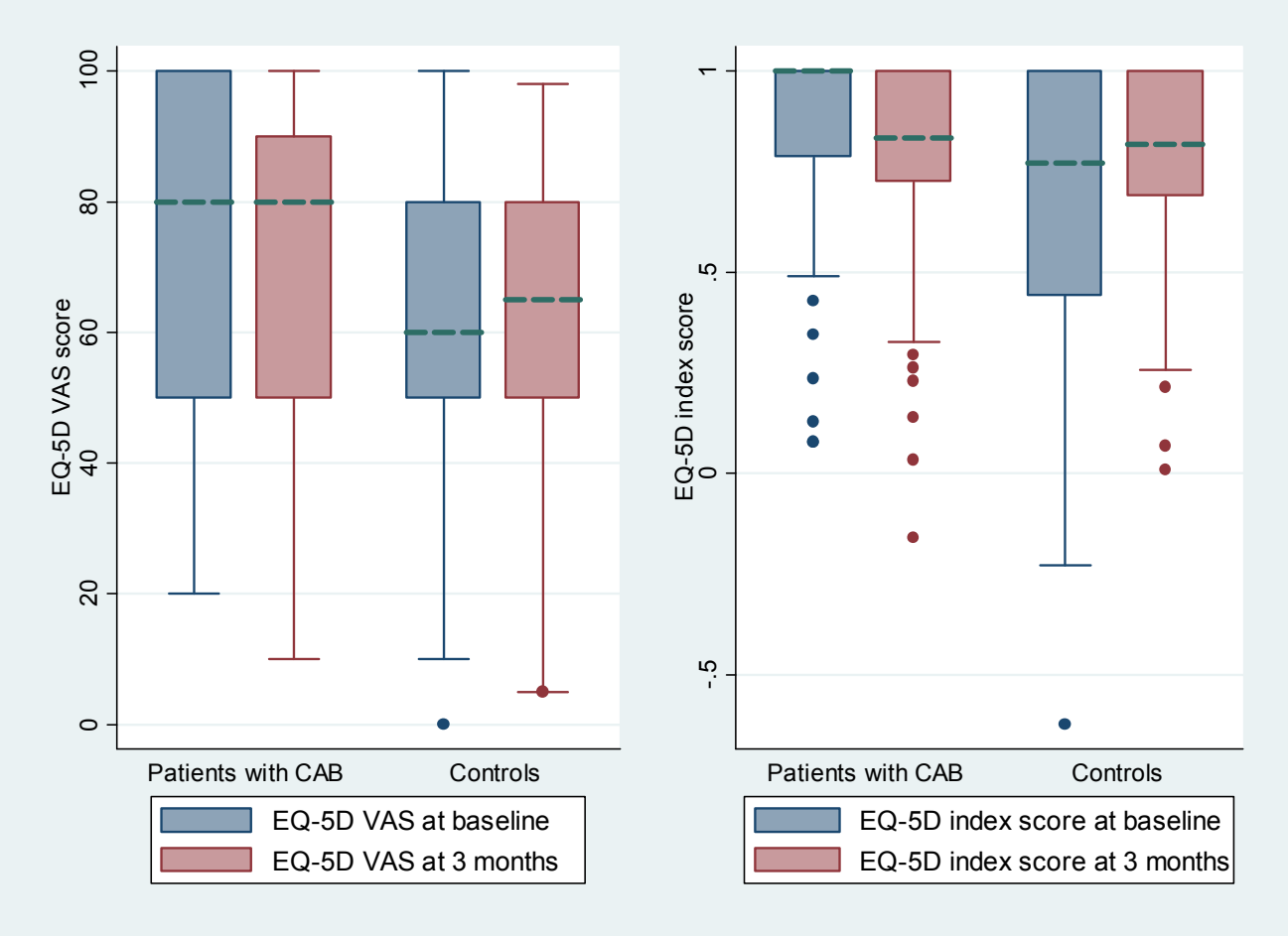
Abbreviations: CAB, community-acquired bacteraemia. [*]Risk difference and risk ratio computed by log-binomial regression. [†]Estimates are adjusted for age and gender. Estimates pertaining to deterioration in HRQOL are also adjusted for any pre-existing disease (yes/no). A (-) denotes that no adjusted estimate was computed because of failure to converge. [‡]Patient's report of worse functional status and HRQOL at follow-up compared with baseline. [§]Deterioration in VAS of at least 10 points.

**Table 3**. Dependence on any help in Barthel-20 items and any problem in EQ-5D dimensions in patients with CAB and culture-negative controls who responded to questionnaires at baseline and 3 month follow-up.

| | Patients with CAB, N=65 | | Ratio of proportions, 3 months vs. baseline | Culture-negative controls, N=67 | | Ratio of proportions, 3 months vs. baseline |
|---|---|---|---|---|---|---|
| | Baseline* | 3 months* | (95% CI) | Baseline* | 3 months* | (95% CI) |
| Need for help, Barthel-20 | | | | | | |
| Feeding | 0 (0) | 2 (1) | - | 4 (3) | 4 (3) | 1.0 (0.4-2.5) |
| Bed to chair | 2 (1) | 5 (3) | 3.0 (0.6-14.9) | 1 (1) | 1 (1) | 1.0 (-) |
| Grooming | 3 (2) | 6 (4) | 2.0 (0.5-8.0) | 9 (6) | 10 (7) | 1.2 (0.6-2.3) |
| Toileting | 3 (2) | 6 (4) | 2.0 (0.5-8.0) | 4 (3) | 3 (2) | 0.7 (0.3-1.5) |
| Bathing | 6 (4) | 14 (9) | 2.3 (1.1-4.7) | 12 (8) | 15 (10) | 1.3 (0.9-1.7) |
| Walking | 3 (2) | 6 (4) | 2.0 (0.8-5.3) | 4 (3) | 3 (2) | 0.7 (0.3-1.5) |
| Walking on stairs | 12 (8) | 12 (8) | 1.0 (0.6-1.8) | 10 (7) | 10.4 (7) | 1.0 (0.7-1.5) |
| Dressing | 6 (4) | 14 (9) | 2.3 (1.0-5.4) | 9 (6) | 4 (3) | 0.5 (0.2-1.1) |
| Bowel control | 3 (2) | 6 (4) | 2.0 (0.5-8.0) | 3 (2) | 4 (3) | 1.5 (0.7-3.4) |
| Bladder control | 9 (6) | 12 (8) | 1.3 (0.6-3.0) | 10 (7) | 7 (5) | 0.7 (0.5-1.1) |
| Any problem, EQ-5D | | | | | | |
| Mobility | 23 (15) | 31 (20) | 1.3 (0.9-2.1) | 37 (25) | 36 (24) | 1.0 (0.7-1.4) |
| Self-care | 8 (5) | 14 (9) | 1.8 (0.8-4.1) | 13 (9) | 15 (10) | 1.1 (0.6-2.1) |
| Usual activities | 18 (12) | 42 (27) | 2.3 (1.4-3.6) | 37 (25) | 48 (32) | 1.3 (0.9-1.8) |
| Pain/discomfort | 26 (17) | 45 (29) | 1.7 (1.2-2.5) | 54 (36) | 45 (30) | 0.8 (0.6-1.1) |
| Anxiety/depression | 14 (9) | 15 (10) | 1.1 (0.6-2.1) | 22 (15) | 21 (14) | 0.9 (0.6-1.4) |

*Data presented as % of N (n).

**Figure 2**. Box plots showing EQ-5D VAS scores and index scores for respondents to baseline and 3 month follow-up questionnaires.



# Declarations of co-authorship

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# Declaration of co-authorship

Full name of the PhD student: Michael Dalager-Pedersen

This declaration concerns the following article/manuscript:

| | |
|---|---|
| Title: | Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study. |
| Authors: | Dalager-Pedersen, Michael<br>Søgaard, Mette<br>Schønheyder, Henrik C<br>Nielsen, Henrik<br>Thomsen, Reimar W |

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: Dalager-Pedersen M, Søgaard M, Schønheyder HC, Nielsen H, Thomsen RW. Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study. Circulation. 2014; Epub ahead of print. doi: 10.1161/CIRCULATIONAHA.113.006699.

If accepted or submitted, state journal:

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No ☒ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

| Element | Extent (A-E) |
|---|---|
| 1. Formulation/identification of the scientific problem | C |
| 2. Planning of the experiments and methodology design and development | D |
| 3. Involvement in the experimental work/clinical studies | D |
| 4. Interpretation of the results | D |
| 5. Writing of the first draft of the manuscript | E |
| 6. Finalization of the manuscript and submission | D |

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B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

| Element | Extent (A-E) |
|---|---|
| 1. Formulation/identification of the scientific problem | C |
| 2. Planning of the experiments and methodology design and development | D |
| 3. Involvement in the experimental work/clinical studies | D |
| 4. Interpretation of the results | D |
| 5. Writing of the first draft of the manuscript | E |
| 6. Finalization of the manuscript and submission | D |

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This declaration concerns the following article/manuscript:

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|---|---|
| Title: | Venous Thromboembolism after Community-Acquired Bacteraemia: A 20-year Danish Cohort Study |
| Authors: | Dalager-Pedersen, Michael<br>Søgaard, Mette<br>Schønheyder, Henrik C.<br>Thomsen, Reimar W.<br>Baron, John A.<br>Nielsen, Henrik |

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

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| 4. Interpretation of the results | D |
| 5. Writing of the first draft of the manuscript | E |
| 6. Finalization of the manuscript and submission | D |

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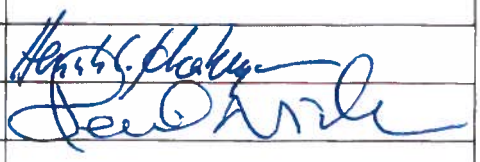
| 25/3 14 | Henrik C. Schønheyder |  |
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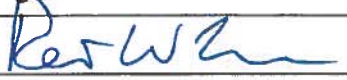
| 24/3-14 | Reimar W. Thomsen |  |
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