Antihypertensive drug use and the risk of sepsis-associated acute renal failure in the elderly.

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Abstract

Objective: To examine the association between exposure to antihypertensive drugs and the occurrence of acute renal failure during sepsis.

Study design: A cohort study of 25 830 Québec residents, aged over 65 years, discharged from an acute care hospital with a diagnosis of sepsis between 1997 2004.

Outcomes: Discharge diagnosis of acute renal failure and in-hospital renal replacement therapy.

Exposure: Outpatient exposure to antihypertensive drugs in the 60 days prior to hospital admission.

Statistical analysis: Crude and adjusted odds ratios for acute renal failure and renal replacement therapy associated with antihypertensive drug exposure were estimated using multivariate logistic regression models including baseline characteristics and comorbidities.

Results: Thiazide diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were associated with an increased risk of both acute renal failure and renal replacement therapy, except in the subgroup with chronic renal failure, for which an increased risk could not be demonstrated. Exposure to loop diuretics was associated with an increased risk of renal replacement therapy, but did not modify the risk of acute renal failure. Simultaneous use of more than two antihypertensive drugs increased the risk of both acute renal failure and of renal replacement therapy.

Conclusion: During sepsis, prior exposure to thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and antihypertensive polytherapy (>2 drugs) increase the risk of sepsis-related acute renal failure and renal replacement therapy.

Résumé.

Objectif : cette étude examine le lien entre l'exposition à des médicaments antihypertenseurs et la survenue d'insuffisance rénale aiguë durant un épisode septique.

Devis de l'étude : une étude de cohorte de 25 830 résidents du Québec, âgés de 65 ans ou plus, hospitalisés entre 1997 et 2004 dans un centre hospitalier de soins aigus, ayant reçu un diagnostic de sepsis au congé de l'hôpital.

Issues : la survenue d'une insuffisance rénale aiguë et l'initiation d'un traitement de remplacement de la fonction rénale.

Exposition : la prise de médicaments antihypertenseurs à domicile dans les 60 jours précédant la date d'admission.

Analyse statistique : les rapports de cote (*odds ratios*) pour l'insuffisance rénale aiguë et pour les traitements de remplacement de fonction rénale, en relation avec l'exposition aux médicaments antihypertenseurs ont été estimés par des modèles de régression logistique multiple tenant compte des caractéristiques initiales et des comorbidités pertinentes.

Résultats : L'exposition aux diurétiques thiazidiques, aux inhibiteurs de l'enzyme de conversion de l'angiotensine et aux bloqueurs des récepteurs de l'angiotensine était associée à un risque accru d'insuffisance rénale aiguë et de traitements de remplacement de la fonction rénale, sauf dans le sous-groupe des insuffisants rénaux chroniques, pour lequel un risque accru n'a pu être démontré. Les diurétiques de l'anse de Henle étaient associés à un risque augmenté de traitement de remplacement de la fonction rénale, mais pas au risque d'insuffisance rénale aiguë. L'usage simultané de plus de deux médicaments antihypertenseurs augmentait les risques d'insuffisance rénale aiguë et de traitements de remplacement de la fonction rénale.

Conclusion : Lors d'un épisode de sepsis, l'exposition préalable aux diurétiques thiazidiques, aux inhibiteurs de l'enzyme de conversion de l'angiotensine, aux bloqueurs des récepteurs de l'angiotensine, ainsi que la polythérapie antihypertensive (> 2 agents antihypertenseurs) augmentent le risque d'insuffisance rénale aiguë et de traitement de remplacement de la fonction rénale.

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Dedication.

Cet ouvrage est dédié à mon épouse Ève-Reine, et à mes enfants, Alexandre, Laure-Hélène et Charles.

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Abbreviations.

ACE	**Angiotensin converting enzyme**
ACEI	**Angiotensin converting enzyme inhibitor**
ADHF	**Acute decompensated heart failure**
ARB	**Angiotensin receptor blocker**
ARF	**Acute renal failure**
CCB	**Calcium channel blocker**
CHF	**Chronic heart failure**
CI	**Confidence interval**
CRF	**Chronic renal failure**
eGFR	**Estimated glomerular filtration rate.**
GFR	**Glomerular filtration rate**
ICD-9 CM	**International classification of diseases, ninth version-clinical modification.**
IQR	**Interquartile range**
NSAID	**Nonsteroidal anti-inflammatory agent**
O.R.	**Odds ratio**
RAMQ	**Régie de l'assurance maladie du Québec**
RRT	**Renal replacement therapy**

Chapter 1-Introduction.

1.1 Epidemiology of sepsis

Sepsis is the contemporary medical term used to designate the generalized inflammatory response to acute infection. Broadly inclusive definitions of sepsis have been proposed and refined in two successive international consensus conferences, based on a composite of clinical criteria and abnormal laboratory results (appendix 1). *Severe sepsis* is defined as sepsis complicated by at least one organ dysfunction, or by shock. *Septic shock is* defined as a sustained decrease in arterial pressure which persists despite adequate fluid resuscitation, and necessitates treatment with intravenous vasopressor drugs [1,2].

Sepsis is one of the most frequent and important syndromes encountered in clinical practice: recent population-based studies of the incidence of sepsis in the USA have reported incidence rates varying between 100 and 300 cases per 100,000 population/year. Age is a major risk factor for sepsis, and an exponential increase in incidence occurs between the ages of sixty-five (500 to 600 per 100,000/year) and eighty-five (1,000 to 2,600 per 100,000/year) [3-5].

Mortality associated with severe sepsis is also much higher in the elderly, with reported case-fatality ratios of 30 to 40% of for individuals aged more than 65, increasing to approximately 70% for those over 85. There has been a major increase in sepsis incidence during the 1980-2000 period, with an average annual increase of 8.7%, resulting in a threefold increase in the annual number of cases during that period. The severity of sepsis, as reflected by the number of diagnosed organ failures, seems to have increased, but case-fatality ratios have decreased, possibly because of improvements in medical care [6].

Because of a large increase in incidence, the total number of deaths attributable to sepsis has increased steadily. Sepsis is presently the tenth leading reported cause of death in the United States.

1.2 Organ dysfunction in sepsis.

Organ dysfunction is a frequent complication of sepsis, the pathophysiology of which is complex. Many possible mechanisms have been implicated, including decreased tissue perfusion, diffuse endothelial damage, activation of the coagulation and fibrinolytic cascades, micro-circulation abnormalities with maldistribution of capillary flow, tissue injury caused by inflammation, altered cellular metabolism, abnormal delivery and extraction of oxygen, and apoptosis. Although all organs/systems can suffer from sepsis-associated injury, the most frequently involved systems, in approximate order of frequency, are the cardiovascular, respiratory, renal, central nervous, digestive and coagulation systems. In sepsis, mortality is usually attributable to the underlying disease, or to nosocomial complications, but the occurrence of any organ dysfunction has a major negative impact on survival [7,8]. Simultaneous dysfunction of organ systems is frequent, and has a major impact on prognosis, the case-fatality ratio of sepsis rising from 15% when there is no organ dysfunction to over 70% with three or more simultaneous organ dysfunctions [9-12].

1.3 Acute renal failure in sepsis.

Acute renal failure is a frequent complication of sepsis, with reported incidences ranging between 10% in population-based studies of sepsis and 50% in ICU-based studies. It is characterized by an acute decrease in kidney function. Clinical manifestations of acute renal failure include decreased urine output (oliguria) and/or a decrease of the glomerular filtration rate (GFR), which increases the serum creatinine concentration, the laboratory marker most frequently used to monitor renal function. Oliguria (defined as a sustained decrease in urine output below 0.3 ml kg^{-1} h^{-1}) is a frequent manifestation of acute renal failure, and is generally associated with a more severe degree of kidney injury. However, in a large proportion of acute renal failure episodes (50-70%), urine output is maintained, despite severe reduction of glomerular filtration rate (*non-oliguric acute renal failure*).

Sepsis is reported to be the cause of 35 to 50% of ARF episodes occurring in intensive care units [13-16] and of 20 to 35% of ARF episodes occurring on general medical/surgical wards [17,18].

In the intensive care unit, sepsis-related ARF is associated with a higher case-fatality ratio (50 to 70%) than other causes of ARF. In individuals with more than one sepsis-related organ dysfunction, occurrence of ARF is an independent risk factor for in-hospital mortality[19]. The pathophysiology of sepsis-associated acute renal failure is complex and remains imperfectly understood [20,21].

The relative contributions of ischemia and inflammation in the genesis of acute septic kidney injury remain debated [22-25], and may vary from patient to patient. Renal ischemia due to hypoperfusion, resulting from decreased blood pressure and vasoconstriction of renal arteries may be an important etiologic factor[26,] but some laboratory and clinical studies indicate that renal perfusion is frequently maintained during severe sepsis, and it has been proposed that kidney injury is predominantly due to inflammation.

In some individuals, prompt correction of hypovolemia by intravenous fluid administration, and reversal of hypotension will result in a rapid recovery of renal function: in this setting, renal parenchyma is presumed not to have been injured significantly. This phenomenon is termed *pre-renal acute renal failure* and is associated with a more favourable prognosis. Other individuals, however, will progress to severe renal insufficiency, despite adequate fluid resuscitation and correction of hypotension. This shutdown of renal function can last from days to weeks. When acute renal failure is sustained and severe (corresponding to a glomerular filtration rate under 15 ml/min), renal replacement therapy becomes a vital necessity, to avoid, or correct, fluid overload, hyperkalemia and other lethal complications of the uremic syndrome. Population-based studies report the use of renal replacement therapy in 5-15 % of ARF episodes of various etiologies[27-30], while in ICU-based studies 20-50% of patients with acute renal failure will receive renal replacement therapy[15,16,18,31,32]. Most individuals who survive ARF will recover adequate renal function within three months, and will no longer require

renal replacement therapy, but a minority (< 10%), typically patients with pre-existing chronic renal impairment, will need long-term treatment with hemodialysis.

1.4 Acute renal failure: clinical and epidemiological diagnosis.

In the clinical setting, two parameters are used to recognize acute renal dysfunction:

A) Oliguria, defined as a decrease in urine output to less than 0.5 ml kg $^{-1}$ h^{-1} for more than six hours. Such a low urine output is not sufficient to maintain homeostasis of body fluids in an adult of normal size.
B) An increase in serum creatinine levels. Creatinine is predominantly produced by striated muscles, enters the blood at a constant rate, and is almost exclusively eliminated by glomerular filtration. In individuals with stable renal function and a normal muscular mass, serum creatinine levels provide a reliable quantitative estimate of the GFR. In the context of acute renal failure, since steady-state concentrations of creatinine are not available, and in individuals with a low muscular mass, the GFR estimate provided by serum creatinine levels is much less precise. In current clinical practice, assessment of the severity of acute renal failure is limited by this lack of precision, and by the non-availability of accurate biological markers of renal parenchymal injury[33-36].

Since even mild, transient decreases in renal function are associated with an increased risk of mortality, it has been suggested that the term «acute kidney injury» be preferred to «acute renal failure», to reflect that mild renal dysfunction, not associated with failure to maintain homeostasis, is still clinically and epidemiologically significant[24,37].

Epidemiologic studies of acute renal failure have been limited by the absence of a universally recognized definition of acute renal failure and by the lack of a satisfactory severity scoring system. This lack of uniformity in definition contributes to important variations in the reported incidences, etiologies and

complication rates of acute renal failure. Recently, in an effort to achieve better standardization, two classifications/staging systems for acute renal injury has been proposed, the RIFLE and the Acute Kidney Injury Network systems, which both use acute elevations of serum creatinine concentration and levels of urine output to stratify the severity of acute renal failure[37,38]. Validation studies suggest that these classification systems have predictive value for in-hospital length of stay and subsequent mortality[39]. The RIFLE and AKIN severity grades have not yet attained widespread use, and the most recent version of the International Classification of Diseases (ICD-10) does not provide a grading system for the severity of acute renal failure.

1.5 Can antihypertensive drugs cause sepsis-associated acute renal failure?

Acute renal failure occurring in the hospital setting is often multifactorial in etiology, with hypovolemia, myocardial dysfunction, toxic insults, arteriosclerotic vascular disease and chronic renal disease contributing importantly to the emergence of ARF.

Drugs can contribute to renal dysfunction and cause kidney injury by various mechanisms: direct cellular toxicity, allergic-type interstitial nephritis, acute urinary retention, hypovolemia, drug-induced hypotension or intrarenal arterial vasoconstriction.

Because of their blood-pressure lowering capacity, all antihypertensive agents have the potential to decrease renal function, since stability of the glomerular filtration rate is critically dependent on adequate arterial pressures. If an excessive reduction of blood pressure is caused by an antihypertensive agent, an acute decline in renal function is inevitable[40].

The potential effects of antihypertensive drugs on kidney function during sepsis deserve attention for several reasons.

First, sepsis is characterized by a fall in arterial pressure, which often evolves to septic shock. Sepsis-induced hypotension is caused by a combination of relative hypovolemia (due to dehydration, venous vasodilation and increased capillary

permeability), systemic arterial vasodilation and myocardial depression. Activation of the sympathetic autonomic nervous system (increasing plasma catecholamine concentrations), and activation of the renin-angiotensin II-aldosterone axis are compensatory responses aimed at increasing cardiac output, restoring vascular tone, maintaining glomerular filtration rate and minimizing hypovolemia through a reduction of urine output[41,42].

Various categories of antihypertensive drugs are likely to blunt these compensatory responses. Diuretic drugs can aggravate hypovolemia by inhibiting salt and water reabsorption in the renal tubules [43,44]. Beta-blockers inhibit sympathetic stimulation of the heart, and inhibit renin release. Angiotensin-converting enzyme inhibitors decrease plasma levels of angiotensin II and aldosterone, while angiotensin receptor blockers inhibit the action of angiotensin II and decrease plasma levels of aldosterone. Angiotensin II and catecholamine-induced vasoconstriction is inhibited by calcium channel blockers, which prevent the increase of cytosolic calcium concentration responsible for vascular smooth muscle contraction.

Second, exposure to antihypertensive drugs is steadily increasing in the elderly population. Chronic hypertension is a major cause of morbidity and mortality in adults, and is one of the most important public health problems worldwide. Blood pressure levels increase steadily with age, and, in Canada, more than half of adults aged over 65 years have chronic hypertension, although a large number are undiagnosed and untreated. Hypertension prevalence is constantly increasing as the proportion of elder citizens in the population increases. Accordingly, there has been a major increase antihypertensive drug use: between 1996 and 2006, the total number of delivered prescriptions of antihypertensive drugs in Canada has doubled, and the proportion of hypertensives taking more than one type of antihypertensive drug has risen from 20% to more than 40% [45-49].

This is related to increased hypertension prevalence, to a greater general awareness of the benefits of hypertension control, and to a more favourable risk-

benefit and side-effect profile of newer antihypertensive drugs. Clinical indications for many of these drugs (ACEIs, ARBs, beta blockers), have also expanded because of demonstrated benefits in the treatment of chronic diseases such as coronary disease, diabetes, chronic heart failure, and chronic renal disease. More than 40 different drugs are currently available for treatment of hypertension. The drugs most commonly used belong to six different categories: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics (thiazide diuretics and loop diuretics), calcium channel blockers (CCBs) and beta-blockers. Of the six major drug categories, four have been associated with acute renal failure: ACEIs, ARBs, loop diuretics, and, to a lesser extent, thiazide diuretics. These associations will be discussed in the following chapter.

Finally, most studies evaluating the causal role of drugs in hospital-acquired acute renal failure have focused on drug therapy administered in the hospital [50]. Antihypertensive agents taken at home could have an impact on renal function during acute sepsis, either because they have a residual effect related to their long duration of action, or because outpatient drug treatment may be maintained in the hospital until overt sepsis and clinical instability become evident.

Chapter 2 - Literature review.

2.1 General risk factors for acute renal failure.

Acute renal failure is most often secondary to another medical condition or to a toxic insult than to a primary kidney disease (such as acute glomerulonephritis or acute interstitial nephritis). Most epidemiologic studies of risk factors for acute renal failure (population-based, hospital-based, or ICU-based studies) do not distinguish between sepsis-related ARF and other etiologies, and do not provide a specific analysis of risk factors in the context of sepsis. However, epidemiologic studies of secondary ARF, irrespective of etiology, have identified the following risk factors.

2.1.1 Demographic characteristics.

Age is undoubtedly a major risk factor for ARF: community-based cohort studies of acute renal failure demonstrate a strong association between the incidence of ARF and advancing age, up to the age of 85 years. [29,30,51].

Advancing age is also recognized as a risk factor for acute renal failure in other clinical contexts such as contrast induced nephropathy [52], cardiac surgery [53], NSAID toxicity [54] etc..

An impact of gender on the risk of acute renal failure is less certain: although a higher risk of acute renal failure with male gender has been reported in some population-based studies[29,30,51,54,55] , other studies have not found a significant association of ARF risk[13,14,53,56-60] . An increase of ARF risk with female gender has been reported in the context of revascularization of coronary disease, but this could be related to the greater age and a greater burden of risk factors of women who underwent this category of procedures[61,62] .

2.1.2 Chronic comorbidities.

Chronic renal failure is the medical comorbidity most consistently and strongly associated with an increased risk of acute renal failure. Hsu et al. have reported on the incidence of acute renal failure in adult members of the Kaiser Permanente health care delivery system (Northern California). Multivariate logistic regression was performed, analysing 602 026 hospitalized adults, of which 1746 developed acute renal failure treated with renal replacement therapy. This analysis demonstrated that the risk of receiving renal replacement therapy was very strongly linked to the severity of pre-existing CRF. Using non-diabetic individuals with an estimated glomerular filtration rate (eGFR) of ≥ 60 ml*min $^{-1}$ as the reference group, they found the adjusted odds ratios for acute renal replacement therapy to be 5.5, 25.0 and 38.2 for subgroups with eGFRs of 30-44 ml*min^{-1}, 15-29 ml*min $^{-1}$, and < 15 ml*min $^{-1}$ respectively. The adjusted odds ratios were even higher (8.2, 33.7 and 44.8) for diabetic individuals with corresponding levels of eGFRs [59].

Other studies have also reported a strong association between pre-existing chronic renal failure and the risk of ARF[14,51-54,56,60].

Epidemiologic studies of chronic heart failure have demonstrated that this common disease is another important risk factor for acute renal failure[57,58,63-65]. In individuals with chronic heart failure, deterioration of renal function often occurs during an acute decompensation of cardiac function: this can be caused by a decrease in cardiac output or in arterial pressure, an increase in central and renal venous pressures or as a complication of drug treatment (which will be discussed in section 2.2). Simultaneous acute impairment of cardiac and renal function is designated as *the cardiorenal syndrome*, and is associated with a less favourable prognosis[66-68] .

Chronic liver disease is an acknowledged risk factor for acute renal failure, particularly when cirrhosis and portal hypertension are present. Cirrhotic patients are at high risk of both bacterial sepsis and gastrointestinal haemorrhage, which frequently precipitate ARF, which is then associated with a mortality exceeding 50%[69,70]. The risk of ARF in these patients appears to be proportional to the severity of the underlying cirrhosis and to the accumulated volume of ascitic fluid [71-74].

Diabetes and chronic hypertension, two highly prevalent diseases, have been identified as independent risk factors for acute renal failure in many clinical settings: population-based studies [51,59] , studies of contrast nephropathy[58,61] , of NSAID nephropathy[54] , in the setting of coronary revascularization[53,62] and during the in-hospital treatment of decompensated heart failure[63,65,75] . This increase in risk is likely to be related to functional and anatomic changes of the renal microvasculature which appear in the early stages of these diseases[76,77].

Atherosclerotic vascular disease has also been reported as a risk factor for acute renal failure. Severe atherosclerotic disease of the renal arteries is a well-known cause of chronic renal failure, but the association of subclinical arterial disease with ARF has recently been demonstrated by the Cardiovascular Health Study, a prospective observational cohort study of more than 5 000 individuals aged over

65, for which a large amount of demographic, clinical and laboratory data was collected at entry in the cohort. Cohort members were afterwards followed for a median period of 10.2 years. During this period, approximately 4% of the cohort developed acute renal failure. Diabetes, hypertension and established coronary disease were independently associated with a greater risk of acute renal failure. Of considerable interest is the fact that baseline markers of subclinical atherosclerotic disease, such as a decreased ankle-arm systolic pressure index and an increased carotid artery intima-media thickness, were also independently associated with an increased ARF risk[51] .

2.2 Acute renal failure risk associated with antihypertensive drugs.

All antihypertensive drugs have the potential to adversely affect renal function, by lowering blood pressure below the levels required to maintain renal perfusion and glomerular filtration. However, in routine clinical use, antihypertensive drugs produce a small, but clinically non-significant (< 5 ml*min^{-1}) decrease in glomerular filtration during the first months of their use[78,79] . This small decrease in renal function is largely offset, on the long-term, by the protective effect of these drugs on kidney function, since adequate control of blood pressure prevents progressive renal vascular sclerosis induced by hypertension[80].

Despite this generally favourable effect, four antihypertensive drug classes have been identified as increasing the risk of acute renal failure in individuals with predisposing comorbidities. The first three classes are the ACEIs, the ARBs and loop diuretics. The fourth class, thiazide diuretics, is cited as a cause of hypovolemia and acute renal failure, but much less data is available to assess the risk of ARF associated with this category of drugs. The other two major antihypertensive drug classes, calcium channel blockers and beta-blockers, have not been associated with acute renal failure[40,81,82].

A new category of antihypertensive drugs, direct renin inhibitors, will not be considered in this review, since they were not in use during the study period.

In the following paragraphs, we will review the literature related to the risk of acute renal failure associated with the first four drug categories, and the risk associated with simultaneous usage of antihypertensive drugs (polytherapy).

2.2.1 Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers:

These two drug categories have been demonstrated to be effective in the prevention and/or treatment of a wide variety of chronic diseases (hypertension, diabetes, chronic heart failure, coronary disease, chronic renal failure). Experimental studies in animals, randomized clinical trial, a large number of retrospective studies and case reports, have all provided extensive evidence that selective antagonism of the renin-angiotensin II-aldosterone axis by these drugs can produce an acute decrease of the glomerular filtration rate. The magnitude of this problem will vary depending on predisposing comorbidities, such as chronic heart failure and chronic renal failure, and on concurrent acute illnesses producing hypotension and/or hypovolemia [40,81,82].

The effects of ACEIs and ARBs on renal function seem to be very comparable, as evidenced by the ONTARGET study [83,84] , a randomized controlled clinical study of 25,620 with cardiovascular disease or diabetes (patients without heart failure), comparing the renal effects of the ACEI ramipril with the ARB telmisartan, and with a combination of both agents. After a median follow-up of 56 months, the incidence of renal impairment (as defined by the attending physician) was reported to be 10.2 % in the group receiving ramipril, and 10.6% in the group receiving telmisartan. Renal impairment was mild, however, and rarely required treatment discontinuation (ramipril 0.7 %, telmisartan 0.8 %) and acute renal failure requiring renal replacement therapy occurred in only 0.15% (ramipril) and 0.23% (telmisartan) of patients.

In clinically stable individuals *without* significant chronic heart failure or renal failure, the risk of ACEIs or ARBs induced acute renal failure seems to be very low. For example, the EUROPA trial, a prospective randomized study of 12,218 patients, compared the ACEI perindopril to placebo for the prevention of

cardiovascular events [85] . After a mean follow-up period of 4.2 years, the incidence of acute renal failure was equal in both treatment groups (0.3%). Similarly, in the VALUE trial [86] , a prospective randomized study of 15,245 patients comparing the ARB Valsartan to Amlodipine for the prevention of cardiovascular events, after a mean follow-up of 4.2 years, the average creatinine serum levels rose from 101 to 108 µmol/l in the Valsartan group, and from 101 to 103 µmol/l in the Amlodipine group, a difference without clinical significance. Furthermore, no case of acute renal failure was reported in either group.

Patients with chronic heart failure or advanced chronic renal failure. appear to be at higher risk of acute renal dysfunction when therapy with ACEIs or ARBs is initiated:

Bridoux et al. reported one of the first retrospective series of 27 patients experiencing acute renal failure (defined as a doubling of serum creatinine levels or a rise over 180 µmol/l) while receiving ACEI treatment [87] . Renal arteriography had been performed to rule out renal artery stenoses. Renal biopsy (performed in 10 patients) showed only tubular necrosis or arteriosclerosis of the small renal arteries. Predisposing factors for acute renal failure were present in all patients: chronic heart failure (nine cases), chronic renal failure (eight cases), diuretic therapy (twenty-four cases), NSAID therapy (six cases), gastrointestinal fluid losses (seven cases). The majority of these cases had multiple predisposing factors.

Bakris et al [88] have reviewed 12 randomized clinical trials reporting on a total of 1102 patients *with chronic renal failure* starting treatment with an angiotensin converting enzyme inhibitor. In these studies, reduction of the glomerular filtration rate occurred within two weeks of treatment initiation, but the average decrease in renal function after six months of therapy was mild, (between 0.4 and 14.4 ml/minute), and at the end of follow-up (study durations of 2 to 5 years), the average decrease in GFR was even less marked (between 0.7 and 7.1 ml/min). Thus, although some reduction in GFR is associated with ACEI therapy in individuals with chronic renal failure, clinically significant acute renal failure is

uncommon, provided no precipitating events occur. The authors also noted that individuals experiencing more important initial decreases in GFR seemed to obtain better long-term protection against progression of renal failure, a therapeutic benefit of ACEIs and ARBs which is attributed to their antihypertensive effects and their ability to reduce proteinuria.

In the CONSENSUS trial[89], which randomized patients with severe heart failure to either placebo (n = 120) or the ACEI enalapril (n = 123), mean serum creatinine levels increased by 13% after two weeks of treatment and remained at that level during the six following months, while there was no significant change of creatinine levels in the placebo group. Thirty-five percent of patients treated with enalapril had an increase in creatinine levels of more than 30% over baseline. Patients with the greatest increase in serum creatinine had lower blood pressure levels during treatment and were receiving higher doses of the loop diuretic furosemide (mean dose: 280 mg). Deterioration of renal function was observed either during concurrent illness, surgery or marked hypotension following enalapril administration.

In the SOLVD study[63], 3379 patients with severe heart failure were assigned to treatment with enalapril, and compared to an equal number of patients treated with placebo. During an average follow-up of 779 days, the incidence of impaired renal function (defined as a rise in serum creatinine greater than 44 µmol/l) was 15% in the enalapril group and 12% in the placebo group.

Packer et al[90] reported a prospective study of 104 patients with severe chronic heart failure: hemodynamic assessment with a pulmonary artery catheter was done before introduction of an ACEI, after the first dose, and after 1 to 3 months of treatment. Deterioration of renal function (defined as an increase in serum creatinine of more than 35 µmol/l) occurred in 34 patients. Compared to those with stable renal function, these individuals had lower baseline right atrial pressure, and received higher doses of furosemide (mean dose 119 mg/24 hour vs. 89 mg/24 hour). After the first dose of the ACEI, and at the end of the study period, the subgroup with significant deterioration of renal functiont was found to

have greater reductions of both left ventricular filling pressures and mean arterial pressures and greater increases in plasma renin activity, suggesting that relative hypovolemia, due to aggressive diuretic treatment, increases the risk of renal function deterioration under ACEI treatment.

Some retrospective studies of renal function impairment in patients hospitalized for acute decompensated heart failure (ADHF) have not found a relation between ACEI exposure and acute renal failure (Krumholz et al.[64], Forman et al.[65], Chittineni et al.[75]). In a fourth, prospective cohort study of 114 patients hospitalized with ADHF, Cruz et al.[91] reported that the 30-day cumulative incidence of ARF was 25%. Although neither exposure to ACEIs or to diuretics was related to the occurrence of ARF, a decrease in mean blood pressure exceeding 25 mm Hg after the introduction of an ACE inhibitor was strongly predictive of acute renal failure.

Overall, despite some discrepancies in the literature, the sum of the accumulated evidence clearly identifies exposure to ACEIs or ARBs as an important risk factor for the development of acute renal failure in individuals with predisposing chronic illnesses.

2.2.2 Loop diuretics and thiazide diuretics.

When diuretics are used to treat uncomplicated hypertension, the associated risk of acute renal failure seems to be very low[40]. In conditions such as heart failure, chronic renal failure and cirrhosis, deterioration of renal function is widely acknowledged as a complication of diuretic therapy, and is believed to result from diuresis-induced hypovolemia[43,44]. However, in published prospective clinical trials of hypertension treatment with thiazide diuretics, the frequency and severity of acute renal failure are not well defined [67,92,93]. For example, published reports from the ALLHAT study, a large-scale trial comparing a thiazide (chlortalidone) to an ACEI (lisinopril) and to a calcium channel blocker (amlodipine) as first-line therapy for hypertension [94,95], do not specify the frequency of acute renal failure. Most of the data on diuretic-associated renal failure originate from studies of in-hospital deterioration of renal function during treatment of acute decompensated

heart failure (ADHF) and outpatient studies of congestive heart failure treatment. To treat congestive heart failure, loop diuretics, rather than thiazide diuretics, are generally used.

In-hospital diuretic use:

Two studies have reported renal function impairment associated with diuretic treatment of individuals hospitalized for acute decompensated heart failure (ADHF): in a nested case-control study of 382 patients (191 ARF cases and 191 controls) Butler et al,[96] using multivariate analysis, demonstrated a greater risk of renal impairment with higher doses of loop diuretics. In another retrospective cohort study of patients hospitalized with heart failure, Sun et al[97], used multivariate analysis to demonstrate a significant risk of renal impairment with higher doses and longer duration of loop diuretic use.

Other retrospective studies of renal impairment during in-hospital ADHF treatment, previously cited, have not found an association between diuretic exposure or dosage and acute renal failure[64,65,75,91].

Outpatient diuretic treatment:

An association of renal function impairment with outpatient diuretic treatment has been observed in outpatients with chronic heart failure:

In the SOLVD study [63] , multivariate logistic regression suggested that the use of either thiazide diuretics or loop diuretics was associated with an increased risk of acute renal failure, while exposure to beta-blockers was associated with a lower risk.

In the prospective study of chronic heart failure patients by Packer et al, previously cited[90], during a six-week observation period, the 34 individuals who developed renal impairment after starting treatment with an ACEI were exposed to significantly higher baseline doses of furosemide (mean dose 119 mg/24 hour) than the 70 individuals whose renal function remained stable (mean dose 89 mg/24 hour).

2.3 Antihypertensive polytherapy.

Although this has not been studied in the context of sepsis, the risk of ARF associated with antihypertensive drug polytherapy has been studied in other clinical settings.

Strong evidence exists for the negative impact of an ACEI + ARB association on renal function: Phillips et al [98] have reported a systematic review of randomized clinical trials comparing combination treatment with ACEIs and ARBs to monotherapy with ACEIs in patients with left ventricular dysfunction. Four randomized clinical trials (with a total of 17,337 patients) met the criteria for inclusion in their review. Pooling the results from these trials revealed that deterioration of renal function occurred in 2.4% of patients on ACEI monotherapy and in 4.1% of patients on ACEI/ARB combination therapy.

The ONTARGET study[83,84], cited previously, demonstrated that combination therapy with telmisartan and ramipril was associated with a higher risk of renal function impairment (13.5%) than monotherapy with either agent (telmisartan 10.6%, and ramipril 10.2%), with an odds ratio of 1.33 (95% C.I. 1.22-1.44). The high frequency of renal function impairment in the ONTARGET study probably results from liberal criteria used by attending physicians to diagnose renal impairment. If a more strict definition of renal impairment (doubling of serum creatinine levels) was used, the frequency of renal impairment was much less, but still higher with combination therapy (1.9% with combination therapy, 1.8% with telmisartan monotherapy, 1.6% with ramipril monotherapy).

There are less data available on the risk associated with the combination of diuretics with ACEIs, ARBs or other categories of antihypertensive drugs. Demonstration of an increased risk with combination therapy comes mainly from retrospective studies of heart failure patients, described in the preceding section [63,97,99].

Chapter 3-Methods.

3.1 Study objectives.

3.1.1 General objective.

To assess if outpatient anti-hypertensive drug exposure is associated with an increased risk of developing acute renal failure in patients hospitalized with sepsis.

3.1.2 Specific objectives.

1) To assess if outpatient exposure to ACEIs, ARBs, loop diuretics or thiazide diuretics are associated with a greater risk of sepsis-associated acute renal failure than use of other first-line antihypertensive drugs, such as beta blockers and calcium channel blockers.

2) To assess if outpatient exposure to a greater number of antihypertensive agents is associated with an increased risk of acute renal failure in patients hospitalized with sepsis.

3.2 Overview of study design.

A cohort was built using the MedEcho database of all acute care hospitalizations in Québec, which is available through the *Régie de l'Assurance Maladie du Québec* (RAMQ), the board which administers the universal state health insurance plan. Patients aged 65 years or more, hospitalized during the years 1997-2004 with either a primary or secondary discharge diagnosis of septicemia or bacteremia were candidates for inclusion in the cohort. A cohort of more than 25,000 patients was thus assembled, and the following information was retrieved from the database: baseline characteristics, discharge diagnoses, year of hospitalization, transfer between acute-care hospitals and in-hospital mortality. This database was linked to other RAMQ databases to obtain data on individual exposure to antihypertensive drugs in the 60-day period preceding the index admission date, and document the use of renal replacement therapy.

3.3 Sources of data:

Data for this study were obtained from administrative databases in Québec, Canada, over the 1996-2004 period. These databases are the Med-Echo database of hospital discharges, the RAMQ prescription drug database and the RAMQ physician claim database. These databases can be cross-linked, using a crypted identification code derived from each individual's health insurance number.

3.3.1 The Med-Echo database provides information from hospital discharge summaries for all acute care hospitalizations in Québec. This includes demographic characteristics, dates of admission and discharge, discharge diagnoses, inpatient procedures and vital status at discharge, which were coded according to the ICD-9-CM classification system during the study period.

Given the centralized and confidential nature of this database, chart review of a subsample of medical files was not possible, so that estimates of the sensitivity and specificity of coding for various diagnoses or therapeutic interventions could not be computed. Previous chart validation studies of the accuracy of ICD-9-CM coding for chronic medical illnesses have demonstrated sensitivities ranging from 20 to 80% and specificities ranging from 90 to 100%, depending on the illnesses studied. For acute renal failure, similar chart validation studies have demonstrated sensitivities ranging from 30 to 50%, and specificities ranging from 90 to 95%. Overall, previous studies demonstrate a good positive predictive value, but a poor negative predictive value for ICD-9 CM coding. Thus, if an illness is recorded in an ICD-9-CM registry such as MedEcho, the diagnosis is very likely to be correct, but if a highly prevalent illness is not coded, it nevertheless may have been present.

3.3.2 The RAMQ drug prescription claim database contains information on prescription drugs dispensed to individuals covered by the state drug insurance plan (in-hospital and ambulatory clinic drug dispensing do not figure in the database). For individuals 65 years and older, prescription drug coverage by the state health care plan is complete. For this reason, we limited our study to

individuals 65 years and older, which ensured complete capture of prescription drug delivery. Information available in this database include drug names, doses, dosage forms, quantity delivered, dispensation dates, treatment durations, encrypted patient identification codes and prescribing physician codes.

3.3.3 The physician fee claim database contains information on physician fee claims for all medical services delivered under the Québec health insurance plan. Information available in the database include patient identification code, type of service provided, date and location of service delivery, dispensing physician and referring physician identification. For in-hospital care, since the vast majority of Québec physicians adhere to the universal state health care plan, reliability of medical service dispensation data is excellent, and provision of renal replacement therapy (intermittent hemodialysis or continuous hemofiltration) can be identified by specific billing code numbers.

3.4 Cohort definition.

3.4.1 Inclusion criteria.

The following three criteria were mandatory for inclusion in the cohort:

A) Age of 65 years or more at the time of index hospitalization.

B) Hospitalization in an acute care hospital in Québec in the period extending from January 1st 1997 to December 31st 2004. January 1st 1997 was chosen as the beginning of the study period, in order to have, for all individuals in the cohort, data for outpatient drug dispensing and medical care in the year preceding the index date of admission.

C) A primary or secondary discharge diagnosis of septicemia or bacteremia (see appendix 2 for corresponding ICD-9-CM codes). Septicemia and bacteremia codes were used for case definition, since sepsis does not appear as a specific diagnosis in the ICD-9-CM classification system. Although bacteremia and septicemia are distinct medical entities, bacteremia is highly likely to produce, at least transiently, a septic response. Similar case

definitions have been used previously in population-based studies of sepsis[3,5,6].

3.4.2 Exclusion criteria.

Individuals were not included in the cohort if one of the two following criteria was met:

A. Duration of index hospitalization exceeding 180 days.
B. Renal replacement therapy (hemodialysis, peritoneal dialysis or continuous hemofiltration) had been provided prior to the index admission date.
C. Prior entry in the cohort for an acute sepsis episode.

3.4.3 Date of entry and duration of follow-up.

Date of entry in the cohort was defined as the admission date of the index hospitalization. Individuals were considered as leaving the cohort on the date of hospital discharge (or on the date of in-hospital death). If individuals had more than one hospitalization with sepsis during the study period, data on subsequent hospitalizations were not used. However, if an individual was discharged to be transferred on the same day to another acute-care hospital, the two hospitalizations were considered a single acute-care episode, and data from the second hospitalization were merged with data from the first hospitalization for subsequent analysis.

3.5 Data retrieval.

3.51 Baseline characteristics.

The following individual characteristics were retrieved: year of hospitalization, age, gender, occurrence of shock, length of hospitalization, in-hospital mortality, and whether septicemia/bacteremia were coded as primary diagnoses or secondary diagnoses.

3.52 Baseline comorbidities.

Presence of the following comorbidities was identified by searching for corresponding ICD-9-CM diagnostic codes in the MedEcho discharge

summaries: hypertension, diabetes, coronary disease, heart failure, chronic renal failure, peripheral arterial disease, and chronic liver disease (see Appendix 3 for a list of corresponding ICD-9-CM codes). An individual was also classified as being diabetic if outpatient dispensing of either insulin or oral hypoglycemic drugs occurred in the 60-day period prior to the index admission (see appendix 5).

3.53 Drug exposure.

Using the RAMQ drug prescription database, prescriptions delivered in the 60-day period preceding the index admission date were reviewed, to identify delivery of the following antihypertensive drugs: thiazide diuretics, loop diuretics, potassium sparing diuretics, Angiotensin converting enzyme inhibitors (ACEIs), Angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers, alpha blockers, arterial vasodilators, CNS agents and ganglioplegics (agents acting on the central nervous system or on the autonomic nervous system), nitrates (oral and percutaneous forms). Dispensation of insulin or oral hypoglycaemic drugs was also recorded as a marker for the presence of diabetes (see Appendices 4 and 5 for a list of antihypertensive and antidiabetic drug categories).

Individuals were classified as exposed to a drug if they had received at least one prescription of the drug in the 60-day period preceding the index admission. If a delivered prescription was a combination of two different antihypertensive drugs (for example an ACE inhibitor and a thiazide diuretic), the individual was considered as having been exposed to both drug categories. Although they were available in the drug prescription database, drug dosages were not entered in the statistical models, because a multivariate analysis including drug doses would necessitate more than thirty drug exposure covariates, a number which would make analysis of the results exceedingly difficult.

3.54 Outcome assessment.

Two outcomes were studied.

The first outcome was acute renal failure, identified by ICD-9-CM codes for acute renal failure in the MedEcho discharge data (see Appendix 2 for a list of

corresponding ICD-9-CM codes), or by the introduction of renal replacement therapy during the index hospitalization (see Appendix 3 for a list of corresponding RAMQ fee claim codes). The MedEcho database does not provide laboratory data, so the severity of acute renal failure (or of pre-existing chronic renal failure) could not be assessed, otherwise than by provision of renal replacement therapy, which is typically initiated when glomerular filtration rates fall below 15 ml min^{-1}.

The second outcome was use of renal replacement therapy during the index hospitalization, identified by specific billing codes for either hemodialysis or hemofiltration initiated during the index hospitalization.

3.6 Statistical analyses.

Descriptive statistics were computed to define baseline cohort characteristics. Analysis of yearly fluctuations in the variables was done to identify time-related trends.

The odds ratios, for the associations between drug exposure and the two outcomes of interest, acute renal failure and renal replacement therapy, were computed using logistic regression. Logistic regression was also used to estimate crude odds ratios for these outcomes in association with each covariate, such as baseline characteristics, baseline comorbidities, and other drug exposures. In order to adjust for confounding, multivariate logistic regression was performed, using two different models.

In the first model (*model A*) drug exposure was analyzed according to documented delivery of specific antihypertensive drug categories in the 60-day period prior to the index admission. The following drug categories were included in the model: thiazide diuretics, loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers. Exposures to less frequently used antihypertensives (potassium sparing diuretics, alpha-blockers, drugs acting on the central nervous system, ganglioplegics, arterial vasodilators, oral or percutaneous nitrates) were also included in the multivariate models, but the analysis of risks associated with drug

class exposure focused on the more commonly used drug categories. If a prescription consisting of a drug combination (such as an ACEI and a thiazide diuretic) was delivered, individuals were considered to have been exposed to both drug categories.

In the second model (*model B)* drug exposure was defined by the number of antihypertensive drug categories delivered in the 60-day period prior to the index admission. This was done to assess if exposure to a greater number of antihypertensive drugs was associated with a greater risk.

The following covariates were included in both models: baseline characteristics (year of admission, age, gender, primary vs. secondary diagnosis of sepsis) and baseline comorbidities (hypertension, diabetes, coronary disease, chronic heart failure, peripheral arterial disease, chronic renal failure, chronic liver disease). Although we recorded the diagnosis of shock in our data, we did not include it as a covariate in either model, because we considered that shock would be likely to stand in the putative causal pathway between antihypertensive drug exposure and the occurrence of acute renal failure, and should not be treated as a possible confounder.

In order to further analyze possible effect modification, the analysis were stratified according to the following criteria:

For the acute renal failure outcome, chronic heart failure and chronic renal failure were used for stratification because these comorbidities were associated with the highest risk of acute renal failure, and were likely to be associated with more frequent exposure to specific drug categories, such as ACEIs, ARBs and loop diuretics. Primary/secondary diagnosis of sepsis was also used for stratification of acute renal failure risk assessment, since cohort members with a secondary diagnosis had a higher risk of acute renal failure, and because in-hospital drug exposure may differ from outpatient drug exposure (the RAMQ databases contain no information on in-hospital drug treatment).

For renal replacement therapy, stratification was limited to the presence or absence of chronic renal failure, because the small number of individuals who

received renal replacement therapy limited the precision of the analysis, and because chronic renal failure proved to be the most important risk factor effect for the outcome of renal replacement therapy, and the most significant modifier of risk estimates for drug exposures.

All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary NC., USA).

3.7 Ethical considerations.

Information within the RAMQ computerized databases is available for research purposes. Strict patient confidentiality is maintained through the use of an encrypted identification code, so that nominal information cannot be retrieved from the data.

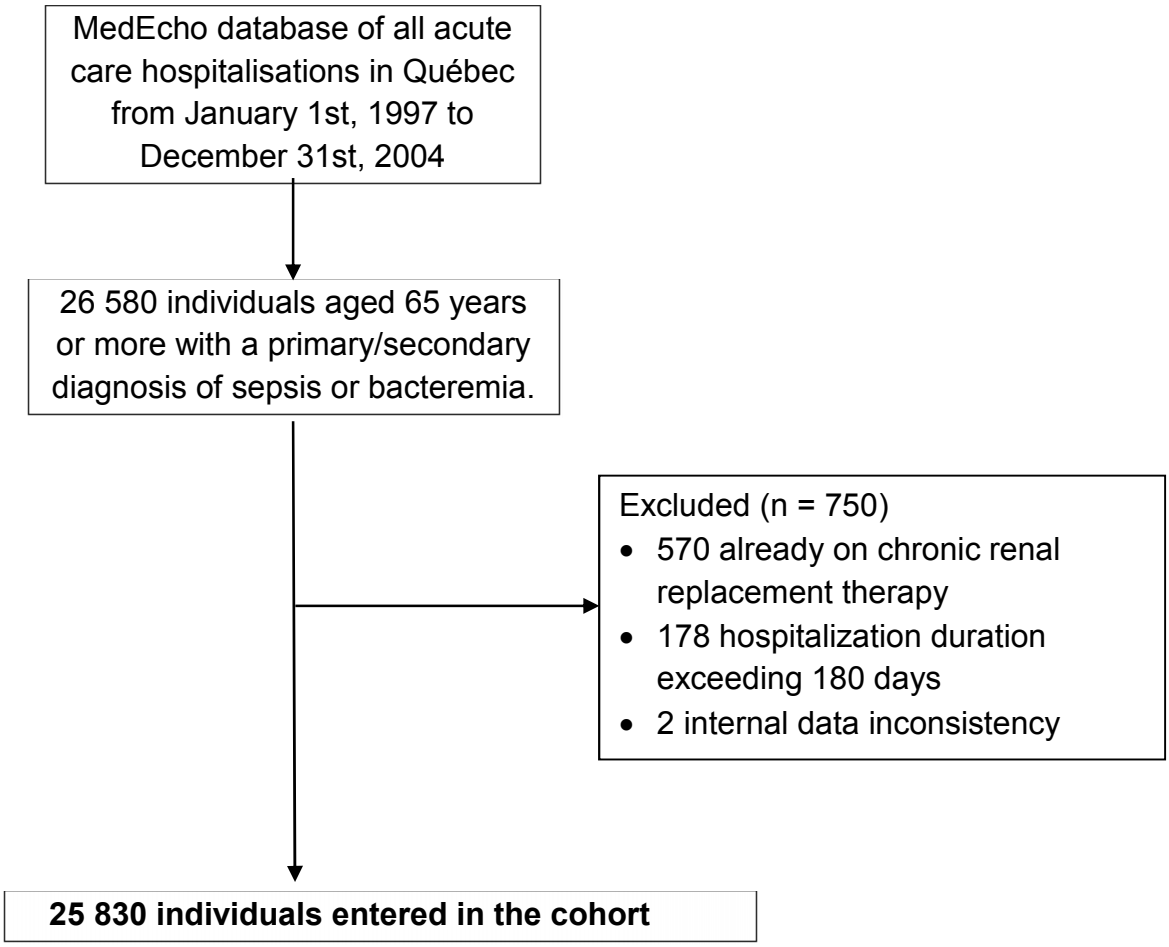
The *Commission d'accès à l'information du Québec* gave consent to our use of the databases for this study. The study protocol was approved by the ethics committee of the McGill University Health Center. As this was an observational, retrospective, non-nominal study, informed consent of patients or surrogates was not required.

Chapter 4-Results.

4.1 Cohort recruitment.

The MedEcho database was searched, and among all acute care hospitalizations in Québec between January 1st 1997 and December 31st 2004, 26 580 individual aged 65 years or more were discharged with a primary or secondary diagnosis of septicemia and/or bacteremia. Of these, 750 individuals were excluded from the cohort: 570 because they had received renal replacement therapy prior to the index hospitalization, 178 because the index hospitalization lasted more than 180 days, and two individuals because of internal data inconsistency. The residual (a total of 25 830 individuals) was included in the cohort (figure 1).

Figure 1.
Flow diagram of recruitment in the cohort.

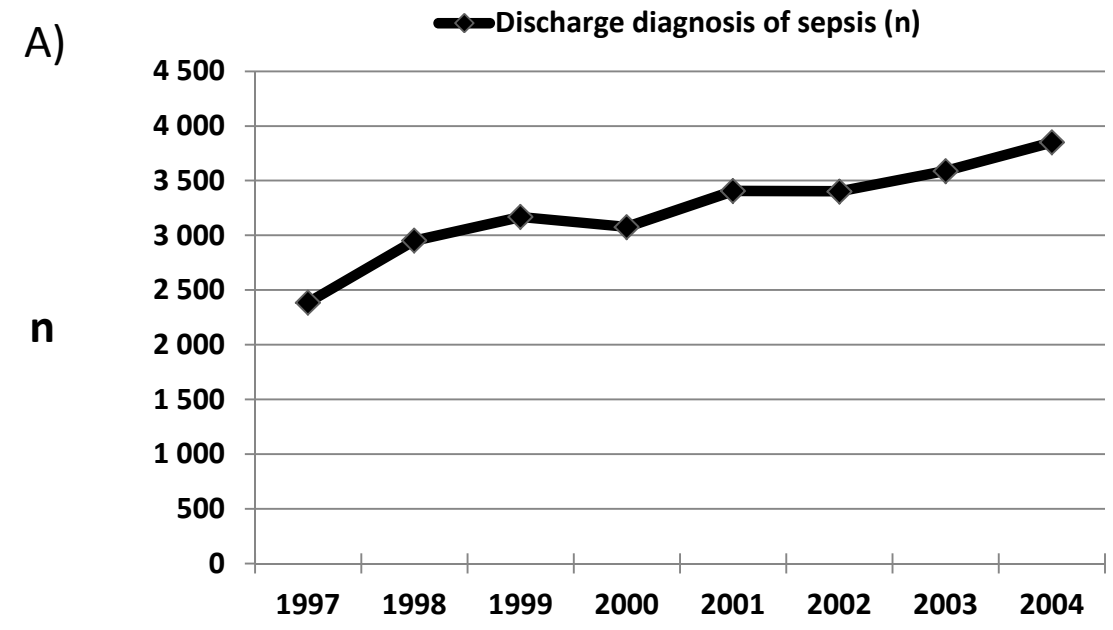


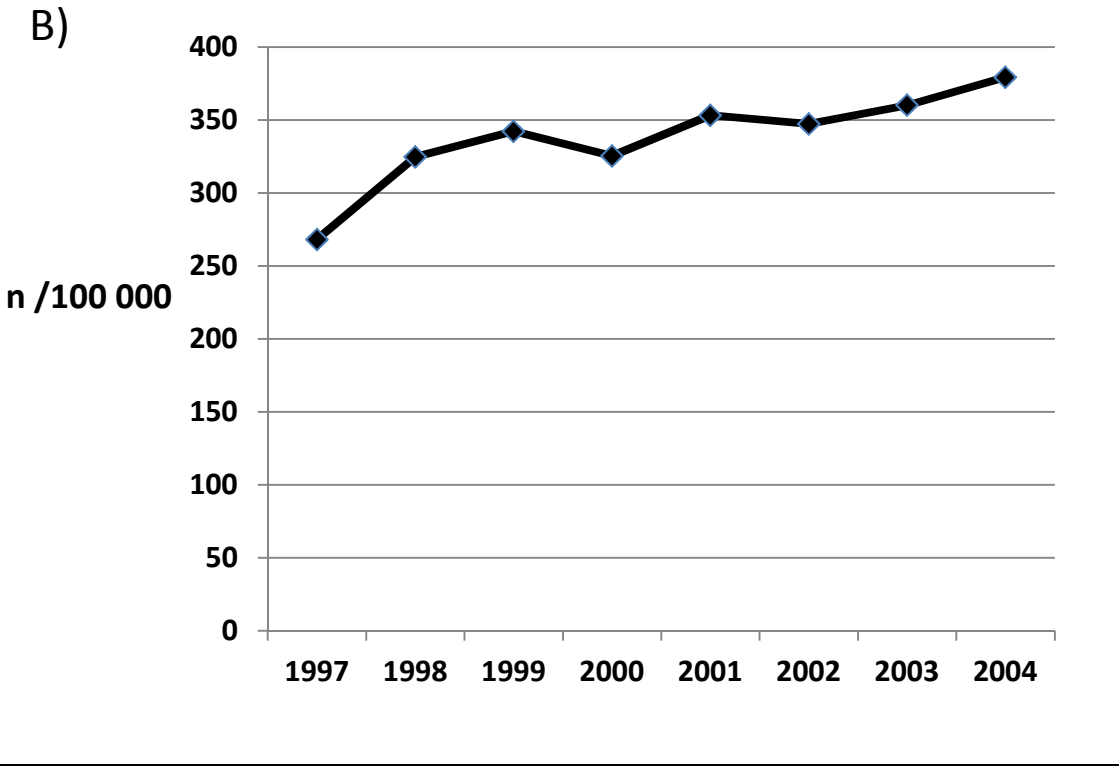
A progressive increase in the annual numbers discharged with a diagnosis of septicemia and/or bacteremia was noted throughout the study period (figure 2), with the annual number of sepsis cases increasing from 2386 to 3851. This corresponds to an increase in incidence rate from 268 cases per 100,000 person-years in 1997 to 379 cases per 100,000 person-years in 2004, for the population of Québec aged 65 years or more (figure 2a and 2b). This important increase in sepsis incidence is similar to what is reported during equivalent time periods in other population-based epidemiologic studies of sepsis.

Figure 2.

A) *Number of individuals included in the cohort by year.*

B) *Population-based (age ≥ 65) incidence of sepsis by year*





4.2 Cohort description and significant trends.

Baseline characteristics and selected outcomes: Table 1 provides baseline characteristics, associated comorbidities and selected outcomes for the entire cohort. This is an elderly cohort, more than 60% of individuals being at least 75 years old, and the proportion of older individuals increasing during the study period. Women and men are almost equally represented, but there is an important difference in the age structure of genders, men outnumbering women in the 65 to 74 years group, and women outnumbering men in the group aged 85 or more (table 2).

Chronic comorbidities: this cohort has a high prevalence of chronic comorbidities: diabetes, hypertension, coronary disease, chronic heart failure, peripheral arterial disease and chronic renal failure (table 1). During the eight-year study period, important increases in the prevalence ratios occurred for hypertension (from 29% to 50%), chronic renal failure (from 14% to 23%), coronary disease (from 25% to 38%) and diabetes (from 24% to 29%) (figure 3A).The prevalence ratio of chronic heart failure and peripheral arterial disease remained fairly stable at approximately 20%, while the prevalence ratio of chronic liver disease increased slightly, but remained low (4 to 6%) (figure 3B).

Table 1. *Baseline characteristics, comorbidities and selected outcomes for the entire cohort (n = 25830).*

Baseline characteristics.	
Year of admission (median, IQR)	2001 (1999-2003)
Age, years (median, IQR)	77 (71-83)
Male gender (%)	13126 (50.8)
Sepsis is a secondary diagnosis (%)	19512 (75.6)
Baseline comorbidities.	
Hypertension (%)	10604 (41.0)
Diabetes (%)	6794 (26.2)
Coronary disease (%)	8751 (33.9)
Chronic heart failure (%)	5001 (19.3)
Chronic renal failure (%)	4513 (17.5)
Peripheral arterial disease (%)	5497 (21.2)
Chronic liver disease (%)	1973 (4.5)
Outcomes	
Shock (%)	2843 (11.0)
Acute renal failure (%)	5585 (17.5)
Hospitalization duration (days), median (IQR)	13 (6-29)
In-hospital mortality (%)	7656 (29.6)

Table 2. *Age distribution of cohort members according to gender.*

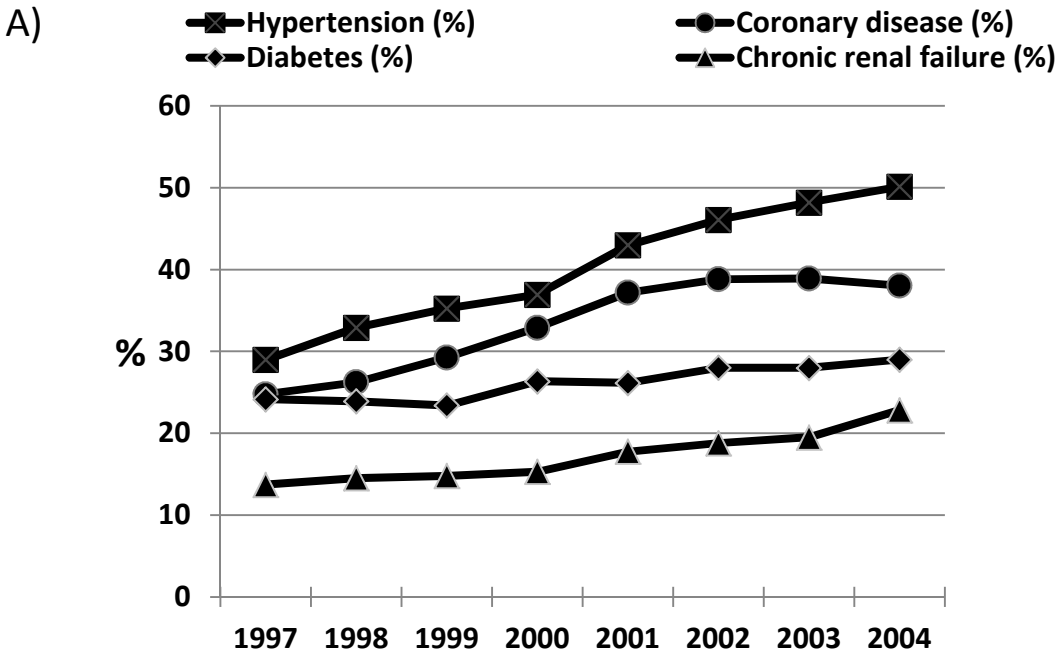
	Women (%)	**Men (%)**	**Total**
65 to 74 years	4194 (42.2)	5747 (57.8)	9941
75 to 84 years	5484 (50.2)	5439 (49.8)	10923
≥ 85 years	3026 (60.9)	1940 (39.1)	4966
Total	12704 (49.2)	13126 (50.8)	25830

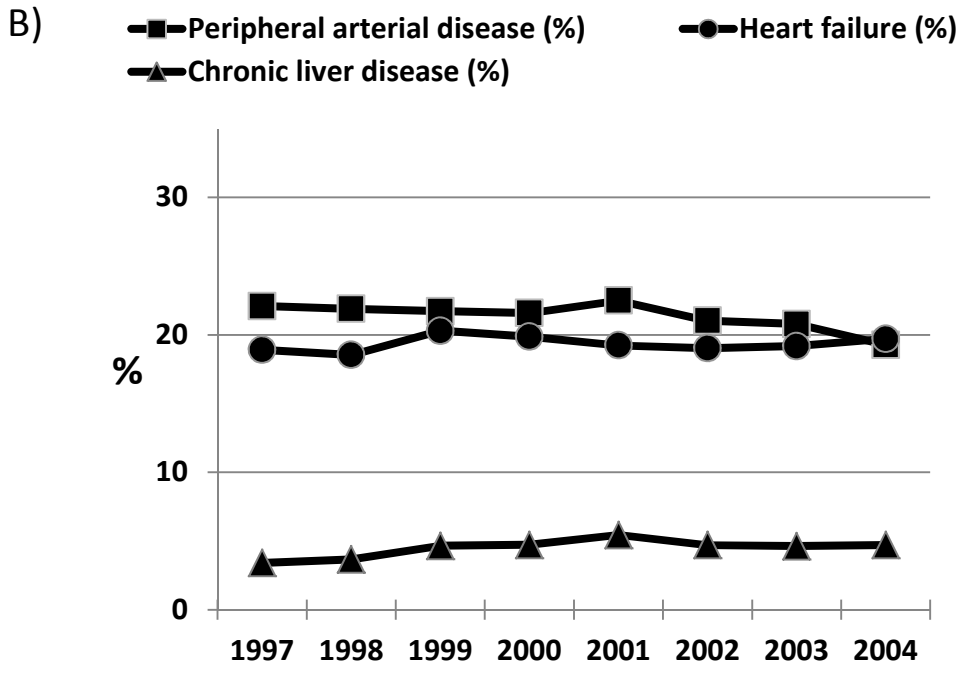
Figure 3.

Prevalence (%) of baseline comorbidities by year of cohort entry.

A) *Hypertension, coronary disease, diabetes and chronic renal failure.*

B) *Peripheral arterial disease, heart failure and chronic liver disease.*





Approximately three fourths (19 512/25 830) of individuals in the cohort received a secondary, rather than primary, discharge diagnosis of sepsis. Individuals with a secondary diagnosis had a more complicated hospital course, as reflected by a greater duration of hospitalization, a higher incidence of acute renal failure, more sepsis-associated organ dysfunctions, and greater in-hospital mortality (table 3).

Table 3: *comparison between individuals with a primary diagnosis of sepsis and individuals with a secondary diagnosis of sepsis.*

	Primary diagnosis n = 6318 n (%)	**Secondary diagnosis n = 19512 n (%)**
Baseline characteristics.		
Age (years) (median, IQR)	78 (72-84)	77 (71-83)
Male gender	3087 (48.9)	10 039 (51.4)
Baseline comorbidities.		
Hypertension	2601 (41.2)	8003 (41.0)
Diabetes	1808 (28.6)	4986 (25.5)
Coronary disease	1992 (31.5)	6759 (34.6)
Chronic heart failure	1095 (17.3)	3906 (20.0)
Chronic renal failure	1202 (19.0)	3311 (17.0)
Peripheral arterial disease	1218 (19.3)	4276 (21.9)
Chronic liver disease	317 (5.0)	856 (4.4)
Outcomes		
Hospitalization duration(days) median (IQR)	8 (4-16)	15 (7-33)
Mean number of acute organ dysfunctions (95% C.I.)	0.47 (0.45-0.49)	0.66 (0.65-0.67)
Shock	540 (8.5)	2303 (11.8)
Acute renal failure	1036 (16.4)	3549 (18.2)
In-hospital mortality	1265 (20.0)	6387 (32.7)

Exposure: drug categories and number of drugs used. Table 4 summarizes the exposure to antihypertensive drugs, defined as at least one prescription filled in the 60-day period preceding the index admission date. Prescriptions of calcium channel blockers were the most frequent (24% of cohort members), followed closely by ACEIs (22%) and loop diuretics (22%). Thiazide diuretics (14%) and beta-blockers (11%) were prescribed less frequently. Other classes of antihypertensive drugs (potassium-sparing diuretics, alpha blockers, nitrates, etc.) were much less frequently used, which is in accordance with contemporary guidelines on the treatment of hypertension[100,101].

Table 4: *Antihypertensive drug exposure .*
- by drug category for the entire cohort (n = 25830).

Drug category	**n (%)**
Calcium channel blockers	6267 (24.2)
ACE inhibitors	5786 (22.2)
Loop diuretics	5735 (22.2)
Thiazides	3700 (14.3)
Beta blockers	2991 (11.5)
Angiotensin receptor blockers	1905 (7.2)
Potassium sparing diuretics	1714 (6.6)
Nitrates	1149 (4.5)
Alpha blockers	570 (2.2)
CNS agents and ganglioplegics	391 (1.5)
Arterial vasodilators	114 (0.4)

Table 5 summarizes the proportion of cohort members exposed to antihypertensive drugs. The majority (67.7%) of cohort members had been exposed to at least one antihypertensive drug prior to hospital admission. Of those exposed, 20.8% were on monotherapy, while 36.9% were on polytherapy.

Table 5. *Antihypertensive drug exposure.*
Simultaneous drug exposure for the entire cohort (n = 25830).

Number of drugs	n (%)
No antihypertensive drugs	10913 (42.3)
One antihypertensive drug	5371 (20.8)
Two antihypertensive drugs	5278 (20.4)
More than two antihypertensive drugs	4268 (16.5)

Trends in antihypertensive drug exposure: drug categories. Figure 4 represents trends in drug exposure during the study period. Exposure to all antihypertensive drug categories increased, the most notable increase occurring with angiotensin receptor blockers (from 1% to 14%), which corresponds to the introduction of ARBs on the Québec drug formulary at the beginning of the study period.

Trends in antihypertensive drug exposure: monotherapy and polytherapy. Figures 5 and 6 reflect the changing pattern of drug exposure during the study period. The proportion of individuals not exposed to antihypertensive drugs decreased from 50% to 35%. Polytherapy increased in frequency: the proportion of cohort entries using more than one drug increased from 29% to 43%. These trends are likely related to improved diagnosis and treatment of arterial hypertension in the general population, but may also be related to the increasing prevalence of chronic comorbidities in the cohort, since some of these diseases (heart failure, chronic renal failure, coronary disease) often necessitate polytherapy with drugs that are also used to treat hypertension (diuretics, ACEIs, ARBs and beta-blockers are used in the treatment of heart failure and of chronic renal failure). Similar trends in drug use have been reported in recent studies of cardiovascular pharmacotherapy in Canadians [45,46,102].

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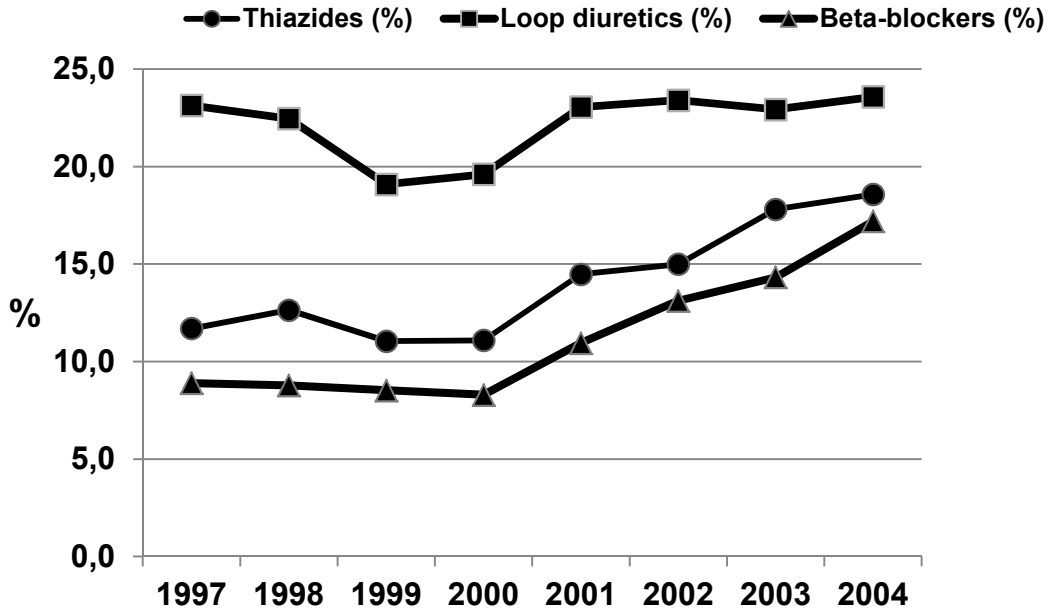
Figure 4.

Prevalence (%) of drug exposure by year of entry in the cohort.

A) thiazide diuretics, loop diuretics and beta-blockers.

B) calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

A)



B)

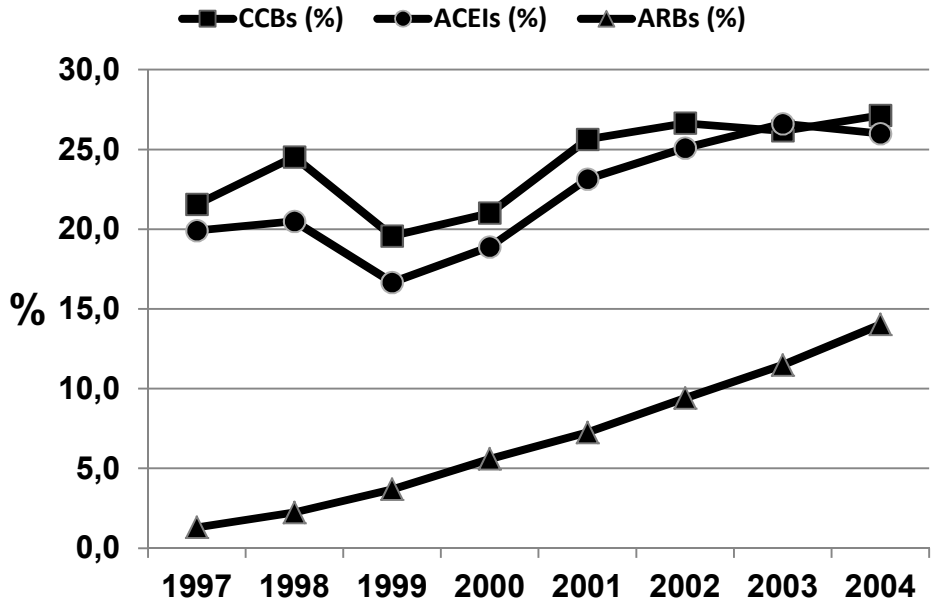


Figure 5.
Prevalence (%) of exposure to at least one antihypertensive drugs by year of cohort entry.

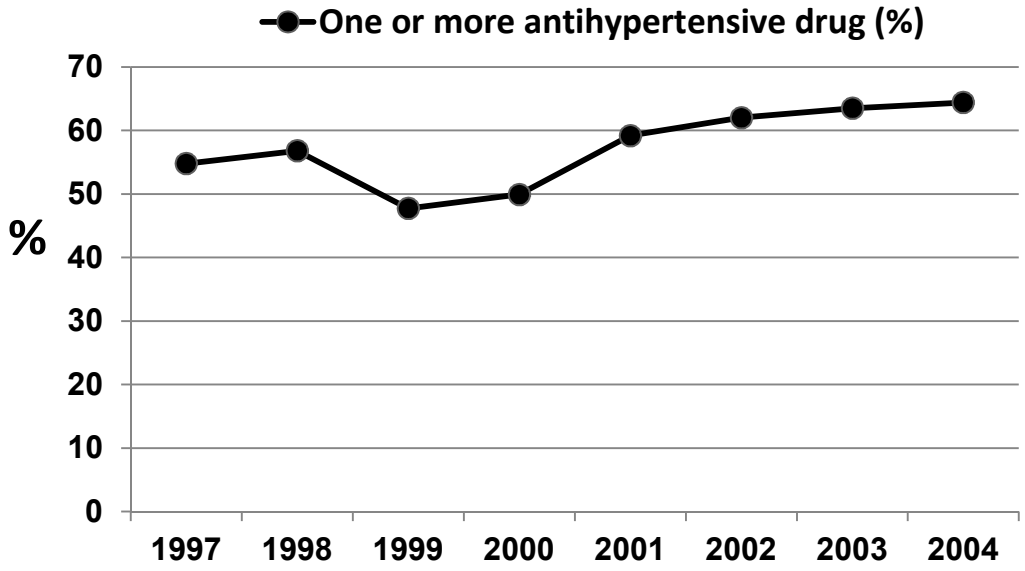
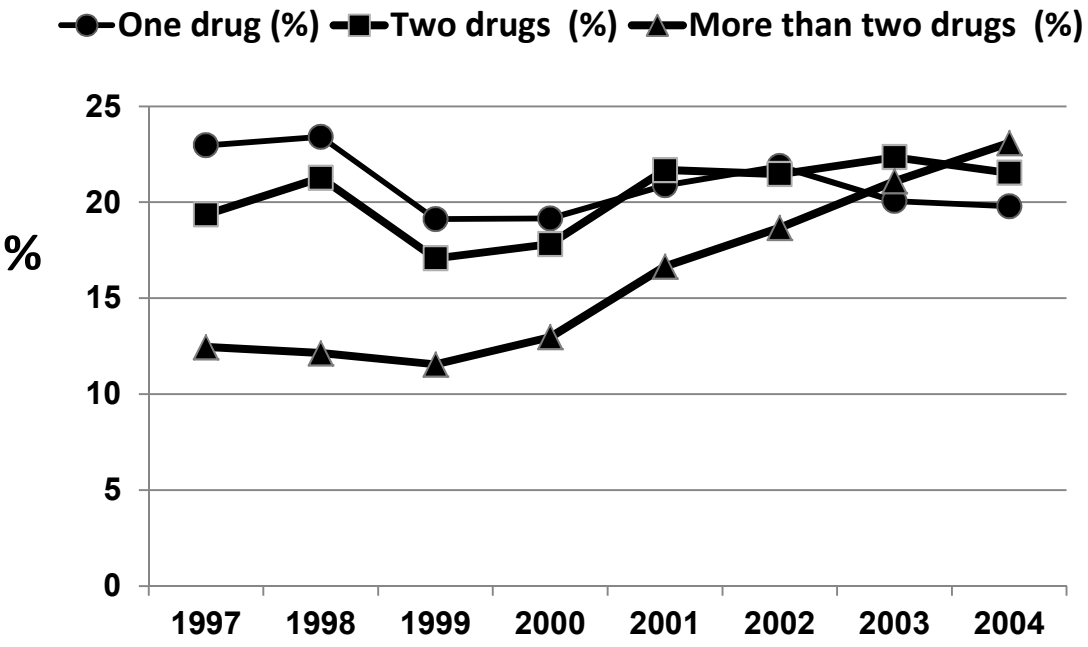


Figure 6.
Prevalence (%) of exposure to antihypertensive drugs: number of drugs used simultaneously, by year of cohort entry.



4.3 Outcomes.

4.3.1 Acute renal failure.

A total of 4585 individuals (17.5%) were diagnosed with acute renal failure. Only one individual had acute renal failure coded as the principal diagnosis; all others had ARF coded as a secondary diagnosis. There was a marked increase in the incidence of acute renal failure during the study: the number of cases increasing from 275 in 1997 to 942 in 2004 (figure 7). Of the acute renal failure cases, approximately one third (1633/4585) had pre-existing chronic renal failure and this proportion remained constant throughout the study period (figure 8).

Figure 7.
Incidence (%) of acute renal failure in cohort members, by year of cohort entry.

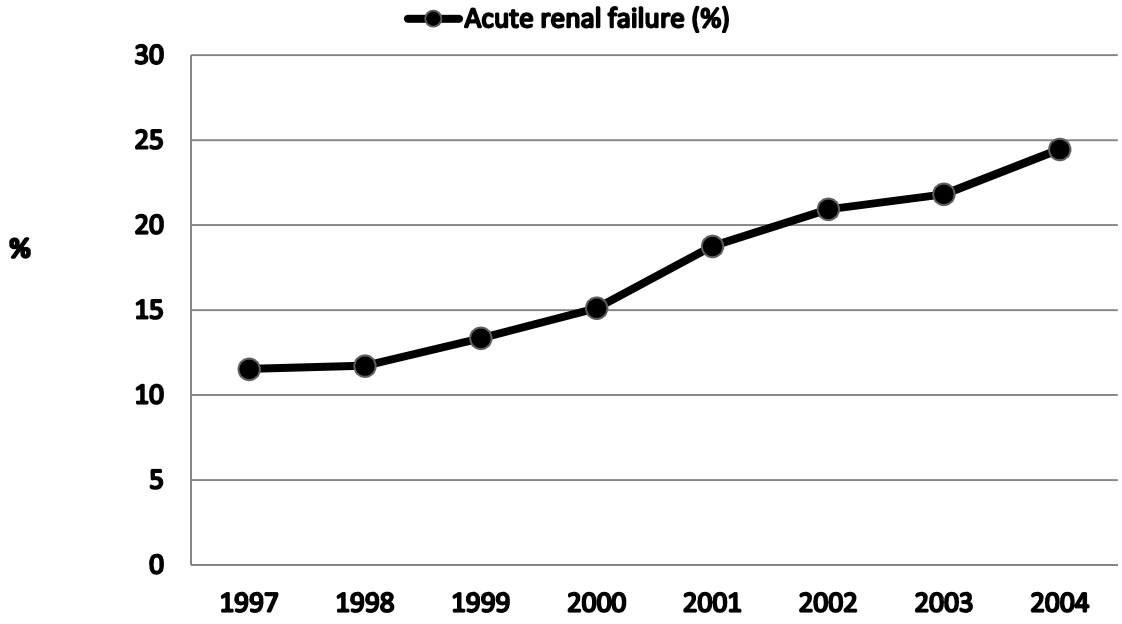


Figure 8.
Number of individuals with acute renal failure (ARF), by year of cohort entry, with and without prior chronic renal failure (CRF).

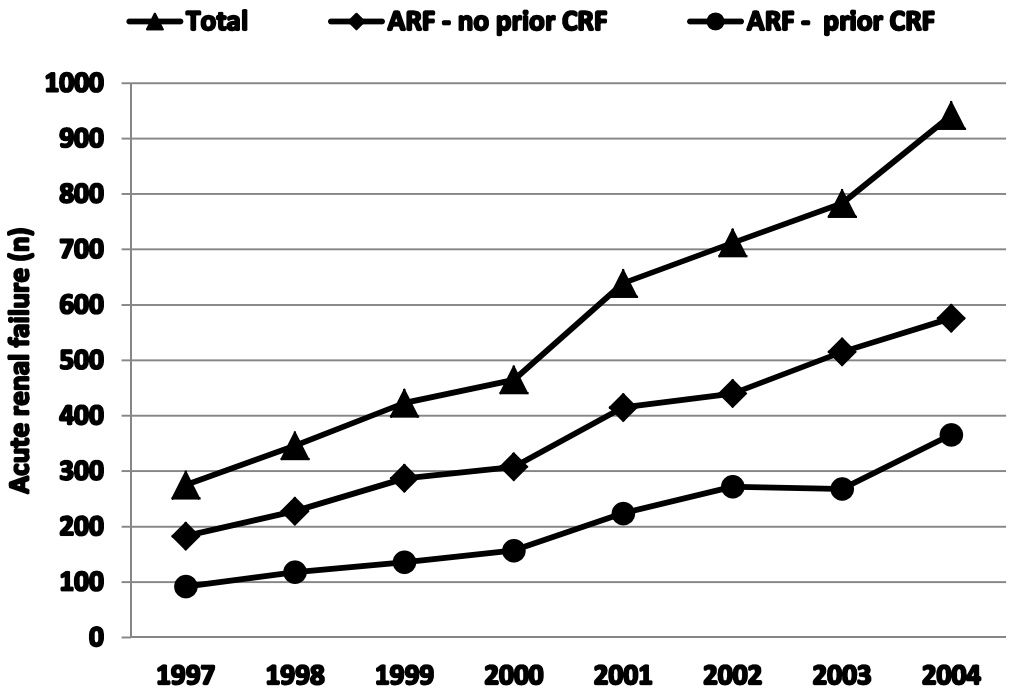


Table 6 compares baseline characteristics, comorbidities and in-hospital mortality of individuals with and without acute renal failure. All the comorbidities under study were more frequent in individuals developing acute renal failure. Acute renal failure was associated with an increased length of stay (median 18 days with ARF compared to 12 days without ARF) and with higher in-hospital mortality (47% with ARF compared to 26% without ARF).

Table 6 *Comparison of subgroups with and without acute renal failure.*

	Without ARF[1] (n = 21245)	With ARF (n = 4585)
Baseline characteristics (%)		
Age (years) (median, IQR)	77 (71-83)	77 (72-83)
Male gender	10 608 (49.9)	2518 (54.9)
Sepsis is a secondary diagnosis	15 963 (75.1)	3549 (77.4)
Baseline comorbidities (%)		
Hypertension	8457 (39.8)	2147 (46.8)
Diabetes	5350 (25.2)	1444 (31.5)
Coronary disease	6808 (32.1)	1943 (42.4)
Chronic heart failure	3607 (17.0)	1394 (30.4)
Chronic renal failure	2880 (13.6)	1633 (35.6)
Peripheral arterial disease	4338 (20.4)	1156 (25.2)
Chronic liver disease	876 (4.1)	297 (6.5)
Outcomes (%)		
Hospitalization duration(days), median (IQR)	12 (6-27)	18 (8-37)
Shock	1748 (8.2)	1095 (23.9)
In-hospital mortality	5506 (25.9)	2146 (46.8)

[1] **ARF: Acute renal failure.**

4.3.2 Renal replacement therapy.

Figure 9 represents the yearly numbers of individuals diagnosed with acute renal failure and the numbers treated with renal replacement therapy. Although there was an increase in the yearly numbers treated with renal replacement therapy (from 60 to 104), this was less important than the increase in ARF diagnosis, so that the proportion of those with ARF who received renal replacement therapy decreased from 22% to 11% (figure 10).

Figure 9.
Number of individuals with acute renal failure (ARF) by year of cohort entry, and number who received renal replacement therapy.

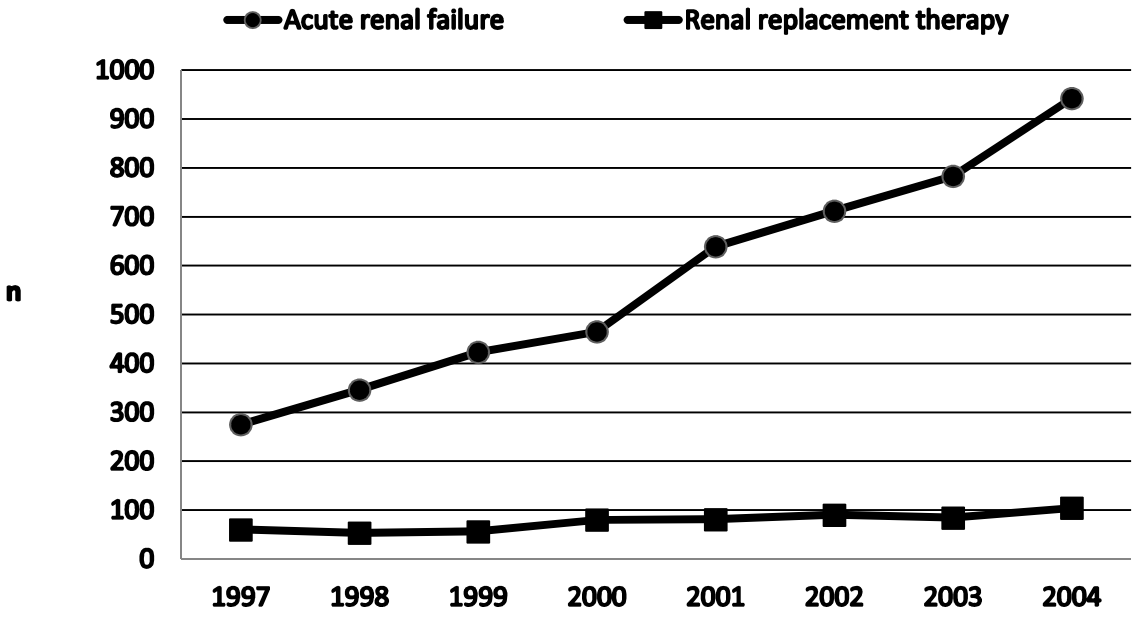
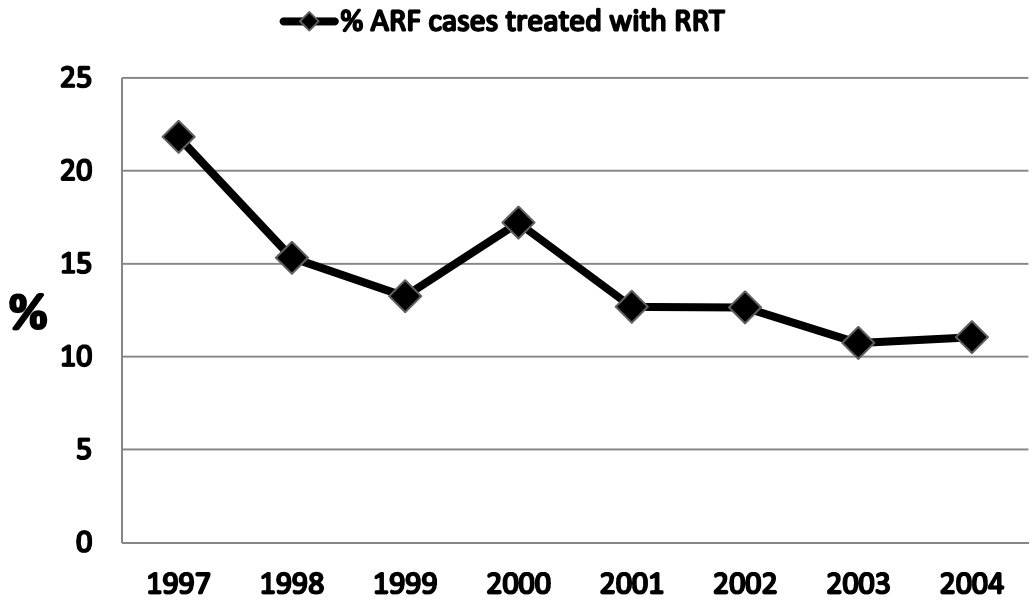


Figure 10.

Percentage of acute renal failure cases (ARF) who received renal replacement therapy (RRT) by year of cohort entry.



Among individuals with ARF treated with renal replacement therapy, important differences existed between those who had pre-existing chronic renal failure and those who did not. Table 7 summarizes these differences: individuals with chronic renal failure were older, and had a greater burden of chronic comorbidities (hypertension, diabetes, coronary disease, chronic heart failure, peripheral arterial disease). Despite this, the severity of sepsis seems to have been lower in the group with prior chronic renal failure, as evidenced by a lower incidence of shock (24% vs. 44%), a lower number of non-renal organ dysfunctions (mean 1.04 vs 1.65) and a lower in-hospital mortality rate (48% vs 65%), as compared to the subgroup without CRF.

Table 7.
Individuals treated with renal replacement therapy: comparison of subgroups with and without chronic renal failure.

	With CRF[1] n = 292 n (%)	Without CRF n = 316 n (%)
Baseline characteristics		
Age (years)(median, IQR)	74 (69-79)	72 (68-77)
Male gender	177 (60.6%)	179 (56.6%)
Sepsis is a secondary diagnosis.	257 (88.0%)	282 (89.2%)
Baseline comorbidities		
Hypertension	192 (65.7%)	104 (32.9%)
Diabetes	124 (42.5%)	84 (26.5%)
Coronary disease	155 (53.1%)	130 (41.1%)
Chronic heart failure	121 (41.4%)	82 (25.9%)
Peripheral arterial disease	115 (39.4%)	77 (24.4%)
Chronic liver disease	8 (2.7%)	21 (6.6%)
Outcomes		
Mean number of non-renal organ dysfunctions (95% C.I.)	1.04 (0.91-1.16)	1.65 (1.52-1.77)
Shock	70 (24.0%)	139 (44.0%)
Hospitalization duration (days), median (IQR)	32 (18-62.5)	30 (16-55)
In-hospital mortality	140 (47.9%)	270 (65.5%)

[1] **CRF: Chronic renal failure**

4.4 Risk assessment.

4.4.1 Risks associated with baseline characteristics and comorbidities.

Risk of acute renal failure.

Table 8 details the risk estimates for acute renal failure associated with baseline characteristics and baseline comorbidities, both in univariate analysis and with multivariate logistic regression (model A).

There is an important increase in the risk of ARF with each passing year of the 1999-2004 period, which corresponds to the important annual increase in ARF incidence previously noted (adjusted O.R. 3.51 per 10 year increase).

There is no sign of increased risk for acute renal failure with advancing age, in either univariate analysis or multivariate analysis. The two older subgroups' risks of acute renal failure are comparable to the younger group's risk.

Male gender is associated with a slightly higher risk of ARF (adjusted O.R. 1.19).

Sepsis as a secondary, rather than a primary diagnosis, is also associated with a slightly higher risk (adjusted O.R. 1.12).

In univariate analysis, all the comorbidities included in model A are associated with an increased risk of ARF, the association being the strongest for chronic renal failure and chronic heart failure. In multivariate analysis, chronic renal failure and chronic heart failure remain the most significant risk factors for ARF, with slightly lower odds ratios. The risk association with chronic liver disease is unchanged. The adjusted odds ratios associated with diabetes, coronary disease and peripheral arterial disease are lower and vary between 1.03 and 1.13. The most important change in risk estimates occurs with hypertension, which is associated with an *increased* risk of ARF in univariate analysis (crude OR 1.33), but with a *lower* risk in the multivariate analysis (adjusted OR 0.91) (table 8).

Table 8.

Risk of acute renal failure associated with baseline characteristics and comorbidities (Model A). Entire cohort (N = 25 830).

	Without ARF[1] (n = 21245) n (%)	With ARF (n = 4585) n (%)	Crude O.R.	Adjusted	
				O.R	95% C.I.
Baseline characteristics.					
Admission year, median	2001	2002	4.17[2]	3.51[2]	3.00-4.10
Age 65 to 74 years	8243 (38.8)	1698 (37.0)	Reference group		
Age 75 to 84 years	8901 (41.9)	2022 (44.1)	1.10	1.00	0.93-1.08
Age ≥ 85 years	4101 (19.3)	865 (18.9)	1.02	0.89	0.81-0.98
Male gender	10608 (49.9)	2518 (54.9)	1.22	1.19	1.11-1.28
Sepsis is a secondary diagnosis	15963 (75.1)	3549 (77.4)	1.13	1.12	1.04-1.22
Baseline comorbidities					
Diabetes	5350 (25.2)	1444 (31.5)	1.37	1.13	1.04-1.22
Coronary disease	6808 (32.1)	1943 (42.4)	1.56	1.12	1.05-1.21
Heart failure	3607 (17.0)	1394 (30.4)	2.14	1.75	1.61-1.90
Chronic renal failure	2880 (13.6)	1633 (35.6)	3.53	2.99	2.76-3.23
Peripheral arterial disease	4338 (20.4)	1156 (25.2)	1.31	1.03	0.96-1.11
Chronic liver disease	876 (4.1)	297 (6.5)	1.61	1.53	1.41-1.89

[1] **ARF: Acute renal failure.**

[2] **Per 10 year increase in admission date.**

Risk of renal replacement therapy.

Table 9 details the risk estimates for renal replacement therapy associated with baseline characteristics and baseline comorbidities, both in univariate analysis and with multivariate logistic regression (model A).

There is possibly an increased risk of renal replacement therapy with entry in the cohort in the later part of the study period. The adjusted odds ratio is 1.21 per 10 year increase in admission date, but the 95% CI includes 1.0 (null effect).

There is a strongly decreasing risk of renal replacement therapy with advancing age: only 24 out of 4966 individuals with ARF aged over 85 received RRT (3.9%). - resulting in an adjusted odds ratio of 0.10. This is likely to reflect differences in therapeutic approach (rather than differences in severity of ARF), since individuals with ARF aged 85 or more had higher in-hospital mortality than younger individuals, whether renal replacement therapy was used or not (mortality 67% vs. 57%, and 53% vs. 43% respectively), suggesting that, for a comparable severity of acute renal failure, older individuals were less likely to receive renal replacement therapy (table 10).

A secondary diagnosis of sepsis is clearly associated with an increased risk of renal replacement therapy, with an adjusted odds ratio of 2.43.

In univariate analysis, all the comorbidities are associated with an increased risk of renal replacement therapy. Multivariate analysis (model A) results are very similar to those obtained when the outcome is acute renal failure. Chronic renal failure is by far the most important risk factor for renal replacement therapy. Chronic heart failure, coronary disease and peripheral arterial disease are also associated with an increased risk of renal replacement therapy, but diabetes, chronic liver disease and hypertension are not (table 9).

Table 9.
Risk of renal replacement therapy associated with baseline characteristics and comorbidities (Model A). Entire cohort (N = 25 830).

	No RRT[1] (n= 25222) n (%)	RRT (n= 608) n (%)	Crude O.R.	Adjusted	
				O.R	95% C.I.
Baseline characteristics.					
Admission year, median	2001	2001	1.45[2]	1.21[2]	0.83-1.76
Age 65 to 74 years	9592 (38.0)	359 (59.1)	Reference group		
Age 75 to 84 years	10698 (42.4)	225 (37.0)	0.56	0.47	0.39-0.56
Age ≥ 85 years	4942 (19.6)	24 (3.95)	0.13	0.10	0.07-0.15
Male gender	12770 (50.6)	356 (58.5)	1.38	1.13	0.95-1.34
Sepsis is a secondary diagnosis	18973 (75.2)	539 (88.7)	2.57	2.43	1.89-3.16
Baseline comorbidities					
Hypertension	10308 (40.9)	296 (48.7)	1.37	0.82	0.68-0.99
Diabetes	6586 (26.1)	208 (34.2)	1.47	0.86	0.71-1.03
Coronary disease	8466 (33.6)	285 (46.9)	1.75	1.20	1.00-1.44
Heart failure	4798 (19.0)	203 (33.4)	2.13	1.49	1.23-1.82
Chronic renal failure	4221 (16.7)	292 (48.0)	4.60	4.19	3.49-5.03
Peripheral arterial disease	5302 (21.0)	192 (31.6)	1.73	1.34	1.11-1.61
Chronic liver disease	1144 (4.5)	29 (4.8)	1.05	0.94	0.63-1.39

[1] **RRT: Renal replacement therapy**

[2] **Per 10 year increase in admission date.**

Table 10.

In-hospital mortality by age group according to acute renal failure (ARF) / renal replacement therapy (RRT) status, stratified by age group.

	ARF(-)[1]	ARF(+) / RRT(-)[2]	ARF(+) / RRT(+)[3]
Age category			
65 to 74 years	1822/8243 (22.1)	535/1339 (40.0)	193/359 (53.8)
75 to 84 years	2213/8901 (26.0)	817/1797 (45.5)	138/225 (61.3)
≥ 85 years	1371/4101 (33.4)	447/841 (53.1)	16/24 (66.7)

[1] **ARF (-) : Absence of acute renal failure.**

[2] **ARF (+)/ RRT (-): Acute renal failure, did not receive renal replacement therapy**

[3] **ARF (+)/ RRT (+): Acute renal failure, received renal replacement therapy.**

4.4.2 Risks associated with exposure to antihypertensive drugs, by category.

Risk of acute renal failure.

Table 11 summarizes the risk of acute renal failure associated with exposure to antihypertensive drug categories in the entire cohort. With univariate analysis, all categories of antihypertensive drugs are associated with an increased risk of acute renal failure, but major changes in the risk estimates occur when multivariate logistic regression is used (model A). The following drug categories are still associated with an increased risk: thiazide diuretics (adjusted OR 1.29), ACEIs (adjusted OR 1.17), ARBs (adjusted OR 1.25), but there is a *neutral* effect of exposure for loop diuretics, beta blockers and calcium channel blockers. The impact of multivariate analysis is most notable for loop diuretics: the odds ratios for this drug category decrease from 1.62 (unadjusted) to 1.06 (adjusted).

Risk of acute renal failure: stratification for chronic heart failure.

Table 12 summarizes the risk estimates (model A) for acute renal failure in subgroups stratified for chronic heart failure. In the subgroup *without* heart failure, exposure to thiazides, ACEIs or ARBs is associated with a higher risk of ARF. In the subgroup *with* chronic heart failure, only thiazides and ARBs are associated with an increased risk.

Risk of acute renal failure: stratification for chronic renal failure.

Table 13 summarizes the risk estimates (model A) for acute renal failure in subgroups stratified for chronic renal failure. In the subgroup *without* chronic renal failure, exposures to thiazides, ACEIs or ARBs are associated with a higher risk of ARF. In the subgroup *with* chronic renal failure, there is no increase in risk with exposure to any anti-hypertensive drug category.

Table 11.
Risk of acute renal failure associated with antihypertensive drug categories (model A). Entire cohort (N = 25 830).

	Without ARF[1] (n= 21245) n (%)	With ARF (n= 4585) n (%)	Crude O.R.	Adjusted	
				O.R	95% C.I.
Drug category					
Thiazides	2903 (13.7)	797 (17.4)	1.33	1.29	1.16-1.43
Loop diuretics	4380 (20.6)	1355 (29.6)	1.62	1.06	0.97-1.16
ACE inhibitors	4490 (21.1)	1296 (28.3)	1.47	1.17	1.08-1.27
Angiotensin receptor blockers	1421 (6.7)	484 (10.6)	1.65	1.25	1.10-1.41
Beta blockers	2376 (11.2)	615 (13.4)	1.23	0.98	0.89-1.09
Calcium channel blockers	4996 (23.5)	1271 (27.7)	1.25	0.98	0.91-1.06

[1] **ARF: Acute renal failure.**

Table 12.

Risk of acute renal failure associated with antihypertensive drug categories (model A). Stratification for chronic heart failure.

Subgroup without chronic heart failure N= 20829

	Without ARF[1] (N = 17638) n (%)	With ARF (N = 3191) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	2590 (14.3)	601 (18.8)	1.27	(1.12-1.43)
Loop diuretics	2767 (15.7)	666 (20.9)	1.09	(0.97-1.21)
ACE inhibitors	3272 (18.5)	796 (24.9)	1.25	(1.13-1.36)
Angiotensin receptor blockers	1135 (6.4)	308 (9.7)	1.21	(1.05-1.41)
Beta blockers	1909 (10.8)	390 (12.2)	0.94	(0.83-1.06)
Calcium channel blockers	3997 (22.7)	829 (26.0)	0.96	(0.88-1.06)

Subgroup with chronic heart failure N= 5001.

	Without ARF (N = 3607) n (%)	With ARF (N = 1394) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	384 (10.7)	196 (14.1)	1.34	1.09-1.65
Loop diuretics	1613 (44.7)	689 (49.4)	1.03	0.88-1.19
ACE inhibitors	1218 (33.8)	500 (35.9)	1.04	0.90-1.21
Angiotensin receptor blockers	286 (7.9)	176 (12.6)	1.33	1.06-1.66
Beta blockers	467 (12.9)	225 (16.1)	1.10	0.92-1.32
Calcium channel blockers	999 (27.7)	442 (31.7)	1.01	0.87-1.17

[1] **ARF: Acute renal failure**

Table 13.

Risk of acute renal failure associated with antihypertensive drug categories (model A). Stratification for chronic renal failure

Subgroup without chronic renal failure N= 21317.

	Without ARF[1] (N = 18365) n (%)	With ARF (N = 2952) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	2472 (13.5)	516 (17.5)	1.33	1.17-1.15
Loop diuretics	3260 (17.7)	693 (23.5)	1.13	1.01-1.25
ACE inhibitors	3633 (19.8)	765 (25.9)	1.21	1.09-1.34
Angiotensin receptor blockers	1135 (6.18)	276 (9.35)	1.30	1.12-1.51
Beta blockers	1966 (1.7)	364 (12.3)	0.98	0.86-1.11
Calcium channel blockers	4023 (21.9)	693 (23.5)	0.97	0.88-1.07

Subgroup with chronic renal failure N= 4513.

	Without ARF (N = 2880) n (%)	With ARF (N = 1633) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	431 (14.9)	281 (17.2)	1.18	0.98-1.42
Loop diuretics	1120 (38.9)	662 (40.5)	0.95	0.82-1.10
ACE inhibitors	857 (29.8)	531 (32.5)	1.09	0.95-1.27
Angiotensin receptor blockers	286 (9.9)	208 (12.7)	1.18	0.96-1.46
Beta blockers	410 (14.3)	251 (15.4)	0.98	0.82-1.17
Calcium channel blockers	973 (33.8)	578 (35.4)	1.00	0.87-1.15

[1] **ARF: Acute renal failure**

Risk of acute renal failure: stratification for primary or secondary diagnosis of sepsis.

Table 14 summarizes the risk estimates (model A) for acute renal failure in subgroups stratified for a primary or a secondary diagnosis of sepsis. In both subgroups, exposure to ACEIs and ARBs is associated with a significant risk of acute renal failure. For thiazide diuretics, the risk is increased only in the subgroup with a secondary diagnosis of sepsis. Other antihypertensive drug categories are not associated with an increased risk in either group.

Risk of renal replacement therapy.

Table 15 summarizes the risk estimates (model A) for renal replacement therapy with multivariate logistic regression applied to the entire cohort. In this analysis, loop diuretics, beta blockers and calcium channel blockers are associated with an increased risk, while thiazides, ACEIs and ARBs are not (which is exactly opposite to the results obtained in the analyses of ARF risk detailed previously). However, if the cohort is stratified for chronic renal failure, major changes in the risk estimates occur, demonstrating important effect measure modification, and in the subgroup without chronic renal failure the drug categories associated with an increased risk of ARF also increase the risk of renal replacement therapy.

Table 16 summarizes the risk estimates (model A) for exposure to drug categories when the cohort is stratified according for chronic renal failure. In the subgroup *without* chronic renal failure, thiazides, ACEIs, ARBs, loop diuretics and beta-blockers are all associated with a higher risk of renal replacement therapy, and only calcium channel blockers are not. On the contrary, in the subgroup *with* chronic renal failure, only loop diuretics and calcium channel blockers are associated with a significantly increased risk of renal replacement therapy. This suggests that there is important residual confounding, or effect modification, within the chronic renal failure subgroup.

Table 14.

Risk of acute renal failure associated with antihypertensive drug categories (model A). Stratification for primary or secondary diagnosis of sepsis.

Subgroup with a primary diagnosis of sepsis N= 6318.

	Without ARF[1] (N = 5282) n (%)	With ARF (N = 1036) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	735 (13.9)	161 (15.5)	1.07	0.86-1.33
Loop diuretics	1180 (22.3)	302 (29.1)	0.93	0.78-1.12
ACE inhibitors	1134 (21.4)	295 (28.5)	1.26	1.06-1.50
Angiotensin receptor blockers	351 (6.7)	114 (11.0)	1.42	1.10-1.83
Beta blockers	578 (10.9)	145 (14.0)	1.11	0.90-1.37
Calcium channel blockers	1249 (23.7)	238 (23.0)	0.73	0.62-0.88

Subgroup with a secondary diagnosis of sepsis N= 19 512.

	Without ARF (N = 5282) n (%)	With ARF (N = 1036) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	2168 (13.6)	636 (17.9)	1.36	1.21-1.53
Loop diuretics	3200 (20.1)	1053 (29.7)	1.11	1.00-1.23
ACE inhibitors	3356 (21.0)	1001 (28.2)	1.15	1.04-1.27
Angiotensin receptor blockers	1070 (6.7)	370 (10.4)	1.21	1.05-1.39
Beta blockers	1798 (11.3)	470 (13.3)	0.94	0.84-1.06
Calcium channel blockers	3747 (23.5)	1033 (29.1)	1.06	0.97-1.16

[1] **ARF: Acute renal failure**

Table 15.

Risk of renal replacement therapy associated with antihypertensive drug categories (model A). Entire cohort (N = 25 830).

	No RRT[1] (n = 25222) n (%)	RRT (n = 608) n (%)	Crude O.R.	Adjusted	
				O.R	95% C.I.
Drug category					
Thiazides	3601 (14.3)	99 (16.3)	1.17	1.18	(0.92-1.51)
Loop diuretics	5507 (21.8)	228 (37.5)	2.15	1.44	(1.17-1.77)
ACE inhibitors	5595 (22.2)	191 (31.4)	1.61	1.13	(0.93-1.38)
Angiotensin receptor blockers	1833 (7.3)	72 (11.8)	1.71	1.22	(0.92-1.62)
Beta blockers	2883 (11.4)	108 (17.8)	1.67	1.25	(1.00-1.57)
Calcium channel blockers	6041 (23.9)	226 (37.2)	1.88	1.33	(1.10-1.61)

[1] **RRT: Renal replacement therapy**

Table 16.

Risk of renal replacement therapy - associated with antihypertensive drug categories (model A). Stratification for chronic renal failure.

Subgroup without chronic renal failure N= 21317.

	No RRT[1] (N= 21 001) n (%)	RRT (N = 316) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	2929 (13.9)	59 (18.7)	1.50	1.08-2.09
Loop diuretics	3870 (18.4)	83 (26.3)	1.41	1.05-2.09
ACE inhibitors	4301 (20.5)	97 (30.7)	1.48	1.12-1.95
Angiotensin receptor blockers	1379 (6.6)	32 (10.1)	1.42	0.95-2.14
Beta blockers	2277 (10.8)	53 (16.8)	1.35	0.99-1.84
Calcium channel blockers	4639 (22.1)	77 (24.3)	0.97	0.74-1.29

Subgroup with chronic renal failure N= 4513.

	No RRT (N = 4221) n (%)	RRT (N = 292) n (%)	Adjusted	
			O.R	95% C.I.
Drug category				
Thiazides	672 (15.9)	40 (13.7)	0.85	0.58-1.24
Loop diuretics	1637 (38.8)	145 (49.7)	1.36	1.03-1.81
ACE inhibitors	1294 (30.7)	94 (32.2)	0.92	0.69-1.22
Angiotensin receptor blockers	454 (10.8)	40 (13.7)	1.15	0.78-1.71
Beta blockers	606 (14.4)	55 (18.9)	1.13	0.81-1.56
Calcium channel blockers	1402 (33.2)	149 (51.0)	1.74	1.34-2.27

[1]**RRT: Renal replacement therapy**

4.4.3 Risk associated with antihypertensive drug polytherapy.

Risk of acute renal failure.

Table 17 summarizes the risks of acute renal failure associated with exposure to monotherapy or polytherapy in the entire cohort. In univariate analysis, a progressively higher risk of ARF is noted as the number of drugs used increases. This is also present with multivariate analysis (model B), but the risk association is not as strong.

Table 17.
Risk of acute renal failure associated with antihypertensive drug polytherapy (model B). Entire cohort (N = 25830).

	Without ARF[1] (n = 21245) n (%)	With ARF (n = 4585) n (%)	Crude O.R.	Adjusted	
				O.R	95% C.I.
Number of drugs delivered					
No drug	9320 (43.9)	1593 (34.7)		Reference group	
One drug	4520 (21.3)	851 (18.6)	1.10	1.01	0.92-1.11
Two drugs	4222 (19.9)	1056 (23.0)	1.46	1.15	1.05-1.26
> Two drugs	3183 (15.0)	1085 (23.7)	1.99	1.29	1.17-1.43

[1] **ARF: Acute renal failure**

Risk of acute renal failure: stratification for chronic heart failure.

Table 18 summarizes the risk estimates (model B) for acute renal failure in subgroups stratified for chronic heart failure In both subgroups, exposure to a greater number of drugs is associated with a greater risk of ARF, suggesting an effect of cumulative exposure.

Risk of acute renal failure: stratification for chronic renal failure.

Table 19 summarizes the risk estimates (model B) for acute renal failure in subgroups stratified for chronic renal failure. In the subgroup *without* chronic renal failure, exposure to a greater number of drugs is associated with a greater risk of ARF. In the subgroup with chronic renal failure, the odds ratios are not significantly increased, suggesting that polytherapy is not a significant risk factor.

Risk of acute renal failure: all stratification for primary or secondary diagnosis of sepsis.

Table 20 summarizes the risk estimates (model B) for acute renal failure in subgroups stratified by a primary or a secondary discharge diagnosis of sepsis. In the subgroup with a primary diagnosis of sepsis, there is no increase in risk of ARF with exposure to a greater number of antihypertensive drugs. In the subgroup with sepsis as a secondary diagnosis however, the increase in risk is detectable.

Table 18.
Risk of acute renal failure associated with antihypertensive drug polytherapy(model B). Stratification for chronic heart failure.

Subgroup without chronic heart failure N= 20829

	Without ARF[1] (N = 17 638) n (%)	With ARF (N = 3191) n (%)	Adjusted	
			O.R	95% C.I.
Number of drugs delivered				
No drug	8265 (46.9)	1249 (39.1)	Reference group	
One drug	3857 (21.9)	639 (20.0)	1.02	0.91-1.13
Two drugs	3246 (18.4)	685 (21.5)	1.18	1.06-1.32
> Two drugs	2270 (12.9)	618 (19.4)	1.32	1.17-1.49

Subgroup with chronic heart failure N= 5001.

	Without ARF[2] (N = 3607) n (%)	With ARF (N = 1394) n (%)	Adjusted	
			O.R	95% C.I.
Number of drugs delivered				
No drug	1055 (29.3)	344 (24.7)	Reference group	
One drug	663 (18.4)	212 (15.2)	0.95	0.77-1.16
Two drugs	976 (27.1)	371 (26.6)	1.05	0.88-1.25
> Two drugs	913 (25.3)	467 (33.5)	1.20	1.01-1.43

[1]**ARF: Acute renal failure**
[2]**ARF: Acute renal failure**

Table 19.
Risk of acute renal failure associated with antihypertensive drug polytherapy(model B). Stratification for chronic renal failure.

Subgroup without chronic renal failure N= 21317.

	Without ARF[1] (N = 18365) n (%)	With ARF (N = 2952) n (%)	Adjusted	
			O.R	95% C.I.
Number of drugs delivered				
No drug	8503 (46.3)	1183 (40.1)	Reference group	
One drug	3991 (21.7)	555 (18.8)	0.96	0.86-1.08
Two drugs	3499 (19.1)	647 (21.9)	1.17	1.05-1.31
> Two drugs	2372 (12.9)	567 (19.2)	1.41	1.25-1.59

Subgroup with chronic renal failure N= 4513.

	Without ARF (N = 2880) n (%)	With ARF (N = 1633) n (%)	Adjusted	
			O.R	95% C.I.
Number of drugs delivered				
No drug	817 (20.4)	410 (25.1)	Reference group	
One drug	529 (18.4)	296 (18.1)	1.01	0.91-1.33
Two drugs	723 (25.1)	409 (25.1)	1.07	0.89-1.27
> Two drugs	811 (22)	518 (31.7)	1.11	0.93-1.32

[1]**ARF: Acute renal failure**

Table 20.

Risk of acute renal failure associated with antihypertensive drug polytherapy (model B). Stratification for primary or secondary diagnosis of sepsis.

Subgroup with a primary diagnosis of sepsis N= 6318.

	Without ARF[1] (N = 5282) n (%)	With ARF (N = 1036) n (%)	Adjusted	
			O.R	95% C.I.
Number of drugs delivered				
No drug	2270 (43.0)	374 (36.1)	Reference group	
One drug	1133 (21.5)	202 (19.5)	1.01	(0.83-1.22)
Two drugs	1048 (19.8)	228 (22.0)	1.03	(0.85-1.25)
> Two drugs	831 (15.7)	232 (22.4)	1.09	(0.89-1.34)

Subgroup with a secondary diagnosis of sepsis N= 19 512.

	Without ARF[1] (N= 15 963) n (%)	With ARF (N = 3549) n (%)	Adjusted	
			O.R	95% C.I.
Number of drugs delivered				
No drug	7050 (44.2)	1219 (34.3)	Reference group	
One drug	3387 (21.2)	649 (18.3)	1.01	0.91-1.13
Two drugs	3174 (19.9)	828 (23.3)	1.19	1.07-1.33
> Two drugs	2352 (14.7)	853 (24.0)	1.36	1.21-1.52

[1]**ARF: Acute renal failure**

Risk of renal replacement therapy.

Table 21 summarizes the risk estimates (model B) for renal replacement therapy resulting from multivariate logistic regression applied to the entire cohort: exposure to a greater number of drugs increases the risk of renal replacement therapy .

Table 21.
Risk of renal replacement therapy associated with antihypertensive drug polytherapy (model B).Entire cohort (N = 25 830).

	No RRT[1] (n=25 222) n (%)	**RRT (n= 608) n (%)**	**Crude O.R.**	**Adjusted**	
				O.R	**95% C.I.**
Number of drugs delivered					
No drug	10751 (42.6)	162 (26.6)		Reference group	
One drug	5258 (20.9)	113 (18.6)	1.43	1.37	1.07-1.76
Two drugs	5129 (20.3)	149 (24.5)	1.93	1.62	1.27-2.06
> Two drugs	4084 (16.2)	184 (30.3)	2.99	1.96	1.54-2.49

[1]**RRT: Renal replacement therapy**

Risk of renal replacement therapy: stratification for chronic renal failure.

Table 22 summarizes the risk estimates (model B) for renal replacement therapy in subgroups stratified by the diagnosis of chronic renal failure. In both subgroups, exposure to a greater number of drugs increases the risk of renal replacement therapy.

Table 22 .

Risk of renal replacement therapy associated with antihypertensive drug polytherapy (model B).Stratification for chronic renal failure.

Subgroup without chronic renal failure N= 21317.

	No RRT[1] (N= 21001) n (%)	**RRT (N= 316) n (%)**	**Adjusted**	
			O.R	**95% C.I.**
Number of drugs delivered				
No drug	9576 (45.6)	106 (34.2)	Reference group	
One drug	4484 (21.3)	62 (19.6)	1.35	0.98-1.86
Two drugs	4067 (19.4)	79 (25.0)	1.83	1.34-2.49
> Two drugs	2872 (13.7)	67 (21.2)	2.05	1.47-2.87

Subgroup with chronic renal failure N= 4513.

	No RRT[1] (N= 4221) n (%)	**RRT (N= 292) n (%)**	**Adjusted**	
			O.R	**95% C.I.**
Number of drugs delivered				
No drug	1173 (27.8)	54 (18.5)	Reference group	
One drug	774 (18.4)	51 (17.5)	1.37	0.92-2.05
Two drugs	1062 (25.2)	70 (24.0)	1.36	0.93-1.98
> Two drugs	1212 (28.7)	117 (40.1)	1.85	1.29-2.64

[1]**RRT: Renal replacement therapy**

Chapter 5. Discussion.

5.1 Summary of study results.

In this retrospective observational study of a cohort of elderly individuals hospitalized with sepsis, multivariate logistic regression was used to estimate the risks of acute renal failure and renal replacement therapy associated with exposure to various antihypertensive drug categories. Six major drug categories were evaluated: thiazide diuretics, loop diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and calcium channel blockers. Multivariate logistic regression was also used to evaluate the risk of acute renal failure and renal replacement therapy associated with exposure to antihypertensive drug polytherapy.

Potential confounders included in the multivariate analysis were: year of entry in the cohort, demographic characteristics, primary or secondary diagnosis of sepsis and baseline comorbidities known to increase the risk of acute renal failure.

Risk acute renal failure associated with baseline characteristics and comorbidities.

The following risk factors are associated with an important increase in ARF risk on multivariate analysis: year of admission, chronic heart failure, chronic renal failure and chronic liver disease.

Other risk factors are also associated with an increased ARF risk: male gender, secondary diagnosis of sepsis, coronary disease and diabetes, but the associations are not as strong (adjusted odds ratios < 1.2).

The presence of peripheral arterial disease does not modify the risk of ARF.

For chronic hypertension, there is an important difference between the results of univariate and multivariate analysis. In univariate analysis, the crude odds ratio (1.33) suggests a higher risk of ARF, but in multivariate analysis, the adjusted odds ratio (0.91) suggests a lower risk.

Risk of renal replacement therapy associated with baseline characteristics and comorbidities.

The increase in risk for renal replacement therapy is similar to the increase in the risk of acute renal failure for the following risk factors: year of admission, male gender, secondary diagnosis of sepsis, chronic heart failure, chronic renal failure, and coronary disease. However, because of the smaller size of the renal replacement therapy group, the risk estimates are less precise and are not statistically different from the null for male gender and secondary diagnosis of sepsis.

For diabetes and peripheral arterial disease the risk associations for renal replacement therapy differ from the associations with acute renal failure: for diabetes, there is no detectable increase in risk of renal replacement therapy, but there is an increase in risk with peripheral arterial disease.

The risk of undergoing renal replacement therapy strongly decreases with advancing age (adjusted odds ratio 0.10 for the oldest age group). This does not seem to reflect a less severe degree of acute renal failure or sepsis in older individuals, since the mortality associated with acute renal failure is significantly higher in the oldest age group, whether they have received renal replacement therapy or not (table 10).

The risk association between chronic hypertension and renal replacement therapy is similar to what is observed for acute renal failure: the crude odds ratio (1.37) suggests an increased risk with chronic hypertension, but the adjusted odds ratio (0.82) suggests the opposite, a «protective» effect of hypertension against RRT.

Risk of acute renal failure with exposure to antihypertensive drug categories.

Thiazide diuretics, ACEIs and ARBs: these three antihypertensive drug categories are associated with an increased risk of ARF. However, in the subgroup of individuals with chronic renal failure, the increase in risk is not detectable.

Loop diuretics, beta blockers and calcium channel blockers are not associated with an increased risk of acute renal failure after adjustment for the other model covariates.

Risk of renal replacement therapy with exposure to antihypertensive drug categories.

Thiazide diuretics, ACEIs and ARBs: these three antihypertensive drug categories are associated with an increased risk of both ARF and renal replacement therapy. However, when the analysis is restricted to the subgroup with chronic renal failure, an increase in risk is no longer detectable.

Loop diuretics: although they are not associated with an increased risk of ARF (adjusted O.R. 1.06), loop diuretics seem to increase the risk of renal replacement therapy (adjusted O.R. 1.44). This is an important discordance: renal replacement therapy is used to treat the most severe forms of ARF, and logic dictates that a drug exposure which increases the risk of severe ARF should also be a risk factor for less severe forms of ARF of the same etiology.

Beta-blockers: exposure to beta-blockers is not associated with a significant risk of renal replacement therapy.

Calcium channel blockers: even though they are not associated with an increased risk of acute renal failure, calcium channel blockers seem to increase the risk of renal replacement therapy. However, this increased risk of RRT seems to be present only in individuals with pre-existing chronic renal failure (adjusted odds ratio 1.74), while the risk is not increased in individuals without chronic renal failure (adjusted odds ratio 0.97).

Risk of acute renal failure associated with antihypertensive drug polytherapy.

Simultaneous exposure to an increasing number of antihypertensive drugs is associated with a greater risk of acute renal failure. This is present in the entire cohort and also in the stratified subgroups, with the exception of the subgroup

with chronic renal failure. This subgroup is the one in which an increased risk with exposure to individual drug categories cannot be demonstrated (section 5.13).

Risk of renal replacement therapy associated with antihypertensive drug polytherapy.

Simultaneous exposure to an increasing number of antihypertensive drugs is also associated with a greater risk of renal replacement therapy in the entire cohort, and after stratification for chronic renal failure. In the subgroup with chronic renal failure, drug polytherapy increases the risk of renal replacement therapy, but not the risk of acute renal failure. This discrepancy is similar to the discordant risk associations observed with loop diuretics for the entire cohort (section 5.14).

5.2 Biological and clinical plausibility of the results.

Risk of acute renal failure and renal replacement therapy associated with associated with baseline characteristics and comorbidities.

Association with the year of admission: there is a remarkable increase in the incidence of acute renal failure during the study period (figures 7, 8 and 9). This is likely to reflect a true increase in ARF incidence, which could be due to the observed increase in the prevalence of predisposing comorbidities. There is also a net increase in exposure to antihypertensive drugs during the same period, and if antihypertensive drug therapy truly increases the risk of ARF, this is likely to contribute to the increased ARF incidence.

However, the large increase in ARF incidence may also be due to increasing sensitivity of acute renal failure diagnosis in the MedEcho database during the study period. Studies of coding accuracy for acute renal failure in database registries have demonstrated variations in diagnostic coding sensitivity between registries, but also variations *within* registries between different time periods. Waikar et al. [103] in a study of coding accuracy for acute renal failure in three Boston hospital registries, have reported a doubling in diagnostic sensitivity of ICD-9-CM registry coding during the 1994-2004 period (from 17% to 35%).

A similar increase in coding sensitivity may have occurred in this study as well: although there was a minor increase in the incidence of renal replacement therapy during the study period, this was much less important than the increase in acute renal failure (figure 9).The net decrease in the yearly proportion of ARF cases treated with renal replacement therapy (figure10) during the study period supports the hypothesis that diagnostic sensitivity of MedEcho database coding for milder cases of acute renal failure improved considerably during the study period.

A chart review of individual files from a subsample of the cohort would have allowed to test this hypothesis, but unfortunately chart review was not possible in the context of this database study.

Lack of association with increasing age: the lack of association of ARF risk with advancing age in this study is opposite to what has been reported in most studies of acute renal failure. The most likely explanation for this discrepancy is diagnostic bias due to selective underreporting of acute renal failure in older subjects. Serum creatinine concentration, the most frequently used marker of renal function, is inversely related to muscular mass. Muscular mass decreasing steadily with advancing age, for a comparable degree of renal failure, serum creatinine levels will not rise as much in an older individual compared to a younger one. Milder cases of acute renal failure may have been underreported in older individuals because smaller elevations in serum creatinine may not have been noticed by care providers.

In this study, increasing age is associated with a much lower probability of receiving renal replacement therapy. This is most likely because less «aggressive» therapeutic strategies were applied to the oldest members of the cohort. Despite the occurrence of severe, potentially life threatening renal dysfunction, it may be decided to abstain from renal replacement therapy in elderly individuals, because they refuse such life-sustaining interventions, or because age-related frailty, severe comorbidities and a very poor prognosis are considered to contraindicate this type of treatment.

Association with male gender: after adjusting for predisposing comorbidities, male gender is associated with an increased risk of acute renal failure and renal replacement therapy. This risk association must be interpreted cautiously, since there could be residual confounding due to a greater severity of predisposing comorbidities in men, and to a lower sensitivity of diagnostic coding for acute renal failure in women, related to their smaller muscular mass (discussed in sections 1.3 and 5.3.2). As noted in the literature review, previous studies of risk factors for acute renal failure have reported variable results as to the association between gender and ARF risk.

Association with a secondary diagnosis of sepsis: a secondary diagnosis of sepsis is associated with a greater risk of both ARF and renal replacement therapy. Since baseline characteristics in the two subgroups (primary/secondary diagnosis of sepsis) are similar, the risk association with a secondary diagnosis is probably due to a more difficult and complicated course of sepsis in the subgroup with a secondary diagnosis.

Association with predisposing comorbidities: the risk associations of chronic renal failure, heart failure, chronic liver disease, diabetes, coronary disease and peripheral arterial disease with either acute renal failure or renal replacement therapy are in agreement with previous studies. For chronic hypertension, the protective effect found in this study could be attributable to information bias: this will be discussed in the last section of this chapter.

Risk of sepsis-associated acute renal failure and renal replacement therapy associated with exposure to drug categories.

Exposure to thiazide and to loop diuretics: thiazide diuretics are associated with an increased risk of both ARF and renal replacement therapy, except in the subgroup with chronic renal failure. On the contrary, loop diuretics are not associated with a greater risk of ARF, but are associated with a greater risk of renal replacement therapy. These results are not in agreement with previous studies of ARF associated with diuretics, since in previous reports, loop diuretics were identified as increasing risk of ARF much more often than thiazide diuretics.

Loop diuretics are known to be more potent diuretics than thiazides and, theoretically, should cause more severe hypovolemia than thiazides during sepsis, and thus be associated with a higher risk of sepsis-associated ARF.

Although these results could be due to confounding (addressed in the next section), distinct pharmacological properties of thiazides and loop diuretics could explain part of this discrepancy. Despite being weaker diuretics, thiazides are considered more efficacious than loop diuretics as antihypertensive agents [43,44].

The following factors could explain the difference in risk associated with these two drug classes:

1. Thiazide drugs have longer elimination half-lifes than loop diuretics, leading to less fluctuation of their effect. In the hours following their administration, loop diuretics will provoke an intense diuresis, but this can be followed by a period of intense renal reabsorption of salt and water, during which diuresis will be low[44]. This decreases the efficacy of loop diuretics, unless they are administered more than once a day. In the context of acute illness, the withdrawal of loop diuretics could be associated with a more rapid reversal of pharmacological effects than the withdrawal of thiazides.
2. The antihypertensive effects of thiazide diuretics may be independent of their diuretic properties: prolonged exposure to thiazide drugs results in a chronic reduction in systemic arterial resistance. The mechanisms of this vasodilatory effect of thiazides are not well understood, but it is known that it will persist for weeks, and even months, after withdrawal of the drug[44]. Return of blood pressure to pre-treatment levels will be delayed as well. This sustained hypotensive effect could explain the negative impact of thiazide diuretics on renal function during sepsis.

In clinical practice, the dosage range for loop diuretics (for furosemide from 20 mg per day to 240 mg per day) is quite larger than the relatively restricted dosage range recommended for thiazide diuretics (for hydrochlorothiazide from 12.5 to 50 mg per day). Individuals may be at risk only when exposed to high doses of loop diuretics, which are typically used in the most severe forms of heart failure

and chronic renal failure. Most of the studies reporting renal impairment with loop diuretics are studies of in-hospital treatment of acute decompensated chronic heart failure (ADHF). In this setting, loop diuretics are frequently administered at high doses, by the intravenous route[92,93]. Smaller doses of loop diuretics, taken by the oral route, may not have a significant impact on renal function during subsequent sepsis.

Exposure to angiotensin converting enzyme inhibitors and angiotensin receptor blockers: exposure to ACEIs and ARBs is associated with an increased risk of ARF and renal replacement therapy, except in the subgroup with pre-existing chronic renal failure. The finding of an association between exposure to of ACEIs or ARBs and sepsis-associated ARF is in agreement with current knowledge on the pharmacology of these agents. Laboratory studies, randomized clinical trials, and a large number of clinical reports have provided extensive evidence that selective antagonism of the renin-angiotensin II-aldosterone axis by these drugs can provoke acute renal impairment. The magnitude of this problem will vary depending on predisposing comorbidities, such as chronic heart failure and chronic renal failure, and on concurrent acute illnesses producing hypotension and/or hypovolemia[40,81,82]. Considering the hypovolemia and hemodynamic instability characteristic of sepsis, the risk association is credible. The absence of exposure-associated risk in the subgroup with chronic renal failure is likely to result from confounding by contraindication and will be discussed in the last section of this chapter.

Exposure to beta-blockers. There is no sign of increased risk for either ARF or renal replacement therapy with exposure to beta-blockers. This finding is in accordance with current knowledge on the pharmacology of these agents. Despite many decades of widespread clinical use of beta-blockers, they have not been identified as a cause or a risk factor for acute renal failure.

Risk association of exposure to calcium channel blockers and renal replacement therapy. Like beta-blockers, calcium channel blockers have been extensively

used for more than 30 years, and have not been associated with an increased risk of ARF. Their positive risk association in this study is limited to the increased risk of renal replacement therapy in the subgroup with chronic renal failure. This discordant result is more likely to result from confounding by contraindication (discussed in the last section of this chapter), than from a true increase in risk.

Risk of sepsis-associated acute renal failure and renal replacement therapy associated with exposure antihypertensive drug polytherapy.

The increase in risk of acute renal failure and renal replacement therapy with exposure to an increasing number of drugs categories is in conformity with expectations. Physiologic adjustment of blood flow to the kidneys involves many different regulation systems, and a great number of endogenous vasoactive agents. It is reasonable to assume that polytherapy with antihypertensive agents, by inhibiting compensatory responses at many steps in these regulatory cascades, would increase the risk of renal function impairment. As noted in the literature review, this has already been well documented for the association of ACEIs with ARBs. Among the subgroup with chronic renal failure, polytherapy is associated with an increased risk of renal replacement therapy, but not of ARF. This discrepancy remains unexplained.

5.3 Methodological issues.

5.3.1 Selection bias.

Selection bias occurs when the selection of individuals entering a study produces a study group that is skewed with respect to the base population, in regard to both exposures and outcomes.

One of the strengths of this study is the use of the MedEcho database, which ensures almost complete capture of elderly Québec residents hospitalized with sepsis during the study period. A small proportion of acutely infected elderly individuals may have been successfully treated on an outpatient basis, rather than in the hospital (for example, mild pneumonia, or urinary tract infection, can

be treated with oral antibiotics on an outpatient basis). These individuals would be missing from the cohort. However, elderly patients selected for treatment on an outpatient basis are likely to experience mild sepsis and have few comorbidities, and should be at very low risk of sepsis-associated acute renal failure. Their absence from the cohort is thus unlikely to cause significant bias. Since an age of 65 or older was required for entry in the cohort, our results may not be generalizable to younger age groups. However, since the elderly have both the highest prevalence of exposure to antihypertensive drugs and the highest incidence of sepsis, the study results remain relevant.

5.3.2 Information bias.

Information bias occurs when available information about study subjects is incomplete or incorrect, in regard to exposures and/or outcomes. When misclassification of exposure is independent of the outcome, and when misclassification of outcome is independent of exposure, bias is said to be non-differential. If exposure misclassification is conditional on the outcome or if outcome misclassification is conditional on the exposure, bias is said to be differential.

For dichotomous outcomes and exposures, such as in this study, non-differential misclassification will bias the effect estimate towards the null, so the effect of exposure on the outcome will appear to be weaker or non-existent [104] . Differential misclassification of exposures or outcomes can produce bias in either direction, weakening a true risk association or creating the illusion of a risk association when, in fact, there is none.

5.3.2.1 Misclassification of outcomes.

Acute renal failure.

The limitations of large databases studies using ICD-9-CM coding discussed in the previous section are also relevant for the reporting of our study's main outcome, acute renal failure. A validation study by chart review [103] discussed earlier, reported sensitivities ranging from 25% to 50%, and specificities greater than 98%, for ICD-9-CM coding of acute renal failure in three teaching hospitals located in Boston. A progressive increase in coding sensitivity was also reported, with average coding sensitivity increasing from 20% to approximately 40% during the 1994-2004 period. This increased sensitivity of coding is likely to affect our data as well and may be in part responsible for the observed increase in ARF in this study, which has been reported in other contemporary database studies[28-30,105].

Important variations in diagnostic criteria for acute renal failure is acknowledged to be a major problem in ARF epidemiology: one limitation of this study is that we did not have access to laboratory data, which would have allowed assessment of ARF severity, and would have improved diagnostic sensitivity. If ARF coding sensitivity increased greatly during the study period, this could lead to confounding of our estimates of drug-associated risk if drug exposure increased greatly during the same time period. This is the case for exposure to ARBs, which increased from 1% to 14%. Having included the year of admission as a covariate in our models should decrease this confounding effect.

The sensitivity of ICD-9-CM coding for acute renal failure is likely to be lowest in the oldest age groups, because of the decreased sensitivity of serum creatinine as a marker of renal function with advancing age (discussed previously). For age-related risk, there is a high probability of differential misclassification bias, and the lack of association between age and acute renal failure risk in our study, which contrasts with the reports of previous ARF epidemiologic studies, is likely to be explained by this information bias.

Similarly, the increased odds ratios associated with male gender could be biased from selective under-diagnosis of acute renal failure in women, related to their smaller muscular mass.

The etiologic attribution of acute renal failure to sepsis could be erroneous in some cases. Individuals with a prolonged hospital stay could have developed ARF from other causes (hemorrhagic or cardiogenic shock, contrast-agent nephrotoxicity, etc.) while they were not in acute sepsis. Since the databases used do not contain information on the respective time frames of sepsis and acute renal failure episodes, it is impossible to identify individuals for whom acute renal failure may have been unrelated to sepsis. However, such etiologic misclassification is unlikely to be related to outpatient drug exposure, and thus should not be the source of significant bias.

Renal replacement therapy.

The RAMQ physician fee claim database should have excellent sensitivity for the provision of renal replacement therapy, since this type of treatment is, in Québec, universally covered by the state health care plan. Since renal replacement therapy is a complex procedure, requiring diligent physician supervision, it is very unlikely that physicians providing renal replacement therapy would neglect claiming fees for this type of therapy. However, renal replacement therapy is an imperfect, biased marker of the occurrence of sepsis-associated acute renal failure for the two following reasons. First, renal replacement therapy is used only in the most severe forms of acute renal failure, when renal function has fallen below 15% of normal levels; so only the most severe cases of acute renal failure (approximately 10% of ARF cases in various studies) will be identified by the provision of renal replacement therapy. Second, despite the occurrence of severe, potentially life threatening renal dysfunction, renal replacement therapy may not be instituted in certain patients with incurable diseases, a very poor prognosis, or because advanced directives refusing life-sustaining interventions have been specified. Thus, an unknown proportion of severe ARF cases will not have been detected by the assessment of renal replacement therapy.

5.3.2.2 Misclassification of exposures.

Misclassification of drug exposures: Use of the RAMQ prescription claim database is one of the strengths of the study, as complete coverage of prescriptions delivered to Québec residents aged 65 years or more is ensured. However, the delivery of the prescription drug does not automatically guarantee drug consumption if there is inadequate compliance to treatment, or modification of drug treatment after drug delivery has been recorded. This is of particular relevance in this study, since the databases used do not contain information on in-hospital drug exposure. Outpatient drug delivery is likely to reflect drug exposure when the individual develops sepsis at home. On the opposite, prescriptions taken at home may not reflect drug exposure properly if sepsis occurs during a complicated hospital stay, after significant modifications of the drug treatment regimen have occurred. We have attempted to correct for this bias by stratifying the analysis according to a primary diagnosis or a secondary of sepsis, with the assumption that individuals with a primary diagnosis of sepsis were more likely to have developed sepsis at home, and that outpatient drug exposure data in this subgroup would be a more accurate reflection of drug exposures immediately before sepsis. In both subgroups, there is a positive association between exposure to ACEIs and ARBs, and subsequent acute renal failure or renal replacement therapy. These risk associations are stronger for the primary than for the secondary diagnosis subgroup, which could be due to some degree of exposure misclassification in the subgroup with a secondary diagnosis, but this does not invalidate the risk associations. Surprisingly, exposure to thiazide diuretics was a significant risk factor in the subgroup with a secondary, but not with a primary, diagnosis of sepsis. We have not found an explanation for this isolated discrepancy.

One limitation of this study is that the rationale for drug prescription cannot be verified. Most drug categories that we have studied have other indications that hypertension: diabetes, coronary disease, chronic heart failure, chronic renal failure etc. The drugs under study can be prescribed to treat hypertension and other comorbidities simultaneously, in accordance with current treatment

guidelines for hypertension. This study reports the risk of sepsis-associated acute renal failure with exposure to antihypertensive drugs, but these drugs may have been prescribed for medical conditions *other than hypertension*. Nonetheless, given the high prevalence of exposure to the studied drugs in the elderly population, the study results remain relevant.

5.3.2.3 Misclassification of covariates.

While data on age and gender are highly reliable, database registries such as MedEcho are likely to be less accurate in the reporting of chronic diseases. The MedEcho database contains ICD-9-CM codes corresponding to the hospital discharge diagnoses entered by physicians and medical archivists. One principal diagnosis and up to 15 secondary diagnoses can be entered in the database. For chronic diseases, accurate reporting will depend on awareness of the condition and its perceived relevance to the acute illness episode. Comorbidities felt to be less relevant are less likely to be coded in the database. Chronic diseases such as hypertension are less likely to be entered after a critical illness, or when the issue is death [106-109].

Various validation studies of ICD-9-CM coding in administrative databases have consistently shown a high specificity (> 90%) but a low sensitivity (25-75%) for chronic comorbidities. For prevalent diseases (> 10%), this will result in a high positive predictive value, but a low negative predictive value, and significant underreporting is a problem [108,110-114].

For the comorbidities that we have studied, this type of selective information bias will tend to draw the effect estimate towards the null, since these chronic diseases are less likely to be coded when the course of sepsis is complicated by organ failure. Thus, the strong and consistent associations of chronic renal failure, chronic heart failure, and chronic liver disease with ARF and renal replacement therapy are very likely be valid.

Hypertension is one of the chronic diseases for which underreporting in databases using ICD-9-CM coding is the greatest, since it is highly prevalent, but

underdiagnosed, and unlikely to be a major problem during an acute episode of sepsis[115]. In our multivariate models, hypertension did not emerge as a risk factor for ARF or renal replacement therapy, and even appeared slightly protective (adjusted O.R.s 0.91 and 0.82 respectively). This protective effect may result from misclassification bias, since individuals with severe sepsis may be less likely to have hypertension entered as a discharge diagnosis (because blood pressures were low during the acute illness, or because hypertension may have seemed less relevant to report). Over-adjustment in our multivariate models may also contribute to the apparent protective effect of hypertension, since hypertension and chronic renal failure have a very strong epidemiologic link; hypertension is a major cause of chronic renal disease, and chronic renal failure very frequently causes hypertension: the percentage of individuals with CRF (GFR < 50 ml min^{-1}) who are hypertensive is reported to be over 85%. The inclusion of chronic renal failure in our multivariate model could have obscured the risk associations between hypertension, ARF and renal replacement therapy. For these reasons, the apparent protective effect of hypertension must be interpreted cautiously, in view of many previous studies of ARF which have identified chronic hypertension as a risk factor.

5.33 Confounding.

Confounding is another major issue in epidemiologic research. It occurs when the association between exposure and outcome is influenced by another variable, associated with both. Confounding can lead to an overestimation or an underestimation of the association between exposure and outcome variables.

Confounding of the risk related to drug exposure.

Confounding by indication, or by contraindication, is a major issue in pharmacoepidemiology. *Confounding by indication* occurs when a risk association between drug exposure and the outcome is not directly related to the drug, but rather by the association of drug treatment with a disease state which is the true causal risk factor. If confounding by the disease is corrected appropriately, drug exposure will not be found to influence outcome. *Confounding*

by contraindication is the reverse situation: a disease associated with the outcome is considered a contraindication to use of a certain drug. If this is the case, individuals with the disease are less likely to be exposed to the drug, which will result in an association that falsely appears protective. If confounding is appropriately corrected, drug exposure will not be found to be protective.

In this study two strategies were used in order to correct for confounding: multivariate logistic regression and stratification.

Multivariate logistic regression.

Using multivariate logistic regression, we modeled the acute renal failure risk according to baseline characteristics, selected comorbidities and drug exposure. The risk associations for ARF and renal replacement therapy were maintained in the multivariate models for thiazide diuretics, ACEIs and ARBs, and exposure to antihypertensive polytherapy. We believe these risk associations are real. For beta-blockers and calcium channel blockers the apparent increase in risk in univariate analysis was no longer detectable in multivariate analysis, suggesting confounding by indication. The interpretation of the results for loop diuretics is more difficult: as noted previously the discrepancy between an increased risk of renal replacement therapy and a neutral risk of ARF cannot be explained satisfactorily by the study data, and could be due to unidentified bias, or residual confounding.

Stratification.

We applied the multivariate logistic models to subgroups of the cohort defined according to the present or absence of chronic heart failure and chronic renal failure, the two comorbidities with the greatest risk of ARF and renal replacement therapy in this study.

Drug exposure: the results of our stratified analysis argue strongly against confounding by indication. When our multivariate models are applied to individuals *without* predisposing comorbidities, the risks associated with drug exposure are still detectable for thiazide diuretics, ACEIs, ARBs and for drug

polytherapy, which reinforces the validity of the unstratified logistic regression analyses.

The results of logistic regressions restricted to the subgroups with predisposing comorbidities are different, particularly in the subgroup with chronic renal failure, in which the risk associations for ARF are no longer detectable, and the risk associations for renal replacement therapy are reversed. This suggests important residual confounding within the subgroup with chronic renal failure. Residual confounding could be due to the fact that this study's database does not allow precise classification of severity of either chronic heart failure or chronic renal failure. In CHF and CRF, the severity of the disease has an important impact on drug prescription. Differences in drug treatment within the subgroups with CHF or CRF could obscure the risks associated with exposure to the drugs under study.

Confounding by contraindication may have occurred in the subgroup with chronic renal failure: individuals with more severe CRF are less likely to receive prescriptions for thiazide diuretics (believed to be inefficacious), or for ACEIs and ARBs (because they provoke hyperkalemia or deterioration of renal function more frequently). For ACEIs and ARBs, several reports[116,117] have confirmed that individuals with more advanced CRF (who, theoretically, should benefit the most from these agents) are less likely to be treated with these agents - possibly because of physicians' reluctance to continue treatment when a decrease in renal function is noted during initiation of therapy with these drugs. *Confounding by indication* could explain the increased risk of renal replacement therapy associated with exposure to calcium channel blockers: individuals with advanced chronic renal failure are more likely to have resistant hypertension, necessitating polytherapy[118]. Since many of the other drug categories are felt to be contraindicated in the presence of advanced CRF, physicians may resort more frequently to calcium channel blockers to treat hypertension in these high risk individuals, which could confound the observed risk.

Given the retrospective nature of this study, and the lack of precision in the assessment of comorbidity severity, we cannot provide a reliable estimate of the

risk of sepsis-associated ARF resulting from antihypertensive drug exposure when chronic renal failure is present. This question warrants further research. To provide a better estimate of sepsis-associated ARF risk in chronic renal failure patients, a cohort study would need to have data on baseline (preadmission) renal function, provided by either baseline serum creatinine levels or estimated glomerular filtration rates (eGFR) using prediction equations. It should also have data on in-hospital creatinine levels. This would allow better stratification of cohort members according to the severity of both chronic renal failure and acute renal failure (expressed as proportional decrease in baseline renal function). Running the logistic regression models amongst subgroups stratified in this manner should remove most of the confounding by indication/contraindication that seems to be obscuring the relationship between drug exposure and outcome in the chronic renal failure subgroup.

Conclusions.

The following conclusions can be drawn from this study.

1. There has been a major increase in the incidence of sepsis in elderly Québec residents during the 1997-2004 period.
2. Exposure to antihypertensive drugs and antihypertensive polytherapy has increased significantly during the same time period.
3. There has been a parallel increase in the proportion of septic individuals developing acute renal failure during the same period.
4. Chronic renal failure and chronic heart failure are the two baseline comorbidities associated with the highest risk of sepsis-associated acute renal failure.
5. Exposure to thiazide diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers is independently associated with an increased risk of sepsis-associated acute renal failure and renal replacement therapy, except in the subgroup of patients with chronic renal failure for whom an increased risk was not demonstrated.
6. Exposure to loop diuretics is independently associated with an increased risk of renal replacement therapy, but an increased risk of acute renal failure cannot be demonstrated.
7. Exposure to beta blockers and calcium channel blockers does not appear to increase risk of sepsis-associated acute renal failure or renal replacement therapy.
8. Simultaneous exposure to a greater number of antihypertensive drugs is independently associated with a progressively greater risk of sepsis-associated acute renal failure and renal replacement therapy.

To our knowledge, this is the first study of outpatient exposure to antihypertensive agents as a risk factor for acute renal failure during sepsis. The subject has considerable clinical relevance, considering the increasing size of the elderly population, the increase in antihypertensive agents use, and the increasing

incidence of sepsis in this age subgroup. Clinicians taking care of elderly patients during an acute infectious episode should be aware of the risk of renal function deterioration associated with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics and antihypertensive polytherapy.

The former drug categories figure in current hypertension treatment guidelines as first-line pharmacologic agents. This is justified by an important number of clinical studies which have consistently demonstrated a significant decrease in cardiovascular and overall mortality resulting from pharmacotherapy with these agents.

Considering this, the demonstration of an increased risk of acute renal failure during sepsis does not not justify modification of current hypertension therapy guidelines. However, during the acute phase of a severe infectious episode, it is probably preferable to interrupt administration of the aforesaid drugs, and to resume treatment only when recovery from sepsis has clearly occurred.

Our study has important limitations, related to its retrospective nature, and to the lack of precision of the diagnostic database. These limitations probably account for two major discrepancies are in our results: the negative results obtained in the chronic renal failure subgroup, and the demonstration of an increased risk of acute dialysis with loop diuretics exposure, without an associated risk of acute renal failure.

Further pharmacoepidemiologic studies of the topic are necessary. The reliability of such studies would be increased by the following aspects of study design. A prospective design, and the use of a database containing prior primary care diagnoses would allow better adjustment for confounding by comorbidities. Laboratory data providing information on baseline and in-hospital renal function would allow better adjustment for confounding by indication and/or contraindication, and better diagnostic sensitivity for the occurrence of acute renal failure, increasing the precision and reliability of risk estimates.

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Appendix 1. Recommended clinical criteria for the diagnosis of sepsis.

Infection[a] documented or suspected, and *some* of the following:

General variables.

- Fever (core temperature > 38.3°C).
- Hypothermia (core temperature < 36°C).
- Heart rate > 90 min^{-1} or > 2 SD above the normal value for age.
- Tachypnea.
- Altered mental status.
- Significant edema or positive fluid balance (> 20 ml/kg over 24 hrs).
- Hyperglycemia (plasma glucose > 7.7 mmol/l) in the absence of diabetes.

Inflammatory variables.

- Leukocytosis (WBC count > 12,000 l^{-1}).
- Leukopenia (WBC count < 4000 l^{-1}).
- Normal WBC count with > 10% immature forms.
- Plasma C-reactive protein > 2 SD above the normal value.
- Plasma procalcitonin > 2 SD above the normal value.

Hemodynamic variables.

- Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, . or a SBP decrease > 40 mm Hg)..
- SvO2 > 70%.
- Cardiac index > 3.5 $l*min^{-1}*m^{-2}$.

Organ dysfunction variables.

- Arterial hypoxemia (PaO2/FIO2 < 300 mm Hg).
- Acute oliguria (urine output < 0.5 $ml*kg^{-1}*hr^{-1}$ for at least 2 hrs).
- Creatinine increase > 45 mmol/l .
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 s).
- Ileus (absent bowel sounds).
- Thrombocytopenia (platelet count < 100,000 l^{-1}).
- Hyperbilirubinemia (plasma total bilirubin > 70 mmol/l).

Tissue perfusion variables.

- Hyperlactatemia (> 1 mmol/l).
- Decreased capillary refill or mottling.

[a] *Infection* defined as a pathologic process induced by a microorganism; WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO2, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

(adapted from Levy et al, 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250-1256)

Appendix 2. ICD-9-CM codes used for diagnoses.

Acute renal failure[1].

ICD-9 CM CODE	Description
584.	Acute kidney failure
572.4	Hepatorenal syndrome
788.5	Oliguria or anuria

Chronic heart failure

ICD-9 CM CODE	Description
398.91	Congestive rheumatic heart failure
402. 01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
416.	Pulmonary heart disease
425.	Cardiomyopathy
428.	Heart failure
429.0	Myocarditis, unspecified
429.1	Myocardial degeneration
429.3	Cardiomegaly

Chronic hypertension

ICD-9 CM CODE	Description
401.	Essential hypertension
402.	Hypertensive heart disease
403.	Hypertensive renal disease
404.	Hypertensive heart and renal disease
405.	Secondary hypertension

[1] Acute renal failure was also diagnosed if renal replacement therapy was initiated during the index hospitalisation, as recorded inthe RAMQ physician fee claims database (see Appendix 2).

Chronic renal failure

ICD-9 CM CODE	Description
250.4	Diabetes with renal manifestations
403.	Hypertensive renal disease
404.	Hypertensive heart and renal disease
582.	Chronic glomerulonephritis
585.	Chronic renal failure
587.	Renal sclerosis, unspecified
588.	Disorders resulting from impaired renal function
753.0	Renal agenesis and dysgenesis

Chronic liver disease

ICD-9 CM CODE	Description
571.	Chronic liver disease and cirrhosis.
572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
573.	Other disorders of liver

Coronary disease

ICD-9 CM CODE	Description
410.	Acute myocardial infarction
411.	Other ischemic heart disease
412.	Old myocardial infarction
413.	Angina pectoris
414.	Other forms of chronic ischemic heart disease
429.7	Certain sequelae of myocardial infarction

Diabetes[1]

ICD-9 CM CODE	Description
250.	Diabetes mellitus

Peripheral arterial disease

ICD-9 CM CODE	Description
433.	Occlusion and stenosis of precerebral arteries
434.	Occlusion and stenosis of cerebral arteries
435.	Transient cerebral ischemia
436.	Acute, but ill-defined, cerebrovascular disease
437.	Other and ill-defined cerebrovascular disease
438.	Late effects of cerebrovascular disease
440.	Atherosclerosis
441.	Aortic aneurysm and dissection
442.	Other aneurysm
443.	Other peripheral vascular disease
444.	Arterial embolism and thrombosis
445.	Atheroembolism

Sepsis[2]

ICD-9 CM CODE	Description
038.	Septicemia
790.7	Bacteremia

[1] Diabetes was also diagnosed if a prescription for an oral antidiabetic agent or for insulin was delivered in the sixty days prior to the index hospitalisation (for detailed drug inventory see Appendix 4).

[2] * A specific ICD9-CM code for sepsis (995.9), introduced after 2004, was not in use during the study period.

Shock[1]

ICD-9 CM CODE	Description
458.9	Hypotension unspecified
785.5	Shock without mention of trauma*
796.3	Nonspecific low blood pressure reading
796.3	Postoperative shock not elsewhere classified

[1] *** A specific ICD9-CM code for septic shock (785.52), introduced after 2004, was not in use during the study period.Shock, was not a criteria for inclusion in the cohort, but was recorded as a marker for the severity of sepsis.**

Appendix 3. *Régie de l'assurance-maladie du Québec* physician billing codes for renal-replacement therapy

Description.	Billing codes.
Hemodialysis, first treatment.	09261 (until May 31, 2002) 15040 (after May 31, 2002)
Hemodialysis, subsequent treatments, between 07h00 and 17h00, weekdays.	09274 (until May 31, 2002) 15041 (after May 31, 2002)
Hemodialysis, subsequent treatments, between 17h00 and 24h00, during weekdays.	09216 (until May 31, 2002) 15043 (after May 31, 2002)
Hemodialysis, subsequent treatments, between 24h00 and 07h00, during weekdays.	09218 (until May 31, 2002) 15045 (after May 31, 2002)
Hemodialysis, subsequent treatments, during weekends.	09262 (until May 31, 2002) 15047 (after May 31, 2002)
Continuous hemofiltration, for the first three days of treatment.	09382
Continuous hemofiltration, after the first three days of treatment.	09383

Appendix 4. Antihypertensive drugs grouped by categories.

Calcium channel blockers	Beta blockers	Thiazide diuretics
amlodipine	acebutolol	bendrofluméthiazide
amlodipine	atenolol	benzthiazide
diltiazem	carvedilol	chlorothiazide
felodipine	esmolol	chlorthalidone
nicardipine	labetalol	hydrochlorothiazide
nifedipine	metoprolol	indapamide
nimodipine	nadolol	metolazone
verapamil	oxprenolol	polythiazide
	pindolol	
	propranolol	
	sotalol	

ACE inhibitors	Angiotensin receptor blockers	Loop diuretics
benazepril	candesartan	bumetanide
captopril	eprosartan	ethacrynic acid
cilazapril	irbesartan	furosemide
enalapril	losartan	torsemide
fosinopril	telmisartan	
lisinopril	valsartan	
perindopril		
quinapril		
ramipril		
trandolapril		

Potassium sparing diuretics	Thiazides - potassium sparing diuretics in combination[1]
amiloride	amiloride with hydrochlorothiazide
spironolactone	spironolactone with hydrochlorothiazide
triamterene	triamterene with hydrochlorothiazide

ACE inhibitors – thiazide in combination[1]	Angiotensin receptor blockers – thiazide in combination[1]	ACE inhibitor- calcium channel blocker in combination[1]
perindopril with indapamide	irbesartan with hydrochlorothiazide	Trandolapril with verapamil
quinapril with hydrochlorothiazide	candesartan with hydrochlorothiazide	
cilazapril with hydrochlorothiazide	eprosartan with hydrochlorothiazide	
enalapril with hydrochlorothiazide	losartan with hydrochlorothiazide	
lisinopril with hydrochlorothiazide	telmisartan with hydrochlorothiazide	
	valsartan with hydrochlorothiazide	

Alpha-blockers	CNS agents and ganglioplegics	Arterial vasodilators	Nitrates[2]
doxazosin	clonidine	diazoxide	isosorbide dinitrate
phentolamine	guanethidine	hydralazine	isosorbide mononitrate
prazosin	methyldopa	minoxidil	glyceryl trinitrate
terazosin	reserpine		
	trimetaphan		

[1] When a drug combination was dispensed, individuals were recorded as being simultaneously exposed to both drug categories.
[2] Only long-acting, percutaneous or oral forms of nitrate drugs were considered. Short acting sublingual forms were not considered to have chronic antihypertensive efficacy in the.

Appendix 5. Antidiabetic drugs.

Individuals were considered to be diabetic if outpatient delivery of the following drugs occurred in the 60 days prior to index hospitalization.

Oral hypoglycemic drugs	Insulins
acarbose	insulin aspart
acetohexamide	insulin detemir
chlorpropamide	insulin glargine
gliclazide	insulin lispro
glimepiride	insulin (all forms)
glyburide	
metformin	
metformin-rosiglitazone combination	
nateglinide	
pioglitazone	
repaglinide	
rosiglitazone	