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Causes of death in patients with rheumatoid arthritis over a 40-year period

With special emphasis on autopsy

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ACADEMIC DISSERTATION

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List of original publications

This thesis is based on the following publications. Their copyright holders have kindly granted permission to reproduce these publications (II-V).

I Koivuniemi R, Paimela L, Leirisalo-Repo M. Causes of death in patients with rheumatoid arthritis during a 21-year period. (Submitted).

II Koivuniemi R, Paimela L, Suomalainen R, Piirainen H, Karesoja M, Helve T, Leirisalo-Repo M. Causes of death in patients with rheumatoid arthritis autopsied during a 40-year period. Rheumatol Int 2008; 28:1245-52.

III Koivuniemi R, Leirisalo-Repo M, Suomalainen R, Piirainen H, Paimela L. Infectious causes of death in patients with rheumatoid arthritis: an autopsy study. Scand J Rheumatol 2006; 35:273-6.

IV Koivuniemi R, Paimela L, Suomalainen R, Leirisalo-Repo M. Amyloidosis as a cause of death in patients with rheumatoid arthritis. Clin Exp Rheumatol 2008; 26:408-13.

V Koivuniemi R, Paimela L, Suomalainen R, Törnroth T, Leirisalo-Repo M. Amyloidosis is frequently undetected in patients with rheumatoid arthritis. Amyloid 2008; 15:262-8.

The publications are referred to in the text by their roman numerals. Some unpublished data is also presented.

Abbreviations

ACS	Acute coronary syndrome
ARA	American Rheumatism Association
ACPA	Anti-citrullinated peptide antibody
ASA	Acetylsalicylic acid
AZA	Azathioprine
CHD	Coronary heart disease
CoD	Cause of death
CRP	C-reactive protein
CVD	Cardiovascular disease
CYC	Cyclophosphamide
DMARD	Disease-modifying anti-rheumatic drug
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
GC	Glucocorticoid
GI	Gastrointestinal
HAQ	Health Assessment Questionnaire
HB	Haemoglobin
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
ICD	the International Classification of Diseases
LDL	Low-density lipoprotein
LPM	Lymphoproliferative malignancy
MHC	Major histocompatibility complex
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RR	Relative risk
SE	Shared epitope
SMR	Standardized mortality ratio
sTNFR	Soluble tumour necrosis factor receptor
TNF	Tumour necrosis factor
WHO	World Health Organization

Abstract

Patients with rheumatoid arthritis (RA) have premature mortality, which is mostly attributed to cardiovascular diseases (CVDs), infections, gastrointestinal (GI) disorders, and RA itself. Some studies report an increased death rate due to lymphoproliferative malignancies (LPMs). Studies on changes in causes of death (CoDs) over time are scarce. One such study reported a decrease in mortality between 1950 and 1981 due to RA, another study a decrease from 1980 to 1997 due to myocardial infarction. The CoDs are nowadays only infrequently verified by autopsy, although autopsy is regarded as the gold standard for determination of CoD. This study aimed to evaluate determinants of mortality in RA patients. The study examined the CoDs over time. The study addresses an autopsy population of RA patients, with non-RA patients serving as reference cases. In the autopsied patients, the study evaluates CoDs over several decades, the contribution of autopsy to the CoD determination, the contribution of RA medication to the CoDs, and the detection rate of reactive systemic amyloid A (AA) amyloidosis at autopsy.

CoDs were studied in 960 RA patients who had been treated at the Kivelä Municipal Hospital in Helsinki and who had died between 1971 and 1991 (Study population A). CoDs were then evaluated in 369 consecutively autopsied RA patients and their reference cases without any rheumatic disease (non-RA) of the same age at death, sex, and year of autopsy from 1952 to 1991 (Study population B). These autopsied patients had also been treated at Kivelä Hospital. To evaluate the contribution of autopsy, CoD assessed by the clinician before autopsy and those determined by the pathologist at autopsy were compared in autopsied RA patients and controls. For each patient, death certificate data were reviewed. The CoD evaluation was based on multiple CoDs, including immediate, underlying, and contributory causes. Furthermore, an intervening antecedent CoD was also analysed when available. In autopsied patients, CoD determination was based on autopsy findings. For the RA patients in Study population B, medical records between 1973 and 1991 were available for analysis of clinical data. To evaluate the ultimate prevalence of amyloidosis, autopsy tissue samples, 90% of which were available, were re-examined systematically. The detection rate of reactive amyloidosis was studied by examining the prevalence of amyloidosis at the following three levels: 1) during the course of RA, 2) at routine examination during autopsy, and 3) at systematic re-examination of autopsy tissue samples.

In Study population A, the leading CoDs were CVDs, RA, and infections. From 1971 to 1991, deaths caused by RA and renal disorders decreased, but no major change occurred in coronary deaths.

In Study population B, the leading CoDs were RA, CVDs, and infections. In these patients, deaths caused by RA also decreased from 1952 to 1991. Over the 40-year period, coronary deaths in RA patients increased, but non-RA patients experienced a decrease in coronary deaths starting in the 1970s. Between clinician-assigned diagnoses of CoD and those determined by the pathologist, RA patients had lower agreement than non-RA patients regarding CVDs (Kappa reliability

measure: 0.31 vs. 0.51) and coronary deaths (0.33 vs. 0.46). In both RA and non-RA patients, malignancies were diagnosed most accurately during the lifetime. For patients treated at any time during RA with disease-modifying anti-rheumatic drugs (DMARDs) and those without (Study population B), autopsy-based CoDs were similar.

In Study population B, amyloidosis caused death in 10% of the RA patients, but in none of the non-RA cases. Of the RA patients and those without RA (total of 739 patients), 90% of autopsy tissue samples were available for re-examination. The re-examination for reactive amyloidosis showed doubling of the prevalence of amyloid compared with the original autopsy reports: from 18% to 30% in RA and from 2% to 4% in non-RA patients. Prevalence of amyloid deposits at re-examination showed no major change over time. In RA patients with amyloid at re-examination, amyloidosis had been diagnosed before autopsy in only 37%, and these patients had a higher level of inflammation during the course of RA, a longer duration of RA, and more disabling RA than RA patients without amyloid. Of RA patients with amyloid, only half were known to have renal failure or proteinuria or both.

In conclusion, the leading CoDs in RA patients were CVDs, RA, and infections. Deaths caused by RA seemed to be decreasing. This appeared not to be true for coronary deaths. Despite advances in diagnostic technology, autopsy remains an important tool in CoD determination. Coronary death being less accurately diagnosed in RA patients may indicate that coronary heart disease (CHD) in RA patients often remains unrecognized during lifetime. Thus, an active search for CHD and its effective treatment is important to reduce cardiovascular mortality. Reactive amyloidosis appears to be common, but is frequently undetected. Not only in RA patients with proteinuria or renal failure or both, but also in those with active, long-lasting, and disabling RA, a systematic search for amyloid is important to enable early diagnosis of amyloidosis, which will require effective suppression of inflammation. Early enhancement of immunosuppressive therapy, including biologicals in persistent active disease, is critical in preventing clinical manifestations of amyloidosis, such as renal failure, which has a poor prognosis.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 0.5-1% of populations worldwide. Development of RA is based on both genetic susceptibility and environmental factors. Exposure to an infection may act as a trigger for RA (Silman and Pearson, 2002). The major basic manifestation of RA is joint involvement, which if ineffectively treated, will eventually lead to disability. Inflammation in RA may occasionally affect extra-articular sites, such as the pericardium or the pleura, as well as the vasculature. Furthermore, long-standing inflammation in RA may cause deposition of amyloid fibrils in the extra-cellular space, leading to the development of reactive systemic amyloid A (AA) amyloidosis. Reactive amyloidosis frequently manifests as proteinuria and later as renal failure with a poor prognosis.

RA is associated not only with functional disability, but also with premature mortality (Kvien, 2004), known since 1953 (Cobb S et al., 1953). The increased mortality is mostly attributed to cardiovascular diseases (CVDs) (Wolfe et al., 1994; Symmons et al., 1998; Goodson et al., 2005). Infections (Symmons et al., 1998; Sihvonen et al., 2004a), especially infections of the respiratory tract (Mutru et al., 1985; Sihvonen et al., 2004a) and urogenital tract (Vandenbroucke et al., 1984), are also important determinants of mortality. Mortality in RA is increased due to gastrointestinal (GI) disorders and RA itself (Wolfe et al., 1994) as well as to reactive amyloidosis associated with RA (Laakso et al., 1986a). Some studies have also found increased mortality due to lymphoproliferative malignancies (LPMs) (Wolfe et al., 1994; Symmons et al., 1998).

Controversial reports on RA patients have emerged with respect to mortality changes over time. During the period from 1964 to 1995, one series suggested the overall mortality rate in Swedish RA patients to decline (Björnådal et al., 2002), but another series on US patients covering a longer period from 1965 to 2005 indicated no improvement in survival (Gonzalez et al., 2007). In cause-specific mortality, very few studies have reported changes over time. In mortality due to RA, an Australian study from the 1950s to the 1980s (Wicks et al., 1988) and a French study from the 1970s to the 1990s (Ziade et al., 2008) showed a significant decline. However, French study covering the period 1970 to 2002 demonstrated that deaths due to RA showed, starting in the mid–1990s, a small rise (Ziade et al., 2008). From 1980 to 1997, a US series revealed mortality due to myocardial infarction to decline (Krishnan et al., 2004). On the other hand, some studies have observed no significant changes in cause-specific mortality (Suzuki et al., 1994; Björnådal et al., 2002). However, only one of these series (Suzuki et al., 1994) was based on autopsied patients. In that series, the autopsy rate of all deceased patients was 58%. In all other longitudinal series, autopsy rates were unreported.

In follow-up studies, cause-of-death (CoD) information may be biased, because all RA patients in such studies are not followed throughout their lifespan. For those patients alive at the end of the study, information about CoDs remains unknown. CoDs vary with RA duration. Mortality risk at least for infections, renal failure, and non-Hodgkin lymphoma rises with RA duration (Symmons et

al., 1998). Furthermore, CoDs are only infrequently verified by autopsy, although clinically determined CoDs without verification by autopsy may be inaccurate (Roulson et al., 2005).

Several studies on RA patients have shown a highly variable prevalence of reactive amyloidosis. In biopsies taken from various sites during lifetime, the prevalence of amyloidosis has ranged from 7% to 19% (Kobayashi et al., 1996; Gomez-Casanovas et al., 2001; El Mansoury et al., 2002; Kuroda et al., 2002; Ishii et al., 2003), and further 78% (Barile et al., 1993). At autopsy, amyloid has been detected in 7% to 61% of the RA cases (Teilum and Lindahl, 1954; Ramirez et al., 1981; Boers et al., 1987; Suzuki et al., 1994). Similarly, mortality rates due to amyloidosis have been variable, ranging from 2% to 24% of RA patients (Mutru et al., 1976; Prior et al., 1984; Laakso et al., 1986a; Lehtinen and Isomäki, 1991; Suzuki et al., 1994; Kvalvik et al., 2000; Martinez et al., 2001). These highly variable figures evidently depend on the different patient populations and search methods, but it is also likely that amyloid in some patients goes undetected.

This study aimes to elucidate determinants of RA mortality by investigating CoDs over a 21-year period. The study then addresses an autopsy population of RA patients and their reference cases. In these patients, the study evaluates CoDs over 40 years, the contribution of autopsy to the CoD determination, the contribution of RA medication in relation to CoDs, and the detection rate of reactive AA amyloidosis.

2. Review of the literature

2.1 History of rheumatoid arthritis

History of rheumatic conditions can be investigated by analysing skeletons from archaeological sites (Rothschild, 1995). Studying mummies by medical imaging, such as the Peruvian mummy Rascar Capac by computed tomographic scan imaging (Appelboom and Struyven, 1999), also provides information about the history of diseases affecting bones. In addition, art and historical texts may provide insights into the origin of RA (Appelboom, 2004). In several of his paintings, Rubens painted finger and wrist deformities resembling RA, and, in fact, he may have been one of the first victims of an epidemic of RA starting in the 16th or 17th century (Appelboom, 2005). RA is believed to have infiltrated to Europe from North America after Columbus had discovered the New World. According to this theory, the sailors bought RA to Europe, when they returned home from America. In the pre-Columbian era, no reports of RA had emerged in Europe (Rothschild, 2001). American Indians have even nowadays a high prevalence of RA (Silman and Pearson, 2002). In European skeletons originating from pre-Columbian times, the findings resembling past arthritis have most likely been conditions other than RA, i.e. gout or spondylarthropathy, which may have originated from ancient Egypt (Appelboom and Russell, 2003).

2.2 Epidemiology of rheumatoid arthritis

In various populations, the prevalence of RA is approximately 0.5 - 1%, with the exception of American Indians, who demonstrate a higher prevalence ranging from 5% to 7% (Silman and Pearson, 2002). Nowadays, 25 - 50 persons of a population of 100 000 will annually develop typical RA (Uhlig and Kvien, 2005; Kaipiainen-Seppänen and Kautiainen, 2006). Studies have reported the prevalence of RA (Jacobsson et al., 1994), at least in female patients (Symmons et al., 2002), and the incidence of RA (Jacobsson et al., 1994; Doran et al., 2002), at least that of rheumatoid factor–positive RA (Kaipiainen-Seppänen and Kautiainen, 2006), to be declining. These findings should, however, be interpreted with caution because of the varying methodologies used in classification of RA (Uhlig and Kvien, 2005). However, the course of disease activity in RA patients has been suggested to become milder in recent years in parallel with more active treatment strategies (Welsing et al., 2005).

2.3 Mortality in rheumatoid arthritis

RA is not only a debilitating disease, but it is also associated with premature mortality. Mortality increases in parallel with duration of RA (Wolfe *et al.*, 1994). Compared with the general population, mortality in RA patients in clinical studies has increased up to 3-fold (Table 1). In population-based studies, mortality in RA patients has been less marked (Table 2). Despite the suggestion that disease activity in RA may have become milder over time, mortality has remained high (Welsing *et al.*, 2005). During recent years, the mortality gap between RA patients and the general population has become even wider (Gonzalez *et al.*, 2007). However, it is only recently that reports have emerged offering explanations for this premature death (Naz and Symmons, 2007).

Table 1 Mortality of rheumatoid arthritis in clinical studies

First author, publication year	Country	Inclusion year(s)	Patients (n)	Deaths (n)	SMR	Autopsy rate (%)	Follow-up duration (years)
Cobb, 1953	USA	NA	583	137	1.30	29	10
Duthie, 1964	UK	1948-51	275	75		NA	9
Male					1.68		
Female					1.52		
Uddin, 1970	Canada	1954-66	475	94		30	10
Male					1.20		
Female					1.34		
Lewis, 1980	UK	1966-76	311	46	1.13	41	11
Allebeck, 1982	Sweden	1971	1165	473	2.50	67	8
Pincus, 1984[a]	USA	1973	75	20	1.32	NA	9
Prior, 1984[b]	UK	1964-78	448	199	3.00	NA	11
Symmons, 1986	UK	1964-78	433	199		NA	18
Total					3.00		
Male					2.60		
Female					3.40		
Reilly, 1990	UK	NA	100	63	1.40	30	25
Pincus, 1994[a]	USA	1973	75	34	1.62	NA	15
Wolfe, 1994	USA, Canada (ARAMIS)	1955-90	3501	922	2.26	NA	up to 35
Alarcon, 1995	USA	1981-86	152[c]	27	1.95	NA	10

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First author, publication year	Country	Inclusion year(s)	Patients (n)	Deaths (n)	SMR	Autopsy rate (%)	Follow-up duration (years)
Wållberg-Jonsson, 1997	Sweden	1979	606	265		46	16
Total					1.57		
Male					1.47		
Female					1.64		
Symmons, 1998[b]	UK	1964-78	448	266	2.70	NA	22
Lindqvist and Eberhardt, 1999	Sweden	1985-89	183	18	0.87	22	10
Sokka, 1999	Finland	1983-85 and	135	25		NA	8-14
Total		1988-89			1.28		
Male					0.98		
Female					1.69		
Kvalvik, 2000	Norway	1977	147	68		NA	16
Total					1.49		
Male					1.26		
Female					1.68		
Martinez, 2001	Spain	1989	182	23	1.85	NA	9
Chehata, 2001	UK	1981-85	288	109		NA	14
Total					1.65		
Male					1.30		
Female					2.11		
Peltomaa, 2002	Finland	1986-89 and 1991-93	150	24	1986-89: 0.93; 1991-93: 1.62	NA	7-14
Thomas, 2003	UK	1981-2000				NA	up to 20
Male			9003	4406	2.07		
Female			24,315	11,471	1.97		
Goodson, 2005	UK	1981-96	1010	470		NA	11
Male					1.45		
Female					1.84		
Young, 2007	UK	1986-97	1429	459	1.27	22	9
Carmona, 2007	Spain	B:2001-6, E:1999-2005	B, E: 789	B: 20; E: 75	B: 0.52; E: 1.50	NA	5

ARAMIS = Arthritis, Rheumatism, and Aging Medical Information; B=BIOBADASER= Spanish register for RA patients treated with anti-tumour necrosis factor (TNF) alpha therapy; E=EMECAR= Spanish register for RA patients to monitor clinical expression, disease activity and progression of RA, and comorbidity; System; f=female; m=male; NA=not available; SMR=standardized mortality rate; asame study population; bsame study population; call patients started methotrexate.

Table 2. Mortality of rheumatoid arthritis in community-based studies

First author, publication year	Country	Inclusion year(s)	Patients (n)	Deaths (n)	SMR	Autopsy rate (%)	Follow-up duration (years)
Linos, 1980	USA	1950-74	521	143	1.16	NA	NA
Allebeck, 1981	Sweden	1965-67	293	84		NA	11
Male					1.92		
Female					1.18		
Doran, 2002[a]	USA	1955-95	609	334	1.27	NA	up to 40
Björnådal, 2002	Sweden	1964-94	61,899	25,353	2.03	NA	up to 32
Goodson, 2002	UK (NOAR)	1990-94	1,236	160		NA	7
Male					1.08		
Female					0.99		
Gabriel, 2003[a]	USA	1955-94	609	NA		NA	14
Total					1.27		
Male					1.08		
Female					1.41		
Sihvonen, 2004a	Finland	1988	1042	384		32	12
Total					2.64		
Male					3.20		
Female					2.53		
Gonzalez, 2007[a]	USA	1955-2000	822	445		NA	12
Total					1.35		
Male					1.12		
Female					1.49		
Gonzalez, 2008b[a]	USA	1955-95				NA	14
Rheumatoid factor +			393	260	1.81		
Rheumatoid factor-			210	138	0.99		

NA=not available; NOAR=Norfolk arthritis register; a primary care-based inception cohort of patients with inflammatory polyarthritis; SMR=standardized mortality rate; asame inception cohort of residents with RA in Rochester, Minnesota.

2.3.1 Predictors of premature mortality

In RA patients, several factors predict mortality. Premature mortality, as well as susceptibility for developing RA, is linked to human leukocyte antigen (HLA)-DRB1 alleles located in the major histocompatibility complex (MHC) of chromosome 6. HLA-DRB1 alleles share amino acid homology, which has been the basis of the so-called shared epitope (SE) hypothesis, in which these

DRB1 molecules bind an RA-inducing peptide(s) (Gregersen et al., 1987; de Vries et al., 2005). The HLA-DRB1 SE genes have been associated not only with increased overall mortality (Farragher et al., 2008), but also with increased mortality due to specific causes such as CVDs (Gonzalez-Gay et al., 2007; Mattey et al., 2007b; Farragher et al., 2008) and malignancies (Mattey et al., 2007b).

Soluble tumour necrosis factor receptor II (sTNFRII) has been linked in RA patients to increased mortality. Elevated levels of sTNFR II are particularly associated with mortality due to CVDs, and these may be used for identifying patients at risk for premature death (Mattey et al., 2007a).

Cigarette smoking has a clear causal connection to development of RA (Symmons et al., 1997). This connection has been reported in seropositive RA (Stolt et al., 2003), especially in men (Heliövaara et al., 1993; Uhlig et al., 1999; Albano et al., 2001). Cigarette smoking also seems to have a negative impact on survival (Goodson et al., 2008a). Low education level (Leigh and Fries, 1991; Wolfe et al., 1994; Wållberg-Jonsson et al., 1999; Pincus et al., 2004; Young et al., 2007) or never married (Leigh and Fries, 1991) have also been associated with increased mortality.

HLA-DRB1 SE alleles have been shown to be exclusively associated with RA patients who are positive for anti-citrullinated peptide antibodies (ACPAs) (Huizinga et al., 2005). In Finnish RA patients, high titres of ACPA have predicted mortality (Sihvonen et al., 2005). The combination of ACPA, smoking, and SE is especially associated with a high risk of premature death (Farragher et al., 2008).

In RA patients, rheumatoid factor (RF) positivity is a predictor of early death (Mitchell et al., 1986; Jacobsson et al., 1993; van Schaardenburg et al., 1993; Wolfe et al., 1994; Heliövaara et al., 1995; Goodson et al., 2002; Mikuls et al., 2002; Sihvonen et al., 2005; Farragher et al., 2007; Young et al., 2007). After adjusting for age, sex, and smoking, RF positivity predicts mortality also in persons with no arthritis (Heliövaara et al., 1995). In RA patients (Goodson et al., 2002; Gonzalez et al., 2008b) as well as in a randomly selected population (Aho et al., 1982), seropositivity for RF was linked to excess cardiovascular mortality.

As in the general population, premature mortality in the RA population is strongly predicted by male gender (Mitchell et al., 1986; Leigh and Fries, 1991; Jacobsson et al., 1993; Wolfe et al., 1994; Young et al., 2007). In RA patients with disease onset at an older age, i.e. $\geq$ 60 years, RA seems to have a more severe course, as measured by disease activity and radiographic damage (van der Heijde et al., 1991). Parallel with this observation, age in RA patients, expressed as an odds ratio, has proven to be a predictor of mortality (Chehata et al., 2001; Young et al., 2007).

Persistently active RA predicts early mortality (Reilly et al., 1990; Wolfe et al., 1994; Chehata et al., 2001; Farragher et al., 2007). Active inflammation in RA seems to be associated with premature cardiovascular death. In RA patients positive for RF, a high erythrocyte sedimentation rate (ESR) predicted overall mortality as well as the risk for development of CVD (Wållberg-Jonsson et al., 1999). This study also observed that DMARD therapy was associated with decreased mortality risk.

In patients with recent onset inflammatory polyarthritis, baseline serum C-reactive protein (CRP) was an independent predictor of subsequent death due to CVD (Goodson et al., 2005). A population-based study on Pima Indians showed joint swelling, independent of other known risk factors, including RA, to be a risk factor for CVD-related death (Jacobsson et al., 2001). Because traditional risk factors, such as tobacco smoking and dyslipidemia, incompletely explain accelerated atherosclerosis in RA patients, systemic inflammation associated with RA may play an important role (Van Doornum et al., 2002).

In RA patients (Leigh and Fries, 1991; Wolfe et al., 2003; Sokka et al., 2004; Farragher et al., 2007; Young et al., 2007) and also in the general population (Sokka et al., 2004), functional disability measured by the Health Assessment Questionnaire (HAQ) is a strong predictor of premature mortality. In RA patients, HAQ has been an important independent predictor also of increased cardiovascular mortality (Farragher et al., 2007). Furthermore, physical measures of functional status, such as grip strength, walking time, and button test, predict untimely overall mortality (Pincus, 2005). These tests, unlike patient questionnaires, bypass socio-cultural differences, the effect of which can be seen if patient questionnaires are used (Pincus, 2005). One advantage in the use of patient questionnaires is that they involve less professional time (Pincus, 2005).

Excess mortality in RA patients is strongly associated with occurrence of extra-articular manifestations (Erhardt et al., 1989; Turesson et al., 2002; Gabriel et al., 2003, Young et al., 2007). Poor prognosis is predicted especially by vasculitis, pericarditis, pleuritis, and Felty's syndrome (Turesson et al., 2002). Furthermore, rheumatic nodules have been linked to increased overall mortality (Wolfe et al., 1994; Chehata et al., 2001) as well as to increased cardiovascular mortality (Naz et al., 2008). Extra-articular features or vascular inflammation have been suggested to identify RA patients at particularly high cardiovascular risk (Naz et al., 2008).

2.3.2 Causes of death

Several RA mortality studies have shown an increased death rate due to CVDs, infections, GI disorders, and LPMs (Table 3).

Table 3. Mortality of rheumatoid arthritis caused by specific disorders represented as standardized mortality ratios

First author, publication year	Cardio-vascular	Cardiac	Cerebro-vascular	Infection[a]	Cancer	LPMs	GI
Inception cohorts							
Goodson, 2002							
Male	0.7	NA	NA	NA	1.6	NA	NA
Female	1.1				0.8		
Goodson, 2005							
Male	1.4	1.5[b]	NA	NA	1.4	NA	NA
Female	1.9	2.0[b]			1.1		
Young, 2007	NA	1.5[b]	1.1	6.8	1.1[c]	2.4	0.9
Established cohorts							
Linos, 1980	NA	1.0[b]	1.4	NA	0.8	NA	NA
Allebeck, 1982	NA	1.5	1.1	3.6	1.1	NA	4.1
Vandenbroucke, 1984	0.9	NA	NA	3.7	0.7	NA	NA
Prior, 1984	2.4	NA	NA	11.1	1.6	NA	6.5
Wolfe, 1994	NA	1.0	1.1	6.2	0.3	8.0	1.5
Wållberg-Jonsson, 1997							
Total	1.5	1.5[b]	1.1	4.2	1.2	3.8	3.4
Male	1.4	1.4[b]	0.6	2.3	1.3	3.2	2.7
Female	1.5	1.7[b]	1.4	5.3	1.1	4.8	4.0
Symmons, 1998							
27 yrs RA duration	2.2	NA	NA	14.9	1.7	35.1[d]	5.0
-1-18 yrs RA duration	2.4			11.1	1.6	26.3[d]	6.5
-19-27 yrs RA duration	1.8			36.6	1.9	81.1[d]	2.2
Kvalvik, 2000	1.3	NA	NA	NA	1.6	NA	NA
Björnådal, 2002	1.8	1.8[b]	1.5	4.8	1.1	NA	3.5
Thomas, 2003							
Male	2.0	1.6[b]	NA	4.9	1.3	1.8	2.8
Female	1.9	2.0[b]		4.0	1.2	2.0	3.2
Sihvonen, 2004[a]	1.9	NA	NA	6.5	2.4	NA	7.6
Carmona, 2007							
BIOBADASER	0.5	NA	NA	11.3	0.3	NA	NA
EMECAR	0.9			18.7	1.0		

Cardiovascular diseases include cardiac and cerebrovascular diseases; cardiac diseases include all cardiac diseases and disorders of vessels, but exclude cerebrovascular diseases; BIOBADASER= Spanish register for RA patients treated with anti-tumour necrosis factor (TNF) alpha therapy; EMECAR= Spanish register for RA patients to monitor clinical expression, disease activity and progression of disease, and co-morbidity (a few RA patients received TNF alpha therapy); GI=gastrointestinal disorders; LPMs=lymphoproliferative malignancies; NA=not available; [a]determination of infection varies; [b]coronary heart disease; [c]solid tumours; [d]non-Hodgkin lymphoma.

2.3.2.1 Cardiovascular diseases

In several RA mortality studies, CVDs have been the leading CoD (Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Kvalvik *et al.*, 2000; Björnådal *et al.*, 2002; Goodson *et al.*, 2002; Sihvonen *et al.*, 2004a; Goodson *et al.*, 2005). However, some studies have observed, compared with the general population (Sokka *et al.*, 1999) or reference cases without RA (Riise *et al.*, 2001b), no increased death rate due to CVDs. This is true especially for the RA mortality studies published before the 1990s (Cobb S *et al.*, 1953; Davis and Engleman, 1974; Mutru *et al.*, 1976; Vandenbroucke *et al.*, 1984). Of cardiovascular deaths, the majority are caused by coronary heart disease (CHD) (Björnådal *et al.*, 2002; Sihvonen *et al.*, 2004a). One of the early studies reporting that RA patients die less frequently than their controls due to CHD suggested acetylsalicylic acid (ASA) to have had a protective effect against coronary events (Davis and Engleman, 1974).

A meta-analysis of RA mortality studies (case-control and cohort studies) covering the period up to 2005 reported increased mortality due to CHD and cerebrovascular diseases (Avina-Zubieta *et al.*, 2008). Furthermore, another meta-analysis on RA (case-control and cohort studies) covering the period up to 2006 made similar observations, but stated that the incidence of fatal cerebrovascular accidents was three times less than that of myocardial infarction (Levy *et al.*, 2008).

Several studies on RA have linked together, even in pre-menopausal female RA patients (Pahor *et al.*, 2006), active inflammation and accelerated atherosclerosis. Accelerated atherosclerosis is suggested to be an important contributor in RA patients to their increased cardiovascular mortality. RA patients are also susceptible to dyslipidemia. Inflammation leads to pro-atherogenic changes in lipoproteins (Nurmohamed, 2007). RA patients are at risk for unrecognized CHD and sudden cardiac death (Maradit-Kremers *et al.*, 2005b). Furthermore, RA patients are susceptible to atypical presentation of acute coronary syndrome (ACS) and have, compared with the general population, worse outcome (Douglas *et al.*, 2006). After ACS, RA patients seem to more frequently experience recurrent ischaemic events and death (Douglas *et al.*, 2006). RA patients also die frequently of heart failure (Mutru *et al.*, 1989). In RA patients, congestive heart failure, rather than CHD, has been suggested to be an important contributor to the excess mortality (Nicola *et al.*, 2006).

2.3.2.2 Rheumatoid arthritis

Mortality in RA patients is frequently attributed to RA itself (Allebeck, 1982; Vandenbroucke *et al.*, 1984; Wolfe *et al.*, 1994). However, on death certificates it remains frequently underreported (Allebeck *et al.*, 1981, Laakso *et al.*, 1986c). RA as a CoD may appear alone or with various associated complications. Pericarditis is a common extra-articular manifestation of RA, but it is only rarely life-threatening (Voskuyl, 2006). On the other hand, mortality appears to be excessive in

patients with an active vasculitic process (Erhardt *et al.*, 1989). Pulmonary fibrosis in association with RA is also linked with excess mortality (Young *et al.*, 2007). Furthermore, medullar compression in the cervical spine may be life-threatening (Sunahara *et al.*, 1997; Riise *et al.*, 2001a). This complication may develop as early as two years after the onset of RA, although it usually develops much later (Weissman *et al.*, 1982). Cervical spine disorders are frequently underestimated as a CoD (Neva *et al.*, 2001). Since neurological symptoms correlate with autopsy findings in the cervical spine only weakly, atlantoaxial dislocation may remain undetected during the lifetime (Mikulowski *et al.*, 1975).

2.3.2.3 Reactive amyloidosis

Reactive systemic AA amyloidosis associated with RA is an important determinant of mortality. High inflammatory activity, including high level of serum amyloid A (SAA), in RA is associated with development of reactive amyloidosis (Tiitinen *et al.*, 1993). With continuous active inflammation, the amyloid load increases (Gillmore *et al.*, 2001). Furthermore, the more extensive the amyloid deposition, the higher the risk of clinical manifestations (Kobayashi *et al.*, 1996). Renal amyloidosis frequently manifests with clinical signs and symptoms (Wright and Calkins, 1981; Browning *et al.*, 1985; Husby, 1992; Lachmann *et al.*, 2007), but clinical manifestations are rare with cardiac involvement (Wright and Calkins, 1981; Browning *et al.*, 1985; Husby, 1992). Amyloidosis may also lead to GI disturbances such as malabsorption (Pettersson and Wegelius, 1972) and diarrhoea (Okuda *et al.*, 1997). In association with amyloidosis, appearance of intractable diarrhoea (Okuda *et al.*, 1997) or renal failure (Cohen and Comerford, 1968; Gertz and Kyle, 1991) is a sign of a poor prognosis. Amyloidosis associated with RA has been estimated to shorten the lifespan by eight years (Myllykangas-Luosujärvi *et al.*, 1999).

In the literature, the prevalence of reactive amyloidosis associated with RA (Table 4) as well as mortality due to amyloidosis (Table 5) varies highly. This variation may arise from different study populations and diagnostic procedures. Techniques for detecting amyloid deposits may differ in sensitivity. Fine-needle aspiration biopsy of subcutaneous fat is the preferred method for screening and diagnosing reactive amyloidosis because it is convenient and safe (Westermark and Stenkvist, 1973; Klemi *et al.*, 1987). However, this technique seems to be more insensitive than rectal (Klemi *et al.*, 1987; Dhillon *et al.*, 1989) or gastroduodenal (Kuroda *et al.*, 2002) biopsies.

Autopsy is regarded, at least in CoD determination, as the gold standard (Goldman *et al.*, 1983; Welsh and Kaplan, 1998). Studies reporting detection rates of amyloid during the lifetime compared with autopsy findings are scarce. Such studies have comprised small populations of 21 patients or fewer. One of these studies reported pre-mortem detection rate of amyloidosis in RA to be as high as 81% at an amyloid clinic (Browning *et al.*, 1985). In another study, amyloidosis was diagnosed before autopsy in one-third of patients with chronic inflammatory disease (Wright and Calkins,

1981). In one early study, less than one-tenth of cases with moderate to severe amyloid deposition were diagnosed before autopsy as having amyloidosis (Teilum and Lindahl, 1954).

Table 4. Prevalence of amyloidosis in rheumatoid arthritis patients

First author, publication year	Country	Inclusion	Patients (n)	Amyloidosis n (%)	Diagnostic procedure	Selection of patients
Teilum, 1954[a]	Denmark	NA	28	17 (61)	Autopsy	Systematic
Arapakis, 1963	UK	NA	115	6 (5)	Rectal biopsy	Consecutive; hospitalized patients
Lender, 1972	Israel	NA	54	6 (11)	Rectal biopsy	Hospitalized patients
Ramirez, 1981	USA	1965-77	76	6 (8)	Autopsy	Consecutive autopsies
Boers, 1987[b]	NL	1958-84	132	14 (11)	Autopsy	Consecutive autopsies
Tiitinen, 1993	Finland	1973-75	102	11 (11)	SFA	Cohort of ERA patients examined systematically
Barile, 1993	Mexico	NA	50	39 (78)	Tru-cut needle subcutaneous abdominal fat biopsy	Outpatients
Suzuki, 1994[c]	Japan	1960-90	81	17 (21)	Autopsy	Consecutive autopsies
Helin, 1995	Finland	1976-92	110	33 (30)	Renal biopsy	Renal disease[d]
Kobayashi, 1996	Japan	1989-91	407	54 (13)	GI biopsy	RA patients attending hospital
Nakano, 1998	Japan	1979-96	158	30 (19)	Renal biopsy	Renal disease[d]
Gomez-Casanovas, 2001	Spain	1983-98	313	61 (20)	SFA	Routine screening; RA>5 years
El Mansoury, 2002	Egypt	Jan, 1999-Aug 1999	112	8 (7)	SFA	Consecutive outpatients; RA $\geq$ years

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.../...

First author, publication year	Country	Inclusion	Patients (n)	Amyloidosis n (%)	Diagnostic procedure	Selection of patients
Kuroda, 2002	Japan	1988-95	1006	71 (7)	GI biopsy	Consecutive inpatients
Ishii, 2003	Japan	NA	217	17 (8)	SFA	RA>5 years
Wakhlu, 2003	India	NA	113	30 (27)	SFA	RA>5 years
Wiland, 2004	Poland	1996-2001	121	35 (29)	SFA	RA patients attending hospital
Calguneri, 2006	Turkey	1988-2003	526	6 (1)	NA	Retrospective survey of medical records

ERA=early rheumatoid arthritis, not more than 6 months; GI=gastrointestinal; NA=not available; NL=the Netherlands; SFA=subcutaneous fat aspiration; [a]two cases with ankylosing spondylitis and the rest with RA; [b]only kidneys examined, autopsy rate 70%; [c]autopsy rate 58% in RA cases; [d]urinary abnormalities or renal dysfunction or both.

Table 5. Deaths in rheumatoid arthritis patients caused by reactive amyloidosis

First author, publication year	Country	Inclusion year(s)	Patients (n)	Deaths (n)	Amyloid deaths n (%)	Autopsy rate (%)	Follow-up duration (years)	Setting
Mutru, 1976	Finland	1959-74	41	41	7 (17)	NA	NA	Autopsy
Prior, 1984	UK	1964-78	448	199	3 (2)	NA	11	Clinical
Laakso, 1986a	Finland	1959-68	1000	356	31 (9)	32	10	Clinical
Reilly, 1990	UK	NA	100	63	4 (6)	30	25	Clinical
Lehtinen, 1991	Finland	1961-66	573	251	61 (24)	NA	23-28	Clinical
Suzuki, 1994	Japan	1960-90	81	81	6 (7)	58	NA	Autopsy
Myllykangas-Luosujärvi, 1999	Finland	1989	1666	1666	97 (6)	27	Cross-sectional	Community
Kvalvik, 2000	Norway	1977	147	68	4 (7) [a]	NA	16	Clinical
Martinez, 2001	Spain	1989	182	23	4 (17)	NA	9	Clinical
Sihvonen, 2004a	Finland	1988	1042	384	28 (7)	32	12	Community

[a]Data from 60 patients available for analysis

2.3.2.4 Infections

Mortality in RA patients is increased due to infections (Allebeck, 1982; Prior *et al.*, 1984; Vandenbroucke *et al.*, 1984; Mutru *et al.*, 1985; Wolfe *et al.*, 1994; Symmons *et al.*, 1998; Sokka *et al.*, 1999), especially of the respiratory (Prior *et al.*, 1984; Vandenbroucke *et al.*, 1984; Mutru *et al.*, 1985; Thomas *et al.*, 2003) and urogenital (Vandenbroucke *et al.*, 1984) tracts. The risk of infectious deaths increases in parallel with RA duration (Symmons *et al.*, 1998). Of infectious deaths, the majority are constituted by respiratory infections (Mutru *et al.*, 1976; Suzuki *et al.*, 1994). Male sex and increasing age seem to predispose to respiratory tract infections (Coyne *et al.*, 2007).

2.3.2.5 Malignancies

Excess mortality in RA patients is attributed to LPMs (Laakso et al., 1986b; Wolfe et al., 1994; Myllykangas-Luosujärvi et al., 1995a; Symmons et al., 1998; Thomas et al., 2003; Sihvonen et al., 2004a). The mortality risk for LPMs increases with RA duration (Myllykangas-Luosujärvi et al., 1995a; Symmons et al., 1998). RA patients seem to have increased risk of lymphoma (Isomäki et al., 1978; Hakulinen et al., 1985; Bäcklund et al., 2006), leukaemia (Isomäki et al., 1978; Hakulinen et al., 1985; Cibere et al., 1997), and myeloma (Isomäki et al., 1978; Hakulinen et al., 1985). The risk of lymphoma is substantially increased in RA patients with very severe disease (Bäcklund et al., 2006). In the development of lymphoma, the major risk determinant appears to be high inflammatory activity, rather than RA medication (Bäcklund et al., 2006). Besides LPM, mortality also seems to be increased due to lung cancer (Thomas et al., 2003). On the other hand, RA patients may have reduced mortality due to malignancies of the GI tract (Laakso et al., 1986b; Thomas et al., 2003). The risk for development of colorectal cancer is especially reduced in RA (Cibere et al., 1997).

Use of ASA and non-ASA non-steroidal anti-inflammatory drugs (NSAIDs) may have protective effects against development of various malignancies, particularly development of colorectal cancer (Gwyn and Sinicrope, 2002). In large prospective epidemiological studies on samples of non-institutionalized US inhabitants, use of ASA has been associated with reduced risk of lung cancer (Schreinemachers and Everson, 1994), breast cancer (Schreinemachers and Everson, 1994; Johnson et al., 2002), and colon cancer (Schreinemachers and Everson, 1994). Furthermore, non-ASA NSAIDs, but not ASA, were associated in a large epidemiological study on British primarycare subjects with slightly reduced risk of lung cancer (Hernandez-Diaz and Garcia Rodriguez, 2007). Prospective randomized trials have shown the NSAID sulindac and the selective cyclo-oxygenase-2 (COX-2) inhibitor celecoxib regress adenomas in patients with familial adenomatous polyposis (Gwyn and Sinicrope, 2002). However, there is some controversy about the suggestion that ASA and non-ASA NSAIDs protect against malignancies. One large prospective cohort study on female RA and osteoarthritis patients reported use of either ASA or non-ASA

NSAIDs to be associated with increased risk of developing non-Hodgkin lymphoma (Cerhan et al., 2003). The authors reported that the increased risk was independent of a history of RA. With respect to mortality, ASA has shown beneficial effects. In a large prospective population-based study on postmenopausal women, use of ASA was associated with decreased overall mortality as well as decreased mortality due to malignancies and CHD (Bardia et al., 2007).

2.3.2.6 Other causes

Mortality in RA is attributed to disorders of the upper GI tract (Sihvonen *et al.*, 2004a) such as haemorrhage (Vandenbroucke *et al.*, 1984). Age, glucocorticoid (GC) use, NSAID dose, disability level, and previous NSAID-induced GI symptoms are independent risk factors for serious GI events (Singh, 1998). In RA patients, mortality due to chronic obstructive pulmonary disease (Thomas *et al.*, 2003) and renal failure (Symmons *et al.*, 1998; Thomas *et al.*, 2003) are also increased. Nephropathy in RA patients presenting with combined haematuria and proteinuria, proteinuria, microalbuminuria, or histologically confirmed amyloidosis is linked to increased mortality, whereas mortality is within expected limits in those with isolated haematuria or mesangial glomerulonephritis (Sihvonen *et al.*, 2004b).

2.3.3 Mortality and rheumatoid arthritis medication

Medication for RA is likely to play a role in mortality. The use of any DMARD (Wållberg-Jonsson *et al.*, 1997), aurothiomalate (Lehtinen and Isomäki, 1991), or anti-tumour necrosis factor (TNF) alpha therapy (Jacobsson *et al.*, 2007) has been associated with reduced mortality. Good response to medication, such as methotrexate (MTX), has been associated with reduced mortality (Krause *et al.*, 2000).

Inflammation in RA seems to play a significant role as a risk factor for the development of atherosclerosis (Van Doornum *et al.*, 2002). The risk of cardiovascular death, which constitutes the majority of deaths in RA, may be reduced by the use of effective medication for RA, such as MTX (Choi *et al.*, 2002; Krishnan *et al.*, 2004). However, there is some controversy about this issue, as the use of MTX increases levels of homocysteine (Landewe *et al.*, 2000). RA patients treated with anti-TNF alpha therapy have a lower risk of developing CVD (Jacobsson *et al.*, 2005). Particularly, RA patients who respond to anti-TNF alpha therapy experience, unlike non-responders, a reduction in the incidence of myocardial infarction (Dixon *et al.*, 2007). This is in agreement with the hypothesis that inflammation contributes to the development of cardiovascular events. Further,

antimalarials appear, at least in patients with systemic lupus erythematosus, to have beneficial effects on lipid profiles (Munro *et al.*, 1997).

GCs and NSAIDs may have unfavourable effects on blood pressure, serum glucose, and lipid profiles, all of which are risk factors for development of CVD (Nashel, 1986; Hermann and Ruschitzka, 2007; Panoulas *et al.*, 2008). Epidemiological studies have raised concern about the safety of both selective COX-2 inhibitors and non-selective NSAIDs (Hippisley-Cox and Coupland, 2005; Gislason *et al.*, 2006). In primary care subjects, use of rofecoxib, diclofenac, and ibuprofen was associated with, after adjustment for several potential confounders, an increased risk of myocardial infarction (Hippisley-Cox and Coupland, 2005). One meta-analysis suggested that use of naproxen may have a slight protective effect against cardiovascular events (Juni *et al.*, 2004), but this issue is controversial (Hippisley-Cox and Coupland, 2005). In patients with previous myocardial infarction, selective COX-2 inhibitors in all dosages and non-selective NSAIDs in high dosages seemed to increase mortality (Gislason *et al.*, 2006). However, use of NSAIDs by patients with recent onset of inflammatory polyarthritis in a primary care-based inception cohort was not associated with cardiovascular mortality (Goodson *et al.*, 2008b).

In the literature, discrepant reports have emerged about the use of GCs and cardiovascular risk. In one population-based cohort study of RA patients, particularly RF-positive patients were after GC exposure at increased risk for cardiovascular events (Davis *et al.*, 2007). Nevertheless, cardiovascular risk in RF-seropositive RA patients recruited from hospital (inpatients, outpatients, and consultation patients) was not associated with GC use (Wållberg-Jonsson *et al.*, 1997). One large case-control study on primary care subjects with at least one prescription of oral GCs showed that use of GCs was associated strongly with heart failure and weakly with ischaemic heart disease (Souverein *et al.*, 2004). That study also reported GCs to have a protective effect against stroke and transient ischaemic attack. The authors suggested that using GCs is a balance between adverse and potentially protective effects. In patients using MTX, the concentration of homocysteine, a known cardiovascular risk factor, may be elevated (Whittle and Hughes, 2004). However, this phenomenon can be offset by using supplemental folates (Whittle and Hughes, 2004).

The use of cyclophosphamide (CYC) is associated with development of cancers, particularly of bladder cancer (Radis *et al.*, 1995; Beauparlant *et al.*, 1999). The use of azathioprine (AZA) is associated with development of lymphomas (Silman *et al.*, 1988; Beauparlant *et al.*, 1999). A meta-analysis covering the period from 1996 to December 2005 reported the use of anti-TNF alpha therapy, i.e. infliximab and adalimumab, to be associated with an increased risk of severe infections and also with dose-dependent increased risk of malignancies such as non-melanoma skin cancers and lymphoma (Bongartz *et al.*, 2006). That analysis, however, has been criticized because it excluded studies on etanercept (Callegari *et al.*, 2006). Furthermore, the analysis was conducted just before publishing a large study on adalimumab (Breedveld *et al.*, 2006). Had this study on adalimumab been included in the meta-analysis, the odds ratio for malignancy would have been lower (Costenbader *et al.*, 2006). One study focusing on biological treatment – including infliximab, etanercept, adalimumab, and anakinra – and malignancies using a large US database

reported the risk for various kinds of skin cancers to be increased, but this was not true for solid tumours or LPMs (Wolfe and Michaud, 2007).

Use of DMARDs, including MTX, does not increase the risk of infection, whereas use of GCs does (Coyne *et al.*, 2007; Lacaille *et al.*, 2008). GC use is especially linked to increased risk of lower respiratory tract infections (Sihvonen *et al.*, 2006; Coyne *et al.*, 2007), which have a relatively high mortality (Coyne *et al.*, 2007). With the exception of one study (Mitchell *et al.*, 1986), GC use has been found to predict mortality (Leigh and Fries, 1991; Wolfe *et al.*, 1994). Wolfe et al (1994) concluded that GC use was a marker of RA severity.

In one population-based RA mortality study, medication contributed to the death of 47 RA patients (3%) who died in 1989 (Myllykangas-Luosujärvi *et al.*, 1995b). In that study, the vast majority of deaths were estimated to be attributed to the use of non-selective NSAIDs or GCs. Use of non-selective NSAIDs increases the risk of serious GI events approximately 3-fold (Lichtenstein *et al.*, 1995). That risk may be higher in the elderly, in those with prior ulcer disease, in those taking concomitant GCs, and in those taking high-dose or multiple NSAIDs (Lichtenstein *et al.*, 1995). Furthermore, NSAID-induced GI injury may occur with no prior symptoms (Singh, 1998). However, the selective COX-2 inhibitors, introduced at the turn of the century, have proven less harmful to GI mucosa (Simon *et al.*, 1999).

The earlier RA medication starts, the better the outcome. RA patients referred early in the disease course do better than those referred late (Symmons *et al.*, 1998). There seems to be a window of opportunity for starting RA medication (Quinn and Emery, 2003; Cush, 2007). An early start of RA medication, preferably during the first three months of symptom onset, seems to be crucial in achieving optimal control of disease progression and improved prognosis (Nell *et al.*, 2004).

2.4 Methodological aspects in rheumatoid arthritis mortality studies

2.4.1 General issues

Several important aspects should be considered when interpreting findings from various RA mortality studies. The number of patients may be highly variable, and conclusions based on only a few RA patients are generally unreliable. Study settings vary from the general population to tertiary care hospitals treating patients with the most severe RA. Furthermore, patients are recruited from various geographical sites. Findings derived from patients treated at a tertiary care hospital may

only be generalized to similar patients. Some RA mortality studies are prospective cohort studies, while others are retrospective, cross-sectional, or autopsy-based studies. Follow-up studies have had highly variable follow-up periods. Furthermore, follow-up studies do not follow all of their RA patients until death, although CoDs change with advanced age as well as along the course of RA (Symmons et al., 1998).

2.4.2 Study populations

RA mortality studies use different inclusion criteria for RA. Several studies have used classification criteria for RA. However, before 1958, no classification criteria existed for RA. In 1958, the American Rheumatism Association (ARA) criteria were created (Ropes, 1959) (Table 6). The 1958 ARA criteria classified the disease as classical, definite, probable, and possible RA based on criteria comprising clinical, serological, radiological, and histological features. The revised ARA criteria from 1987 were based on those earlier criteria, but accommodated the characteristic pattern of joint involvement more precisely (Arnett *et al.*, 1988) (Table 7). However, no RA classification criteria are absolutely specific and sensitive. One review article reported that the 1958 ARA criteria showed a sensitivity varying from 71% to 100% and a specificity varying from 77% to 98%; and the 1987 ARA criteria showed a sensitivity from 66% to 95% and a specificity from 74% to 98% (MacGregor, 1995). That review also stated that the 1987 ARA criteria may have enhanced specificity, compared with the 1958 criteria, but sensitivity may be reduced (MacGregor, 1995). Another review article estimated that the 1958 ARA criteria possess a weakness because much emphasis is placed on soft-tissue swelling, which has low specificity and poor interobserver reproducibility (Aho *et al.*, 1998). That review article considered the presence of clinical arthritis or deformities of previous arthritis, associated with RF positivity or radiological changes typical of RA, to be a more reliable measure of clinically significant chronic peripheral arthritis, i.e. RA, than RA defined by the 1958 ARA criteria (Aho *et al.*, 1998) (Table 8). A study on prevalence of RA in the United Kingdom suggested a similar approach (Symmons *et al.*, 2002). In that study, besides active arthritis presenting with joint swelling, the authors also analyzed joint deformities as a sequela to previous arthritis. Therefore, those RA patients who were in remission at the time of the study could also be detected. Furthermore, the 1987 ARA criteria have been unable, among patients with recent onset of inflammatory polyarthritis, to distinguish between patients who later develop persistent, disabling, and erosive polyarthritis and those who do not (Harrison *et al.*, 1998).

Table 6. The 1958 American Rheumatism Association (ARA) criteria for rheumatoid arthritis

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint (observed by a physician).
3. Swelling (soft tissue thickening or fluid, not bony overgrowth alone) in at least one joint (observed by a physician).
4. Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms between the two joint involvements may be no more than 3 months).
5. Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of the mid-phalangeal, MCP, or MTP joints is acceptable without absolute symmetry). Terminal IP joint involvement will not satisfy the criterion.
6. Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces, or in juxta-articular regions.
7. X-ray changes typical of RA (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes). Degenerative changes do not exclude patients from any group classified as RA.
8. Positive agglutination test demonstration of RF by any method, which in two laboratories has been positive in not over 5% of normal controls, or positive streptococcal agglutination test.
9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).
10. Characteristic histological changes in synovial membrane with three or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form “lymphoid nodules”; deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.
11. Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

Classical RA requires 7/11 criteria with 1-5 present continuously for 6 weeks;

Definite RA requires 5/11 criteria with 1-5 present continuously for 6 weeks;

Probable RA requires 3/11 criteria with at least one of 1-5 present continuously for 6 weeks;

Possible RA requires two of the following criteria and a total duration of joint symptoms of at least three weeks: (1) Morning stiffness, (2) tenderness or pain on motion with a history of recurrence or persistence for three weeks, (3) history or observation of joint swelling, (4) subcutaneous nodules, (5) elevated sedimentation rate or C-reactive protein, or (6) iritis. MCP=metacarpophalangeal; MTP=metatarsophalangeal; IP=interphalangeal; RA=rheumatoid arthritis; RF=rheumatoid factor.

Exclusions: Typical rash of systemic lupus erythematosus, high concentration of lupus erythematosus cells, histological evidence of periarteritis nodosa, weakness of the neck, trunk, and pharyngeal muscles or persistent muscle swelling of dermatomyositis, scleroderma, rheumatic fever, gouty arthritis, tophi, acute infectious arthritis, joint tuberculosis, Reiter's syndrome, shoulder-hand syndrome, hypertrophic pulmonary osteoarthropathy, neuroarthropathy, homogentisic acid in the urine, histological evidence of sarcoid or a positive Kveim test, multiple myeloma, erythema nodosum, leukaemia or lymphoma, or agammaglobulinaemia. Adapted from Ropes et al (1959). Modified and re-printed with kind permission of BMJ Publishing Group Ltd.

Table 7. The revised 1987 ARA criteria for rheumatoid arthritis

1.	Morning stiffness	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement for at least 6 weeks.
2.	Arthritis in three or more joint areas[a]	Soft tissue swelling or fluid (not bony overgrowth) observed by a physician, present simultaneously for at least 6 weeks.
3.	Arthritis of hand joints	Swelling of wrist MCP or PIP for at least 6 weeks.
4.	Symmetrical arthritis	Simultaneous involvement of the same joint areas (defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry) for at least 6 weeks.
5.	Rheumatoid nodules	Subcutaneous nodules over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6.	Rheumatoid factor	Detected by a method positive in less than 5% of normal controls.
7.	Radiographic changes	Typical for RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (OA changes alone do not qualify).

At least four criteria must be fulfilled for classification as RA. MCP=metacarpophalangeal; MTP=metatarsophalangeal; OA=osteoarthritis; PIP=proximal interphalangeal; RA=rheumatoid arthritis. [a]Possible areas: right or left PIP, MCP, wrist, elbow, knee, ankle, MTP. Adapted from Arnett et al (1988). Modified and re-printed with kind permission of Wiley Interscience.

Table 8. Classification criteria for chronic rheumatoid arthritis suggested by Aho et al

1.	Clinical arthritis (or deformities of past arthritis)
2.	Positive rheumatoid factor serology
3.	Radiographic changes typical of rheumatoid arthritis

Diagnosis of rheumatoid arthritis requires presence of clinical arthritis associated with positive serology or characteristic radiographic changes or both. Adapted from Aho et al (1998).

2.4.3 Presentation of results

Early studies on RA mortality have used proportional mortality statistics, which express deaths from a particular cause as a percentage of the total number of deaths. This may cause misinterpretations. Monson and Hall (1976) reported deaths from malignancies in patients with RA or osteoarthritis to be less than expected using proportional mortality analysis, but more than expected using absolute figures. When using absolute figures, mortality can be expressed over a follow-up period as relative risk (RR), which compares the number of deaths in a RA population with the number of deaths in a non-RA population, or as standardized mortality ratio (SMR), which compares the number of deaths in a RA population to the number of deaths in the general population. Some issues to consider emerge when interpreting SMR, which is used in several studies. SMR is influenced by the background population from which the RA population is drawn and by the length of follow-up. The longer patients are followed up, the more likely the SMR is to approach 1. This is explained by the fact that all patients eventually die. If the follow-up is extended sufficiently long, e.g. 100 years, the SMR will be 1. Mortality can also be expressed as a life-table survival curve showing cumulative probability of survival of a cohort. Furthermore, mortality can be expressed as a shortening of lifespan (Symmons, 1988; Myllykangas-Luosujärvi *et al.*, 1995; Naz and Symmons, 2007).

Official death certificates have three classes of CoDs, i.e. immediate, underlying, and contributory, all of which have an effect on CoD sequence. This sequencing of CoDs is based on guidelines established by the World Health Organization (WHO). Underlying CoD is the basic disease that initiated the cascade of morbid events leading to death. Immediate CoD is the final disease or condition directly causing death. Contributory CoDs are coexisting conditions that contributed to death, but did not result in the underlying CoD. Underlying and immediate CoDs are always required in the CoD sequence.

CoD analyses are frequently based on solely the underlying CoD. However, an analysis based solely on underlying cause may underestimate the contribution of a disease (Redelings *et al.*, 2006), such as heart failure (Murdoch *et al.*, 1998) and chronic obstructive pulmonary disease (Fuhrman *et al.*, 2006), to mortality. Because chronic diseases, such as RA, often cause death in association with other co-morbidities, it is preferable to analyse the contribution of chronic disorders to mortality by using multiple CoDs (Ziade *et al.*, 2008).

2.4.4 Accuracy of cause-of-death data

CoD determination is frequently based on clinical judgement without verification by autopsy, although autopsy is regarded as the gold standard (Goldman *et al.*, 1983; Welsh and Kaplan, 1998). A meta-analysis covering the years 1980 to 2004 reported that without autopsy discrepancies between clinical diagnoses of CoD and those made at autopsy had been detected in 46% of cases (Roulson *et al.*, 2005). Despite advances in medical technology, clinically determined CoD may be inaccurate (Kirch and Schafii, 1996). Especially in CoD determination for critically ill patients, autopsy is important (Roosen *et al.*, 2000; Twigg *et al.*, 2001; Perkins *et al.*, 2003; Combes *et al.*, 2004). In such patients, discrepant major diagnoses before autopsy have ranged from 20% to 39% (Roosen *et al.*, 2000; Twigg *et al.*, 2001; Perkins *et al.*, 2003; Combes *et al.*, 2004).

The main diagnoses leading to discrepancies in general patient populations have been pulmonary embolism, CVDs, including myocardial infarction, and infections (Roulson *et al.*, 2005). Furthermore, reactive AA amyloidosis, which can be a life-threatening manifestation of RA, may go undetected during the lifetime (Teilum and Lindahl, 1954; Wright and Calkins, 1981; Browning *et al.*, 1985).

Classification of CoDs according to the International Classification of Diseases (ICD) system may also cause bias in interpretation of RA mortality studies. Infections are classified, except for septicaemia and epidemic infections, under the organ system that they affect. Reactive amyloidosis associated with RA may appear, according to its typical clinical manifestation, as renal failure. Furthermore, information about reactive amyloidosis in an analysis of underlying CoDs may remain undiscovered because, according to guidelines of the WHO, it is not to be coded as an underlying CoD. According to the WHO, reactive amyloidosis may appear as an immediate, contributory, or intervening antecedent CoD.

National mortality statistics are likely to be deficient. Of death certificates, 10% (Ermenc, 1999) to as high as 96% (Pritt *et al.*, 2005) are completed inappropriately. Errors may also occur at the coding stage.

3. Aims of the study

The aim of this study was to evaluate determinants of RA mortality by clarifying CoDs and their changes over time, with special emphasis on CoDs in a population of autopsied RA patients, with non-RA patients serving as reference cases. This study also evaluated the contribution of autopsy to CoD determination, the contribution of RA medication to CoDs, and the detection rate of amyloid deposits.

Specific aims were as follows:

1. To analyse in a large RA population CoDs and changes in CoDs over a 21-year period (Study I).

2. To evaluate whether CoDs were similar in RA patients not autopsied and those who had undergone autopsy (Study I).

3. To examine in consecutively autopsied RA patients and their reference cases CoDs and changes in CoDs over 40 years (Study II), especially CoDs due to infections (Study III) or reactive amyloidosis (Study IV).

4. To investigate the contribution of autopsy to CoD diagnoses (Studies II-IV).

5. To clarify the detection rate of reactive amyloidosis in autopsied RA patients at three levels: 1) during the course of RA, 2) at routine autopsy, and 3) at systematic re-examination of autopsy tissue samples of the same patients (Study V).

6. To evaluate the contribution of RA medication to CoDs (Studies II-IV).

4. Patients and methods

4.1 Setting

Patients had been treated at Kivelä Municipal Hospital, Helsinki, Finland. During the study period, the hospital was an acute-care facility responsible for specialized health care of internal diseases and for primary to tertiary treatment of RA in the Helsinki area. The RA patients were treated by rheumatologists, and it was standard practice to commence treatment with a DMARD in the hospital ward.

4.2 Patients

4.2.1 Study population A

All RA patients treated and deceased between 1971 and 1991 at Kivelä Hospital were identified from the Hospital Discharge Register maintained by the National Research and Development Centre for Welfare and Health (STAKES). Of the 3186 RA patients treated as inpatients because of RA, 960 died (712 females, 248 males). Statistics Finland provided the information on their death certificates. Because the identification code came into regular use at the beginning of the 1970s, the study included RA patients deceased from 1971 onwards. Over the 21 year period, the autopsy rate declined (p-value for linear trend=0.010) (Figure 1). The cut-off year for the study was set at 1991.

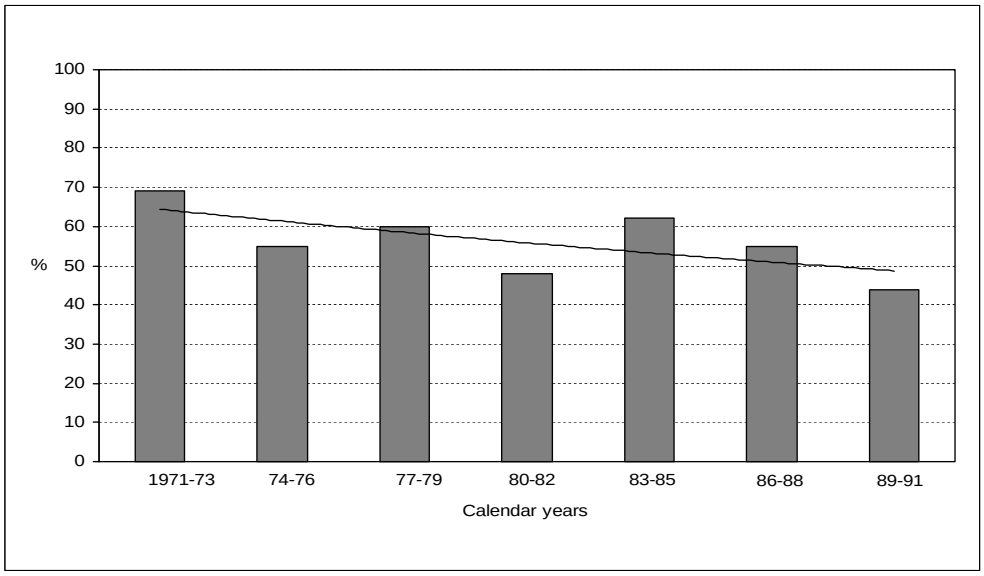

Figure 1. Autopsy rate of RA patients from 1971 to 1991, Study population A (unpublished data).

RA patients died frequently at secondary or tertiary care hospitals (Table 9). Of the 960 patients, 223 (23%) died at Kivelä Hospital. Of these patients, 65% were autopsied at Kivelä Hospital (unpublished data).

Table 9. Rate of autopsies according to the location of death

Location of death	All autopsies n (%)[a]	Medical autopsy n (%)[a]	Medicolegal autopsy n (%)[a]
Secondary or tertiary care hospital[b]	389 (65)	347 (58)	42 (7)
Primary care hospital	42 (20)	36 (17)	6 (3)
Home	58 (70)	13 (16)	45 (54)
Primary care centre	1 (100)	1 (100)	0 (0)
Old age home	6 (15)	6 (15)	0 (0)
Other	17 (74)	2 (9)	15 (65)
Total	513 (53)	405 (42)	108 (11)

[a]proportion of autopsies of all deaths at that particular location; [b]municipal or central hospital (unpublished data).

4.2.2 Study population B

All patients with a diagnosis of RA were identified from the autopsy register at Kivelä Hospital. This register, covering the years from 1946 to 1991, included referrals for autopsy with clinicians' diagnoses of CoD, autopsy reports, and CoD data. For each of the consecutively autopsied 591 RA patients, the next autopsied patient without any rheumatic disorder (non-RA) of the same sex, the same age at death (within a 2-year margin), and the same year of autopsy was chosen as a reference case. Patients with RA, spondylarthropathy, systemic lupus erythematosus, or any other rheumatic disorder, but not those with degenerative joint disease, were excluded from the non-RA population. Because 95% of the medical records before 1973 had been destroyed (archiving legislation, 1989) and because no international diagnostic criteria existed for RA before 1958, modified criteria for RA were set according to Aho et al (1998) (Table 8) in a review article on epidemiology of RA in Finland. The Aho group criteria were modified as follows: (i) for RA patients with unavailable medical records, diagnosis was based on the following findings at autopsy: erosions or macroscopic synovitis of a dissected joint or deformities typical of chronic RA at inspection or any combination of these, and (ii) if medical records were available, patients with clinical polyarthritis and joint erosions or rheumatic involvement of the cervical spine on radiographs or positive RF or both were included. Those RA patients who fulfilled these modified criteria (and their reference cases) were included in the study. Because very few RA patients fulfilled the modified criteria for RA earlier, the starting point for the study was 1952. Between 1952 and 1991, the mean autopsy rate was 67%. The autopsy rate declined from the late 1980s to the 1990s (Figure 2).

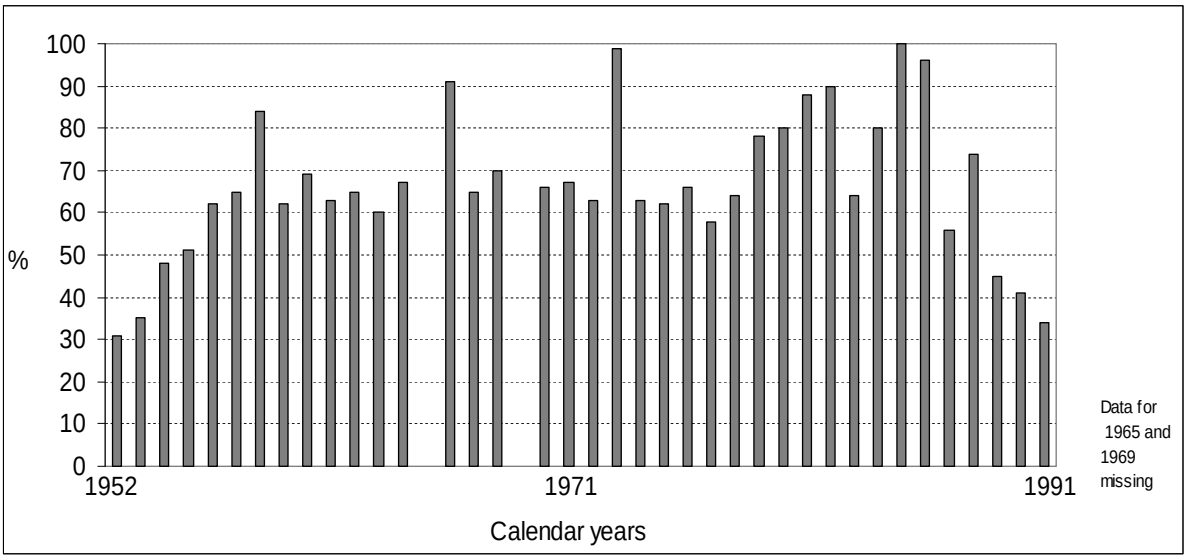

Figure 2. Autopsy rate from 1952 to 1991, Study population B (unpublished data).

Patients with an autopsy referral from a trauma hospital (Töölö Hospital) or a psychiatric hospital (the Hesperia Hospital) were excluded. Data for infectious CoDs were available for 369 RA patients and 371 non-RA patients, but one non-RA patient was subsequently excluded from analyses because of insufficient data. Thus, the patient pool in the other analyses comprised 369 RA patients (280 females, 89 males), with 370 non-RA patients (282 females, 88 males) serving as reference cases. Study population B contained 145 RA patients who were also included in Study population A. See Figure 3 for selection of patients and Table 10 for inclusion criteria fulfilled by the RA patients in Study population B.

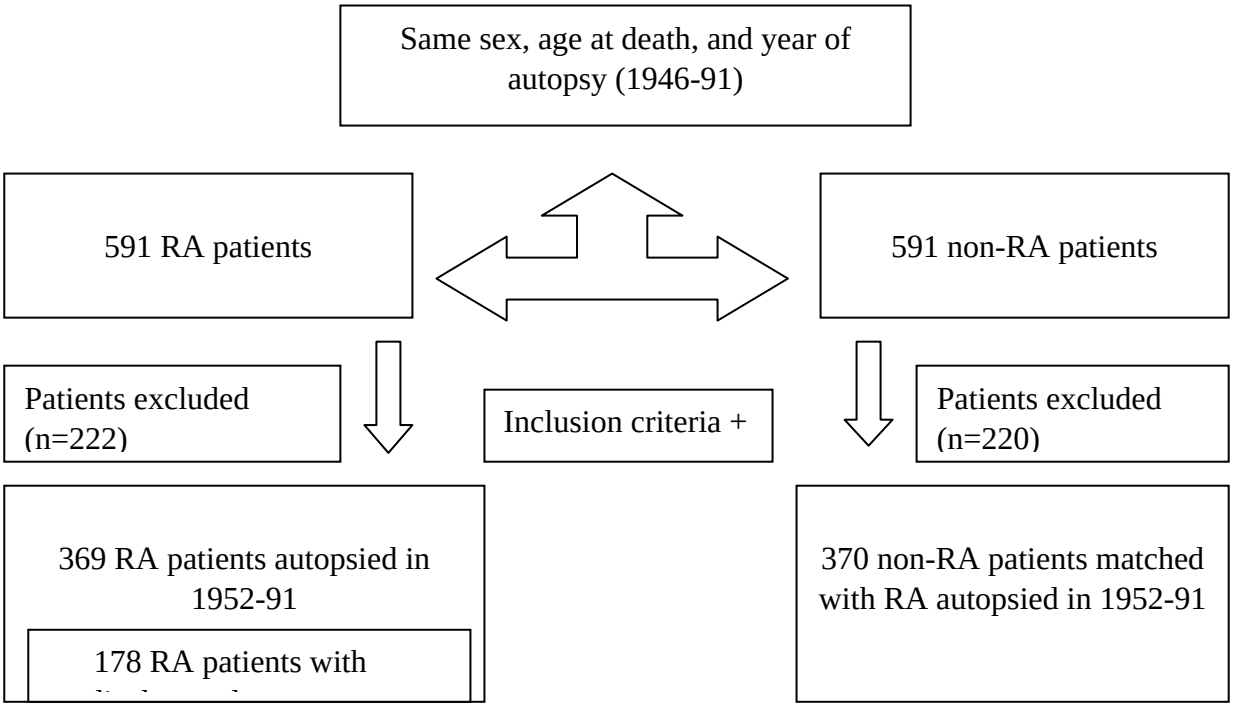

Figure 3. Patient selection. Inclusion of patients: clinical or autopsy criteria or both fulfilled. Patients from a trauma or psychiatric hospital excluded. Analysis of infectious deaths included 371 non-RA cases, see text above for explanation.

Table 10. Inclusion criteria fulfilled by rheumatoid arthritis patients

Clinical criteria[a]:	Number of patients (Positive finding/all studied)
Polyarthritis	
- with positive rheumatoid factor, but no radiographic changes	12/178
- with rheumatic changes on radiographs[b], but negative rheumatoid factor	17/178
- with positive rheumatoid factor and rheumatic changes on radiographs	149/178
Autopsy criteria[c]:	
Synovitis or erosions or both in a dissected joint	113/140
Findings of chronic RA at inspection	262/275
Both findings of dissected joint and chronic RA at inspection	74/353

[a]based on medical records systematically available between 1973 and 1991; [b]erosions of joints or rheumatic involvement of the cervical spine; [c]based on autopsy reports between 1952 and 1991.

The time period 1952 to 1972 included 183 RA and 185 non-RA patients. From 1973 to 1991, the corresponding figures were 186 and 185. Before 1973, only very few medical records were available. Therefore, subsequent analyses of clinical data are based on medical records of RA patients autopsied from 1973 onwards. Of the 186 RA patients autopsied between 1973 and 1991, medical records were available for 175. Clinical characteristics of these patients were evaluated (Table 11). However, descriptions of clinical features of RA were unavailable for some patients with limited medical records were very limited. Extra-articular features, for example, were investigated for 162 RA patients (Table 12, unpublished data). In RA patients, information was also recorded regarding the presence of co-morbid conditions, life-time biopsy findings for detecting amyloid, and functional status estimated according to Steinbrocker (1949).

Table 11. Clinical data recorded from medical records for 175 rheumatoid arthritis patients autopsied from 1973 to 1991

Rheumatoid factor	Regarded as positive:
	i) + (if qualitative)
	ii) Latex ≥ 32 (a reciprocal of titre)
	iii) Waaler-Rose ≥ 64 (a reciprocal of titre)
Duration of RA	Time period from diagnosis of RA to death (years)
Extra-articular features	Presence of rheumatic nodules, serositides, rheumatic lung involvement, rheumatic eye involvement, vasculitis, and neuropathy estimated to be associated with RA, Felty's syndrome, or any combination of these
Radiographic changes	Presence of erosions in joints or rheumatic involvement of the cervical spine
Medication	i) Disease-modifying anti-rheumatic drugs
	ii) Glucocorticoids
	iii) Cumulative duration of the use of these drugs
Laboratory tests	Mean of the values:
	i) Erythrocyte sedimentation rate
	ii) Blood haemoglobin
	iii) Persistent proteinuria[a] defined as:
	- proteinuria ≥ 1+/3+, if semi-quantitative (urine dipstick)
	- urinary protein secretion ≥ 0.3 g/24 h.
Orthopaedic operations	Synovectomy, prosthetic joint replacement, resection of metatarsophalangeal joints, arthrodesis, atlanto-occipital fusion operation, or any combination of these
Abnormalities in ECG	Ischaemia, conduction defects, arrhythmias, low voltage, or any combination of these
Functional status	From I to IV according to Steinbrocker et al (1949)

ECG=electrocardiogram; [a]persistent proteinuria was recorded when proteinuria was detected in medical records at least twice.

Table 12. Clinical features of RA patients autopsied from 1973 to 1991

Clinical feature	RA patients
Rheumatoid factor positivity[a]; n (%)	151 (92)
Radiographic changes typical of RA[b]; n (%)	151 (94)
Extra-articular features[c]; n (%)	72 (44)
- Rheumatic nodules	14 (9)
- Pericarditis	1 (0.6)
- Pleuritis	20 (13)
- Vasculitis	8 (5)
- Neuropathy	3 (1.9)
- Rheumatic involvement of lungs	45 (28)
- Secondary sicca syndrome	2 (1.3)
- Felty's syndrome	2 (1.3)
Duration of RA (years); mean±SD	17±11
Steinbrocker III-IV; n (%)	137 (82)
Orthopaedic operations; n (%)	56 (35)
Radiotherapy; n (%)	16 (10)
Erythrocyte sedimentation rate (mm/h); mean±SD	57±24
Blood haemoglobin (g/l); mean±SD	116±16

[a]data available for 164 patients; [b]data available for 160 patients; [c]data available for 162 RA patients (unpublished data).

Between 1973 and 1991, at least one DMARD, as a monotherapy or in combination, had been used by 138 patients (82%). Of the RA patients autopsied from 1973 to 1991, 86 (53%) had been on GCs, 142 (95%) on ASA, and 160 (99%) on some other NSAID. Between 1973 and 1991, the most frequently used DMARDs were aurothiomalate with or without antimalarials (106 patients). A few patients had been on cyclophosphamide (seven patients) or azathioprine (three patients). The most frequently used first DMARD was aurothiomalate or antimalarials, as a monotherapy or in combination (Figure 4). The median duration of DMARD usage was 3 years (Figure 5), and the median duration of RA for patients using DMARD was 16 years (IQR; 10-26). Thus, duration of treatment with DMARDs covered approximately one-fifth of the RA duration. The median duration of GC usage was 2 years (Figure 5), and the median duration of RA for patients using GCs was 17 years (IQR; 10-28). Thus, duration of treatment with GCs covered approximately one-eight of the RA duration. Between 1973 and 1991, the proportion of patients receiving DMARDs or GCs or both and the cumulative time on these drugs remained unchanged (data not shown).

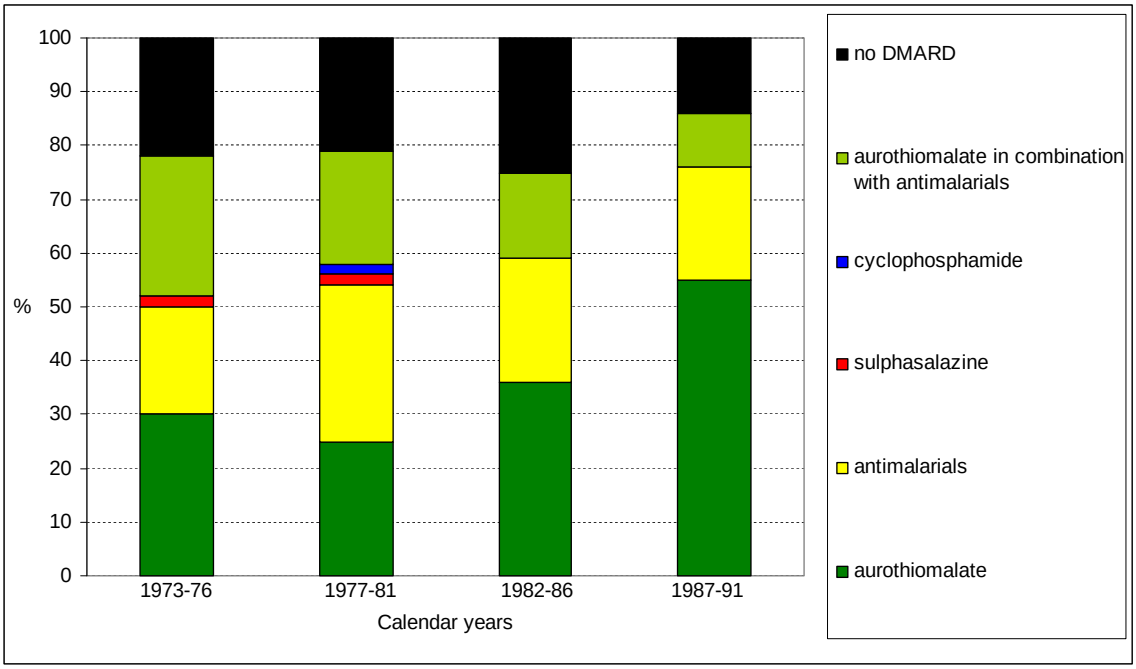

Figure 4. First medication for rheumatoid arthritis from 1973 to 1991 (unpublished data).

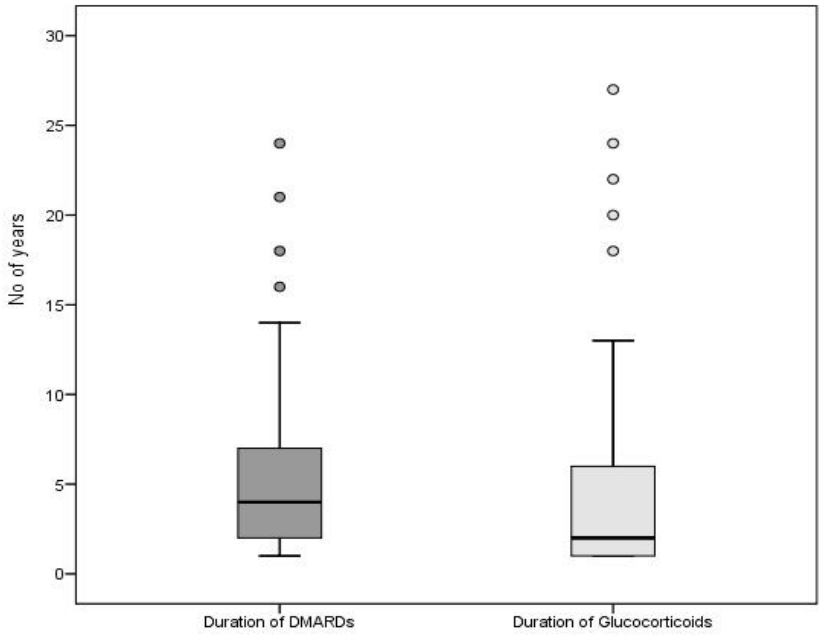

Figure 5. Duration of DMARDs in 129 RA patients and duration of GCs in 81 RA patients autopsied from 1973 to 1991. The box represents median (horizontal line in the box) and interquartile range (IQR). Whiskers show 5th and 95th percentiles. Circles represent outliers (unpublished figure).

All patients underwent complete autopsies. These autopsies included macroscopic assessment of the brain and internal organs, along with histological examination of routine samples (e.g. heart, lungs, liver, and kidneys) and organs with suspected abnormality. Furthermore, autopsies included inspection of the musculoskeletal system and histological examination of joints, when arthritis was suspected.

4.3 Methods

CoDs and their changes over a 21-year period were examined in a large population of RA patients (Study population A). A population of autopsied RA patients with non-RA patients serving as reference cases was examined next. In autopsied patients, the study evaluates CoDs and their changes over 40 years (Study population B), the accuracy of CoD determination, the contribution of DMARDs to the CoDs, and the detection rate of reactive amyloidosis.

The CoD data were obtained from death certificates (Study populations A and B). Unless otherwise stated, CoD data included multiple CoDs, i.e. immediate, underlying, contributory, and intervening antecedent CoDs. The CoD data for autopsied patients were based on autopsy.

Proportional mortality statistics, which express deaths from a particular cause as a percentage of the total number of deaths, may cause bias. To overcome this, this study evaluated multiple CoDs, the immediate cause, the underlying cause, and, with respect to CVDs, also of atherosclerotic findings in coronary arteries at autopsy (Study population B).

Data about CoDs before autopsy estimated by the clinician were derived from referrals for autopsy (Study population B). The accuracy of CoD determination was examined by comparing the diagnosis set by the clinician before autopsy with that determined at autopsy by the pathologist (Study population B).

In Study population B, clinical data during the course of RA were obtained from medical records systematically available from 1973 onwards. This data included the detection rate of amyloidosis during the course of RA, clinical features of RA, and medication for RA.

In Study population B, macroscopic and histological data were obtained from autopsy reports. This data included findings of reactive amyloidosis at any site and atherosclerotic findings in coronary arteries.

The detection rate of amyloidosis was examined at three levels 1) during the course of RA (data from medical records), 2) at the time of routine autopsies of RA and non-RA cases (data from autopsy reports), and 3) at re-examination of tissue samples taken from the same RA and non-RA cases. Furthermore, typing of amyloid was conducted in kidney samples.

4.3.1 Causes of death

Causes of death were recorded as follows:

Cardiovascular diseases: i) Cardiac: coronary heart disease; pericarditis, myocarditis, or endocarditis, or any combination of these; hypertensive heart disease, valvular disease, heart failure, cor pulmonale, and cardiomyopathy.
ii) Cerebrovascular: cerebral infarction, haemorrhage, and cerebrovascular atherosclerosis.
iii) Vascular: pulmonary embolism, aortic aneurysm, and vasculitis.

Respiratory diseases: chronic obstructive pulmonary disease, pulmonary fibrosis, or emphysema, or any combination of these, pulmonary infarction, bronchial asthma, and bronchiectasis.

Renal diseases: nephropathy of unknown aetiology, glomerulonephritis, and interstitial nephritis.

Gastrointestinal disorders: peptic ulcer, diverticular disease of the colon, inflammatory bowel diseases, mesenteric arterial infarction, paralytic ileus, appendicitis, cholecystitis, pancreatitis, hepatitis, and cirrhosis of the liver.

Endocrinological diseases: diabetes mellitus, Addison's disease, hyper- or hypothyreosis, and hyper- or hypoparathyreosis.

Infections: pulmonary infections, tuberculosis, sepsis, peritonitis, pyelonephritis, infections of the central nervous system, sexually transmitted diseases, and gastroenteritis.

Rheumatoid arthritis: RA with or without secondary complications, such as reactive amyloidosis, serositides, rheumatic lung involvement, or rheumatic eye involvement, Felty's syndrome, vasculitis, and neuropathy.

Malignancies: malignancies of various internal organs, breast, skin, bone, and the haematopoietic system

Haematological diseases: aplastic anaemia, leukocytopenia, and thrombocytopenia

4.3.2 Contribution of autopsy to cause-of-death diagnosis

If a CoD was not mentioned on referral by the clinician, but determined as such at autopsy by the pathologist, the CoD was considered to be unrecognized by the clinician. Besides false-negative CoDs, there may also be false-positive CoDs. Therefore, agreement between clinical diagnoses of CoDs and those determined at autopsy was estimated by the kappa reliability measure, in which agreement between diagnoses was low at <0.40, medium at 0.40–0.75, and high at >0.75.

4.3.3 Autopsy tissue samples

In Study population B, autopsy tissue samples were re-examined in 328 RA patients (89%) and in 336 non-RA patients (91%) to detect amyloid deposits. One pathologist (R.S.) analysed these samples, which were stained with Congo red, under polarized light for birefringent amyloid without knowledge of either clinical or autopsy data. Similarly, another pathologist (T.T.) conducted typing of amyloid by immunohistochemical methods (antiserum against amyloid A) in kidney samples. A patient with amyloid deposits in any tissue was defined as having reactive amyloidosis.

4.3.4 Statistical analysis

Statistical analysis was performed with the NCSS software (NCSS 6.0; Statistical software, Kaysville, UT, USA) and with SPSS software (SPSS, Inc., Chicago, IL, USA). Comparisons between groups for binary variables were performed with χ^2 or Fisher's exact test as appropriate. Continuous variables were compared by using Student's t-test. Statistical significance for hypotheses of linearity was evaluated by analysis of variance (ANOVA), Cochran-Armitage test, or linear-by-linear association test. Logistic regression analysis was applied to obtain age- and sex-adjusted probabilities. Agreement between clinical and autopsy-based diagnoses of CoDs was determined by the kappa reliability measure. No adjustment was made for multiple testing, but this information can be obtained by multiplying the p-value by the number of comparisons made. A p-value of less than 0.05 was considered significant.

5. Ethical considerations

The Ethics Committee of Helsinki University Central Hospital provided a favourable opinion on the study protocol. Ministry of Social Affairs and Health approved the study protocol. Statistics Finland gave permission to use of CoD data.

6. Results and discussion

Study population A comprised 960 RA patients, 53% of whom were autopsied. Study population B comprised 369 autopsied RA patients, with 371 autopsied non-RA patients serving as reference cases. In Study population B, data for infectious CoDs were available for 369 RA patients and 371 non-RA patients, but one non-RA patient was subsequently excluded from analyses because of insufficient data.

6.1 Study population A

In patients deceased between 1971 and 1991, the mean age at death $\pm$ standard deviation (SD) was 71 $\pm$ 10 years. During the 21-year period, the mean age at death increased in females from 64 to 74 years (p-value for linear trend<0.001) and in males from 66 to 70 years (non-significant).

6.1.1 Causes of death

In Study population A, CVDs, infections, and RA itself were the most frequent CoDs (Table 13), in accordance with several RA mortality studies reporting increased death rate due to CVDs (Allebeck, 1982; Prior *et al.*, 1984; Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Björnådal *et al.*, 2002; Sihvonen *et al.*, 2004a; Goodson *et al.*, 2005), infections (Allebeck, 1982; Prior *et al.*, 1984; Vandenbroucke *et al.*, 1984; Wolfe *et al.*, 1994; Symmons *et al.*, 1998; Sokka *et al.*, 1999; Björnådal *et al.*, 2002; Sihvonen *et al.*, 2004a), and RA (Allebeck, 1982; Vandenbroucke *et al.*, 1984; Wolfe *et al.*, 1994; Björnådal *et al.*, 2002).

Table 13. Causes of death in rheumatoid arthritis patients in Study population A

	Multiple cause of death n (%)	Underlying cause of death n (%)
Cardiovascular[a]	586 (61)	443 (46)
Coronary heart disease	349 (36)	275 (29)
Cerebrovascular[b]	115 (12)	81 (8)
Heart failure[b]	62 (7)	17 (2)
Rheumatoid arthritis	430 (45)	172 (18)
Infections	271 (28)	75 (8)
Respiratory[b]	173 (18)	48 (5)
Urinary tract[b]	36 (4)	7 (1)
Sepsis[b]	26 (3)	6 (1)
Tuberculosis[b, c]	16 (2)	6 (1)
Malignancies	126 (13)	112 (12)
Lymphoproliferative[b]	15 (2)	16 (2)
Gastrointestinal diseases	84 (9)	43 (5)
Emergency gastrointestinal disorders[b, d]	9 (1)	5 (1)
Renal diseases	69 (7)	6 (1)
Renal failure[b]	55 (6)	1 (0.1)
Endocrinological	44 (5)	9 (1)
Diabetes[b]	42 (4)	0 (0)
Respiratory diseases	52 (5)	27 (3)
Haematological diseases	9 (1)	5 (1)
Total number of patients	960	

[a]including cardiac, cerebrovascular, and vascular causes of death; [b]unpublished data; [c]at any site; [d]peptic ulcer with complication, perforation of intestine, or mesenteric infarction, or any combination of these.

Analysis of only underlying CoD, instead of multiple CoDs, seems to underestimate contribution of various diseases to mortality (see Table 13). However, several RA mortality studies have analysed only underlying CoD. To enable comparison of the findings in this study with those of others, multiple CoDs as well as underlying CoDs were analyzed.

Of the 960 RA patients in Study population A, CVD was an underlying CoD in 443 (46%), consistent with the results of others (Allebeck *et al.*, 1981; Wållberg-Jonsson *et al.*, 1997; Kvalvik

et al., 2000; Sihvonen *et al.*, 2004a). Some studies have, however, found lower prevalences (Martinez *et al.*, 2001; Young *et al.*, 2007). One Japanese autopsy-based study reported a very low figure (17%) for CVD deaths (Suzuki *et al.*, 1994). The study did not, however, specify, whether these were underlying causes. In Study population A, CHD constituted the majority of cardiovascular CoDs, in parallel with other reports (Wållberg-Jonsson *et al.*, 1997; Kvalvik *et al.*, 2000; Young *et al.*, 2007). Of the RA patients in Study population A, CHD appeared as an underlying CoD in 29%, resembling the findings of other authors (Wållberg-Jonsson *et al.*, 1997; Kvalvik *et al.*, 2000; Young *et al.*, 2007) (Table 14).

In a multiple CoD analysis, death was caused by infection in 28% of RA patients. Of these patients, infection was an underlying CoD in only 8%, a figure close to that reported for Norwegian RA patients for 1977-92 (Kvalvik *et al.*, 2000). One Spanish follow-up study covering the period from 1989 to 1998 (Martinez *et al.*, 2001) reported a higher proportion of infections than that observed in Study population A (Table 14). Higher proportions of infections have also been found in autopsy-based studies covering the period 1959-74 (24%) (Mutru *et al.*, 1976) and 1960-90 (24%) (Suzuki *et al.*, 1994). These two studies did not report whether these were underlying CoDs. One contributing factor to the high proportion of infections may be that these three studies did not use the ICD coding system in which infections are recorded under the organ system that they affect (Mutru *et al.*, 1976; Suzuki *et al.*, 1994; Martinez *et al.*, 2001). However, the explanation for the rather low proportion of infections in Study population A, where ICD coding was also not used, remains unclear. The majority of infections in RA patients here were infections of the respiratory tract, similar to other reports (Prior *et al.*, 1984; Vandenbroucke *et al.*, 1984; Mutru *et al.*, 1985; Symmons *et al.*, 1998; Sihvonen *et al.*, 2004a).

RA was the CoD in 45% of patients in a multiple CoD analysis and in 18% of patients in an analysis of underlying CoD, the latter figure being close to that of hospital-based follow-up studies using underlying CoD (Allebeck, 1982; Symmons *et al.*, 1998; Kvalvik *et al.*, 2000). Compared with the current finding of 18% of RA patients having RA as an underlying CoD, one population-based study of Swedish RA patients reported a 3-fold lower figure (Allebeck *et al.*, 1981) (Table 14). The authors noted that RA is often underreported on death certificates.

Table 14. Underlying causes of death in rheumatoid arthritis mortality studies

First author, publication year	Deaths (n)	CVD (%)	CHD (%)	Infection (%)	RA (%)	GI (%)	Resp (%)	Urogen (%)	Mal (%)	LPMs (%)
Allebeck, 1981	84	49	NA	2	5[a]	6	1	0	24	NA
Allebeck, 1982	473	37	NA	1	20[a]	8	5	4	12	NA
Wållberg-Jonsson, 1997	265	53	30	2	9[a]	6	9	2	14	3
Symmons, 1998	266	39	NA	3	15[a]	5	15	4	17	NA
Kvalvik, 2000	68	43	22	9	17	NA	NA	NA	24	NA
Martinez, 2001[b]	23	21	NA	21	NA	NA	NA	NA	8	NA
Sihvonen, 2004a	384	43	NA	2	8[a]	5	8	4	18	NA
Young, 2007	459	31	24	5[c]	NA	3	22	2[d]	24	4

CVD=cardiovascular disease; CHD=coronary heart disease; GI=gastrointestinal; LPMs=lymphoproliferative malignancies; Mal=malignancy; NA=not available; RA=rheumatoid arthritis; Resp=respiratory; Urogen=urogenital; [a]musculoskeletal disorders; [b]the ICD coding system not used in classification of causes of death; [c]septicaemia; [d]renal failure.

Death due to reactive amyloidosis occurred in 9% of RA patients, close to the findings of a Finnish hospital-based study (Laakso *et al.*, 1986a). Of the 89 patients with amyloidosis in the present study, 44% had renal failure as a CoD. Other RA-associated complications than amyloidosis were very uncommon. These complications included peri- or myocarditis or both (seven patients), acute medullar compression of the cervical spine or Felty's syndrome (three patients both), rheumatic lung involvement or renal failure (two patients both), vasculitis, pleuritis, pulmonary fibrosis and pneumonitis, some unspecified extra-articular feature, and tetraparesis as a consequence of medullar compression at the region CIV-V after atlanto-occipital fusion operation (one patient each).

Several hospital-based follow-up studies have reported higher mortality due to reactive amyloidosis in Finland (9-24%) (Mutru *et al.*, 1976; Laakso *et al.*, 1986a; Lehtinen and Isomäki, 1991) than in other European countries (2-7%) (Prior *et al.*, 1984; Reilly *et al.*, 1990; Kvalvik *et al.*, 2000), except for Spain (17%) (Martinez *et al.*, 2001) (Table 5). Deaths caused by reactive amyloidosis, thus, seem to occur more commonly in Finland than in other countries. Genetic susceptibility for amyloidosis has been suggested to contribute to this, even though one study found no link between occurrence of reactive amyloidosis and HLA antigens of 60 Finnish RA patients (Tiitinen *et al.*, 1992). The authors suggested that in development of amyloidosis prolonged inflammation may play a more important role than genetic factors. Findings regarding mortality due to reactive amyloidosis are too variable to draw any definite conclusions. Additional studies are thus needed to confirm whether Finnish RA patients are more susceptible to amyloidosis than other populations.

No significant sex-related differences existed in mortality due to amyloidosis; amyloidosis caused death in 71 females (10%) and 18 males (7%) (p=0.196). This observation is similar to that of a Finnish population-based study, in which mortality due to amyloidosis was higher, albeit not significantly, in females than in males (6.2% vs. 4.8%) (Myllykangas-Luosujärvi *et al.*, 1999).

Patients died frequently due to malignancies originating from the lungs and the lymphatic system (Table 15). This is in agreement with studies showing RA patients to be at risk for death from LPMs (Laakso *et al.*, 1986b; Symmons *et al.*, 1998; Thomas *et al.*, 2003; Sihvonen *et al.*, 2004a) and lung cancer (Thomas *et al.*, 2003). The RA patients here died frequently due to malignancies of the GI tract, inconsistent with studies reporting RA patients' reduced mortality due to GI malignancies (Laakso *et al.*, 1986b, Thomas *et al.*, 2003). Breast cancer was also a frequent CoD.

Table 15. Deaths caused by various malignancies from 1971 to 1991 in Study population A

Multiple cause of death; site	Total n (%)
Lung	34 (4)
Gastrointestinal tract[a]	19 (2)
Lymphoproliferative	15 (2)
Lymphoma	10 (1)
Breast	15 (2)
Gynaecological[b]	8 (0.8)
Pancreas	7 (0.7)
Brain	6 (0.6)
Liver	4 (0.4)
Gallbladder	3 (0.3)
Kidney	3 (0.3)
Melanoma	2 (0.2)
Prostate-testis	2 (0.2)
Larynx	1 (0.1)
Thyroid gland	1 (0.1)
Other	6 (0.6)
Total	126 (13)

[a]oesophagus, stomach, colon, or any combination of these; [b]including ovarian, uterus, and cervical cancers, or any combination of these (unpublished data).

6.1.2 Changes in causes of death over time

From 1971 to 1991, deaths caused by RA declined (Figure 6; p-value for linearity<0.001), in accordance with other authors' observations of a decline in deaths caused by RA from 1950 to 1981 (Wicks *et al.*, 1988) and from the 1970s to the 1990s (Ziade *et al.*, 2008). No significant change was detected in deaths due to amyloidosis over the 21-year period, although renal deaths declined (Figure 7; p-value for linearity=0.010). Because reactive amyloidosis frequently manifests as renal failure, this might merely reflect deaths caused by amyloidosis. However, withdrawal of phenacetin in Finland in 1965 may contribute to the decline in renal deaths. The banning of phenacetin has been shown to be followed by a decrease in mortality caused by renal disorders (Sillanpää *et al.*, 1982). No significant changes occurred from 1971 to 1991 in deaths due to other disorders.

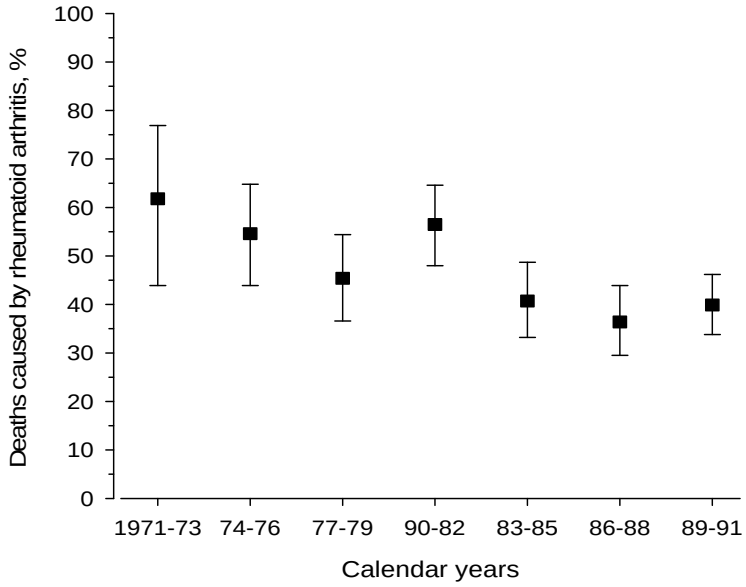

Figure 6. Sex- and age-adjusted deaths caused by rheumatoid arthritis with 95% confidence intervals. Multiple causes of death.

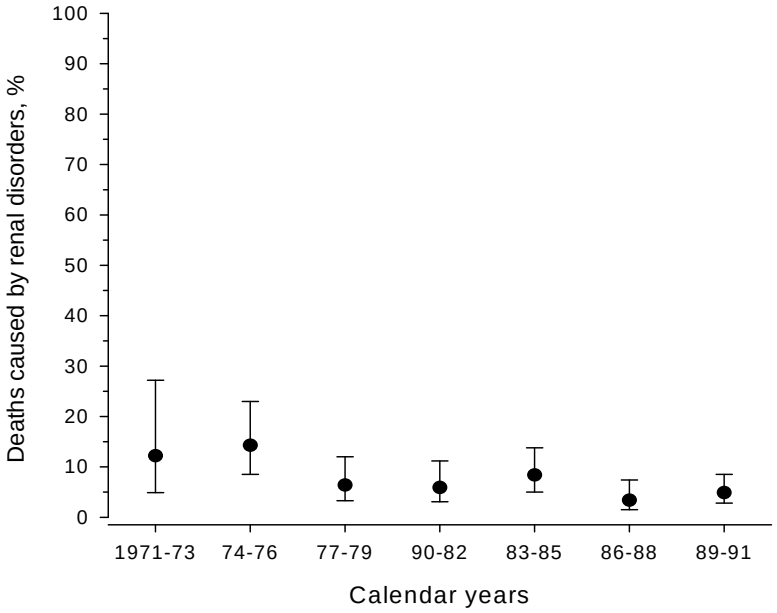

Figure 7. Sex- and age-adjusted deaths caused by renal disorders with 95% confidence intervals. Multiple causes of death.

6.1.3 Causes of death determined clinically and at autopsy

Between autopsied RA patients (n=513) and those not autopsied (n=447), no significant differences emerged in CVDs in an analysis of underlying CoD (45% vs. 47%; p=0.539), immediate CoD (50% vs. 46%; p=0.190), or multiple CoDs (both 61%; p=0.985). Similarly, no significant differences between these patient groups appeared in multiple CoD analysis of infectious, malignant, respiratory, or haematological diseases (data not shown). These findings suggest that, with respect to these disorders, non-autopsy and autopsy RA populations may be similar. However, compared with those not autopsied, autopsied patients died more frequently of CHD (40% vs. 33%; p=0.026) and GI disorders (13% vs. 4%; p<0.001), but less frequently of RA (38% vs. 52%; p<0.001), endocrinological diseases (2% vs. 7%; p<0.001), cerebrovascular diseases (10% vs. 14%; p=0.037) (unpublished data), and renal diseases (6% vs. 9%; p=0.049).

In non-autopsied patients, the explanation for more frequent deaths due to RA, endocrinological diseases, cerebrovascular diseases, and renal diseases is unclear. However, in cerebrovascular and renal diseases, the difference between autopsied and non-autopsied individuals was barely significant. Diabetes constituted the majority of endocrinological diseases (Table 13). Diabetes and RA are both clinical diagnoses, a fact that may contribute to these observations. Clinicians had likely regarded autopsy as unnecessary in cases of severe RA or severe diabetes. Compared with

autopsied RA patients, non-autopsied patients seemed to have more unspecific CoDs, such as renal failure (4% vs. 8%; p=0.002) and heart failure (3% vs. 11%; p<0.001). Furthermore, renal failure in non-autopsied patients constituted the majority of renal deaths. In non-autopsied patients, renal disease was detected in 40 patients, 37 of whom had renal failure. However, renal failure merely represents a common end-stage for various renal disorders and offers no information about the underlying disorder. The same is true for heart failure.

Autopsied RA patients, compared with non-autopsied RA patients, more frequently had CHD as a CoD. Furthermore, death rate due to GI disorders was 3-fold higher in autopsied patients. Several explanations emerge for these findings. One explanation may be that autopsied patients who died due to CHD and GI disorders were more often referred for autopsy. Another explanation may be that these disorders remained undetected during the lifetime. This explanation is supported by several observations. RA patients are susceptible to silent coronary deaths (Maradit-Kremers *et al.*, 2005b; Douglas *et al.*, 2006). One study of 272 autopsied cases showed that even if the major disease category of CVD is correct, the specific type of CVD may be incorrect (Kircher *et al.*, 1985). This seems to also have been reflected here. Autopsied and non-autopsied patients had similar proportions of CVDs, but autopsied patients more frequently died due to CHD. Furthermore, myocardial infarction in critically ill patients is often overlooked (Roosen *et al.*, 2000; Twigg *et al.*, 2001; Perkins *et al.*, 2003). With respect to GI disorders, the RA patients here likely were frequently on NSAIDs, which promote GI complications. One explanation for more frequent GI-related deaths in autopsied patients may be that RA patients are susceptible to serious GI complications, which frequently occur without warning signs or symptoms (Singh, 1998). In addition, GI haemorrhage in critically ill patients may be overlooked by the treating physician (Roosen *et al.*, 2000).

Death caused by amyloidosis was found in similar proportions in both autopsied RA patients and those not autopsied (10% vs. 9%; p=0.420). This may indicate that the autopsy and non-autopsy populations are similar. On the other hand, it is also possible that amyloid deaths in those without autopsy may have gone undiscovered. RA-associated peri- or myocarditis or both was observed more frequently in autopsied patients (six patients) than in those not autopsied (one patient), although the difference was insignificant (p=0.129). It is also noteworthy that deaths caused by medullar compression after cervical subluxation were only detected in autopsied patients (three patients). In autopsied patients, other RA-associated complications were Felty's syndrome (three patients), pulmonary fibrosis (two patients), renal failure, pleuritis, and extra-articular feature not specified (one patient each). In those not autopsied, such complications were vasculitis, pulmonary fibrosis, tetraparesis as a consequence of medullar compression in region CIV-V after atlanto-occipital fusion operation, and renal failure (one patient each).

6.2 Study population B

Age at death in Study population B increased between 1952 and 1991, the mean age at death ± SD being 70 ± 9 years. As in the general population, the mean age at death increased over the 40 years in females from 66 to 77 years (p-value for linear trend<0.001) and in males from 58 to 73 years (p-value for linear trend=0.001) (Figure 8).

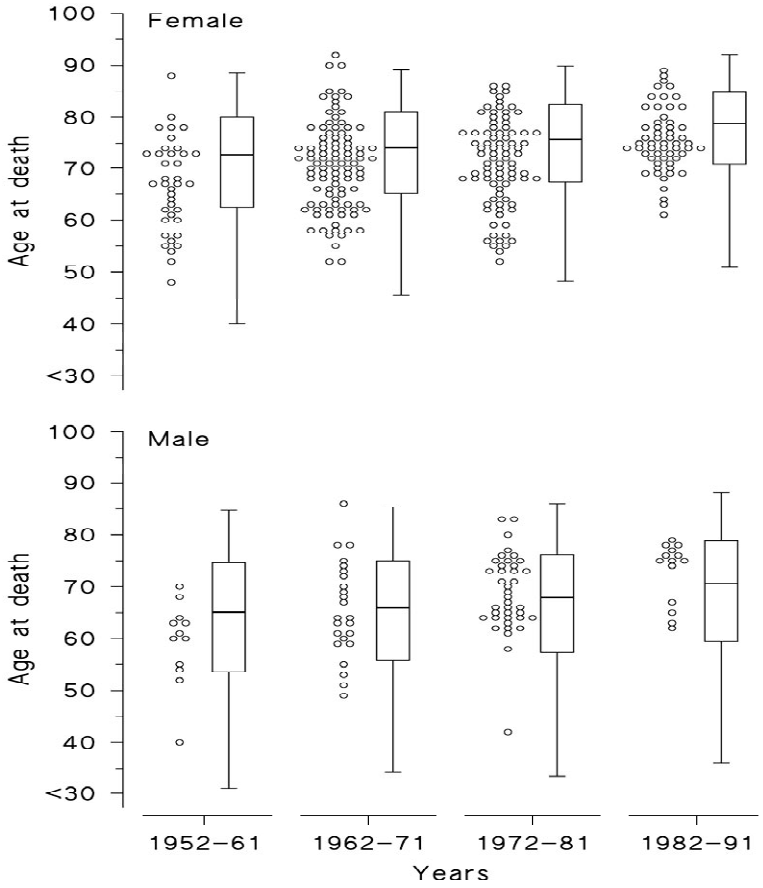

Figure 8. Age of female and male rheumatoid arthritis patients at death compared with that of the Finnish general population at ten-year intervals. Open circles show rheumatoid arthritis patients and box plots show the whole Finnish population. The box presents median (horizontal line in the box) and interquartile range (IQR). Whiskers show the 5th and 95th percentiles (unpublished data)

6.2.1 Causes of death

Autopsied RA patients died most frequently due to RA, CVDs, and infections (Table 16). When multiple CoDs were analysed, RA caused death in 255 patients (69%). As an immediate CoD, RA was found in only 21 patients (6%).

Table 16. Causes of death determined at autopsy from 1952 to 1991 in Study population B

	Multiple cause of death			Immediate cause of death		
	RA patients n (%)	non-RA patients n (%)	p-value	RA patients n (%)	non-RA patients n (%)	p-value
Cardiovascular[a]	205 (56)	275 (74)	<0.001	153 (42)	208 (56)	<0.001
Coronary heart disease	91 (25)	129 (35)	0.002	52 (14)	74 (20)	0.033
Cerebrovascular[b]	50 (14)	93 (25)	<0.001	29 (8)	52 (14)	0.007
Congestive heart failure[b]	9 (2)	8 (2)	0.802	9 (2)	8 (2)	0.802
Infections	131 (36)	96 (26)	0.005	110 (30)	79 (21)	0.008
Respiratory	80 (22)	80 (22)	0.969	75 (20)[b]	71 (19)[b]	0.698
Urinary tract	31 (8)	10 (3)	<0.001	15 (4)[b]	3 (1)[b]	0.004
Sepsis	6 (2)	2 (1)	0.176	6 (2)[b]	2 (1)[b]	0.154
Tuberculosis[c]	11 (3)	8 (2)	0.478	11 (3)[b]	8 (2)[b]	0.482
Malignancies	43 (12)	68 (18)	0.011	30 (8)	44 (12)	0.089
Lymphoproliferative[b]	7 (2)	5 (1)	0.557	6 (2)	3 (1)	0.312
Renal disorders	22 (6)	3 (1)	<0.001	25 (7)	4 (1)	<0.001
Renal failure[b]	11 (3)	0 (0)	0.001	8 (2)	0 (0)	0.004
Endocrinological diseases	14 (4)	54 (15)	<0.001	0 (0)	2 (0.5)	0.499
Diabetes	11 (3)	43 (12)	<0.001	0 (0)	1 (0.3)	1.000
GI disorders	38 (10)	44 (12)	0.499	15 (4)	16 (4)	0.860
Emergency GI disorders[b]	4 (1)	4 (1)	0.997	4 (1)	4 (1)	0.997
Respiratory disorders	36 (10)	24 (7)	0.101	9 (2)	9 (2)	0.995

GI=gastrointestinal; RA=rheumatoid arthritis; [a]including cardiac, cerebrovascular, and vascular diseases; [b]unpublished data; [c]at any site.

Compared with autopsied non-RA patients, autopsied RA patients died in a multiple CoD analysis more frequently due to infections and renal disorders, but less frequently due to CVDs, malignancies, and endocrinological disorders. The use of proportional CoD statistics may cause bias because the proportion of deaths from RA was high. To overcome this effect a separate analysis of immediate CoD alone was conducted. As a result, no significant difference was detected between RA and non-RA patients in deaths caused by endocrinological disorders and malignancies. However, RA patients died in an analysis of immediate CoD less frequently of CVDs (including CHD and cerebrovascular diseases), but more frequently of infections and renal disorders (Table 16). Excess renal deaths in RA patients may be associated with use of NSAIDs, such as phenacetin, or with reactive amyloidosis.

CVD was an underlying CoD in 219 non-RA subjects (59%) and in 128 RA subjects (35%) ($p<0.001$); the latter figure is close to that of others (Allebeck, 1982; Symmons *et al.*, 1998; Sihvonen *et al.*, 2004a) (Table 14). One explanation for less frequent cardiovascular deaths in RA patients may be that the non-RA patient population selection process was biased. This explanation is supported by the fact that Kivelä Hospital was an acute care hospital responsible for specialized health care of such internal diseases as CVDs and diabetes. CHD was an underlying CoD in 101 non-RA patients (27%) and 64 RA patients (17%; $p=0.001$) (unpublished data). The proportion of coronary deaths in RA patients was lower than in other reports covering later periods (Wållberg-Jonsson *et al.*, 1997; Kvalvik *et al.*, 2000; Young *et al.*, 2007). The explanation for this lower occurrence of coronary deaths in the study here is unclear. I can only speculate that this difference may have arisen from coronary deaths being less frequent at the beginning of this study, which covered the period from 1952 to 1991.

Of patients in Study population B, RA as a CoD in multiple cause analysis and in underlying CoD analysis was observed, in 69% and 31% of patients, respectively, the latter figure higher than that reported in several other studies (Allebeck *et al.*, 1981; Allebeck, 1982; Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Kvalvik *et al.*, 2000; Sihvonen *et al.*, 2004a; Young *et al.*, 2007) (Table 14). The reason behind the high proportion of deaths due to RA at autopsy is obscure. One explanation is that the higher rate of RA deaths may merely reflect a more severe RA course in patients dying during the first two decades of the study (1952-71) compared with the later periods (1972-91) (Allebeck, 1982; Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Kvalvik *et al.*, 2000; Sihvonen *et al.*, 2004a; Young *et al.*, 2007). The course of disease activity in RA patients has been suggested to have become milder (Welsing *et al.*, 2005). This is supported by the finding of deaths caused by RA declining. However, no evidence indicates that all-cause mortality in RA patients has declined (Tables 1 and 2). Another explanation is that autopsy may reveal RA-related deaths that would otherwise have gone undetected. Studies have shown that the contribution of RA to mortality may be underestimated (Allebeck *et al.*, 1981), especially when the underlying CoD is malignancy or CVD (Laakso *et al.*, 1986c).

Of the RA patients in Study population B, amyloidosis caused death in approximately 10%. Other RA-associated complications were very uncommon. These included acute medullar compression of the cervical spine (three patients), Felty's syndrome (two patients), vasculitis, myo- or pericarditis or both, rheumatic lung involvement, agranulocytosis with splenomegaly, and chronic laryngitis (one patient each).

In Study population B, amyloidosis caused death in 22 (8%) female and in 13 (15%) male (p=0.060) RA patients. This indicates no sex-related difference in RA patients in amyloid deaths. This finding of no gender difference is contrary to one hospital-based 10-year follow-up study reporting more females (12.8% vs. 5.8%) to have died from amyloidosis (Laakso *et al.*, 1986a). However, those findings may be biased, because only RA patients aged 40 years or over were included in that study. Furthermore, autopsy, the gold standard for determination of CoD (Goldman *et al.*, 1983; Welsh and Kaplan, 1998), was performed in only one-third of the RA cases in that Finnish study.

In Study population B with no systematic cervical spine examination, only approximately 1% of the RA patients died due to medullar compression of the cervical spine, close to the findings in 81 RA patients routinely autopsied (1.2%) (Suzuki *et al.*, 1994). These figures are both, however, much lower than that reported in a study of 104 RA patients with their cervical spines autopsied systematically (10%) (Mikulowski *et al.*, 1975).

Of the RA patients, approximately one-third, in analysis of immediate or multiple CoDs, died due to infections. Of infections, the majority were attributed to infections of the respiratory tract and the urinary tract (Table 16). As an underlying CoD, infection was observed in 38 autopsied RA patients (10%), close to the observation from a hospital-based follow-up study covering the period 1977 to 1992 (Kvalvik *et al.*, 2000). Autopsy-based studies, comprising 81 patients or fewer, have reported proportions 2-fold higher than that found in the current autopsy study (Mutru *et al.*, 1976; Suzuki *et al.*, 1994). Compared with the non-RA patients, the RA patients here died significantly more frequently from infections (Table 16). Respiratory infections were as frequent in RA patients as in non-RA patients (22% vs. 22%; p=0.969). However, the proportion of deaths caused by urinary tract infections in RA patients, compared with non-RA cases, was almost 3-fold higher (8% vs. 3%; p<0.001), in accordance with the findings in a 10-year follow-up study of 1000 RA patients reporting more deaths due to urinary tract infections in female RA patients than in non-RA females (Laakso *et al.*, 1986a).

RA patients died more frequently than the reference cases due to renal disorders (Table 16), resembling the findings of others (Symmons *et al.*, 1998; Thomas *et al.*, 2003). This overpresentation of renal disorders in RA may be linked to use of NSAIDs or reactive amyloidosis. GI deaths were not more frequent in RA patients (Table 16), contrary to the observations of others (Vandenbroucke *et al.*, 1984; Sihvonen *et al.*, 2004a). This may be explained by Kivelä Hospital having no surgical facilities.

RA patients died significantly less frequently than non-RA patients due to malignancies (Table 17, unpublished data), in parallel with a 35-year follow-up study (Wolfe *et al.*, 1994). However, the RA patients died significantly more frequently of lymphoma (Table 17), consistent with Symmons et al (1998) and Sihvonen et al (2004a). As in a 20-year study reporting increased risk in RA patients dying of lung cancer (Thomas *et al.*, 2003), lung cancer was more common, albeit non-significantly, in the RA patients (Table 17). The current study suggested no reduced mortality due to malignancies of the GI tract, contrary to some other authors (Laakso *et al.*, 1986b; Thomas *et al.*, 2003). Autopsied RA patients died less frequently than non-RA patients of breast cancer and gynaecological cancers. Some studies have reported findings similar to ours. In one hospital-based study comprising 1165 RA patients followed for 8 years, breast cancer caused death in three RA patients, while the expected number was 5.2, a non-significant finding (Allebeck, 1982). In another hospital-based study on 1000 RA patients and their controls followed for 10 years, breast cancer was a CoD in only one RA patient and six controls (Laakso *et al.*, 1986b). In that same study, uterine or ovarian cancer was a CoD in three RA patients and six controls. In a study on 81 autopsied RA patients and 243 controls, ovarian cancer caused death in 2% of RA patients and 11% of controls (Suzuki *et al.*, 1994). ASA, frequently used by RA patients in this study, has been associated in large epidemiological studies with reduced risk of breast cancer (Schreinemachers and Everson, 1994; Johnson *et al.*, 2002). ASA has also shown beneficial effects with respect to mortality. In one large prospective population-based study on postmenopausal women, use of ASA was linked to decreased overall mortality as well as to decreased mortality from malignancies (Bardia *et al.*, 2007). However, as the numbers of patients have been small, these results suggesting reduced mortality risk of breast cancer and gynaecological malignancy in RA should be analysed with caution.

Table 17. Deaths caused by various malignancies from 1952 to 1991 in Study population B

Multiple cause of death; site	RA patients n (%)	non-RA patients n (%)	p-value
Lung	12 (3)	8 (2)	0.361
Lymphoproliferative	7 (2)	5 (1.4)	0.557
Lymphoma	5 (1.4)	0 (0)	0.031
Gastrointestinal tract[a]	7 (1.9)	8 (2.2)	0.798
Gallbladder	3 (0.8)	2 (0.5)	0.686
Liver	2 (0.5)	6 (1.6)	0.286
Brain	2 (0.5)	5 (1.4)	0.451
Pancreas	2 (0.5)	2 (0.5)	1.000
Melanoma	2 (0.5)	1 (0.3)	0.624
Breast	1 (0.3)	8 (2.2)	0.038
Gynaecological[b]	0 (0)	7 (1.9)	0.015
Kidney	0 (0)	3 (0.8)	0.249
Prostate-testis	0 (0)	1 (0.3)	1.000
Other	3 (0.8)	10 (2.7)	0.051
Total	43 (12)	68 (18)	0.011

[a]esophagus, stomach, colon, or any combination of these (unpublished data); [b]including ovarian, uterus, and cervical cancer, or any combination of these.

6.2.2 Changes in causes of death over time

In autopsied RA patients, deaths caused by CHD increased throughout the 40-year study period (p-value for linearity=0.021), but coronary deaths in non-RA cases showed a decline, starting in the 1970s (p-value for linearity=0.13) (Figure 9). The observation in the RA patients here is contrary to one study on American RA patients reporting a decline in mortality during 1980 to 1997 due to acute myocardial infarction (Krishnan *et al.*, 2004). However, one large meta-analysis of cardiovascular mortality in RA covering the period until 2005 reported that the risk of cardiovascular death was higher in RA patients enrolled after 1987 than in those enrolled earlier (Avina-Zubieta *et al.*, 2008). Other studies, covering the 1960s to the 1990s, have observed no significant changes in mortality due to specific causes (Suzuki *et al.*, 1994; Björnådal *et al.*, 2002).

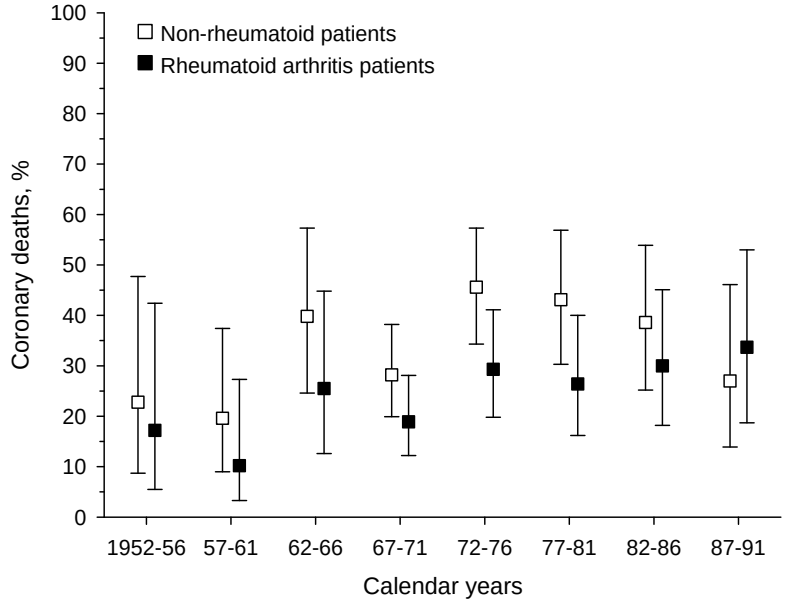

Figure 9. Sex- and age-adjusted coronary deaths with 95% confidence intervals according non-rheumatoid and rheumatoid arthritis patients. Multiple causes of death.

As the proportional decrease in mortality due to RA might contribute to the frequency of other CoDs, immediate coronary deaths as well as atherosclerotic findings in coronary arteries at autopsy for the period 1952 to 1991 were analysed separately. In the analysis of immediate CoD, RA patients showed an increasing trend, with only a slight decline at the end of the study in coronary deaths (p-value for linearity during the whole study period<0.001), while a steeper and earlier decline occurred after an increase in non-RA patients (p-value for linearity during the whole study period=0.009) (data not shown).

Between the two patient groups, no significant differences emerged during the 40−year period in either immediate (data not shown) or all coronary deaths (Figure 9).

At autopsy, atherosclerotic findings in coronary arteries were detected in 221 (46%) RA patients and in 259 (54%) non-RA patients (p=0.004; unpublished data). Over the 40 years, autopsy revealed in RA patients (p-value for linearity=0.73) and in their controls (p-value for linearity=0.11) no significant changes in atherosclerotic findings in coronary arteries (Figure 10).

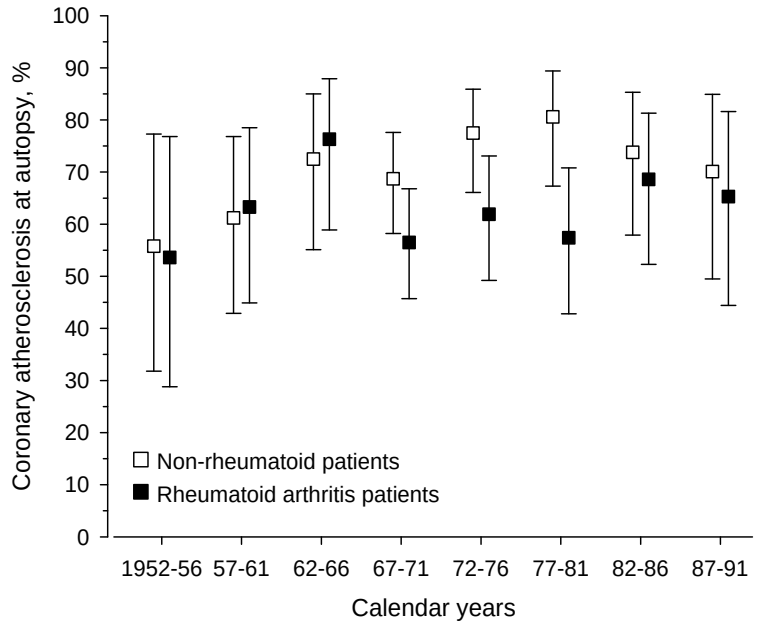

Figure 10. Sex- and age-adjusted coronary atherosclerosis at autopsy with 95% confidence intervals according to non-rheumatoid (n=362) and rheumatoid arthritis patients (n=363) (unpublished data).

Several explanations can be tendered for the increasing trend in coronary deaths in RA patients. One explanation is RA medication. Effective suppression of active inflammation in RA is suggested to prevent development of atherosclerosis (Van Doornum *et al.*, 2002). The RA patients in the current study may have been treated for their RA less actively than American RA patients, 11-37% of whom used MTX (Krishnan *et al.*, 2004). Of the RA patients here, approximately 80% used DMARDs, including cytostatics other than MTX, i.e. CYC (seven patients) and AZA (three patients). However, DMARD duration was short and likely had not been started early in the disease course. On the other hand, the use of GCs among American patients was slightly more common than among the patients here. GCs were used by 60% of American patients and 50% of the patients in the present study.

Another explanation may be that CHD in RA patients during the lifetime remained undetected. Coronary deaths in RA patients, compared with non-RA patients, had been diagnosed less accurately (Kappa reliability test; 0.33 vs. 0.46). Studies have shown RA patients to be susceptible to silent coronary events (Maradit-Kremers *et al.*, 2005b;

Douglas *et al.*, 2006). This observation may explain the inaccuracy in diagnosis of coronary deaths in the RA patients here. However, the finding that subjects without RA may have their CHD diagnosed more accurately might explain the decline in coronary deaths in non-RA patients from the 1970s onwards, in line with a general trend in Finland (Salonen *et al.*, 1983). I can only speculate that because CHD was diagnosed in non-RA patients more accurately they may have gained more benefit from the development of diagnostic techniques and treatment of CHD.

For the increasing trend in coronary deaths in RA, a further explanation may be use of non-ASA NSAIDs. Although some non-ASA NSAIDs, such as indomethacin, were in use earlier (Jäättelä, 1981), various new NSAIDs were introduced in Finland in the late 1970s (Martio, 1993). In RA patients, the frequent use of non-ASA NSAIDs, which has been associated with an increased risk for cardiovascular events (Hermann and Ruschitzka, 2007), may also have affected the increasing trend of coronary deaths. Even the concomitant use of low-dose ASA with non-ASA NSAIDs does not abrogate the cardiovascular risk (Hermann and Ruschitzka, 2007). However, ASA may have played some role in mortality from CHD in RA patients before the 1970s. An autopsy-based study that showed RA patients to die less frequently than controls from CHD, a result similar to the findings here, suggested ASA to have been a protective agent against coronary events (Davis and Engleman, 1974).

While coronary deaths in non-RA patients showed a decline at the end of the study, coronary deaths in RA patients were on the rise (Figure 10), with the exception of a minor decline in the immediate coronary deaths at the very end of the study (data not shown). Despite all of these changes in coronary deaths, atherosclerotic findings in coronary arteries showed no significant changes over time. The explanation for the differences between coronary deaths and coronary findings is obscure. One explanation for the increasing trend in coronary atherosclerosis may be that statins did not become available in Finland until the 1980s (Martikainen *et al.*, 1996).

From 1952 to 1991, deaths caused by RA declined (p-value for linearity=0.002) (Figure 11), resembling findings of other studies (Wicks *et al.*, 1988; Ziade *et al.*, 2008). The French population-based study reported RA-related deaths from the 1970s to decline, but then, particularly in the oldest patients, they showed a small rise starting in the mid-1990s (Ziade *et al.*, 2008).

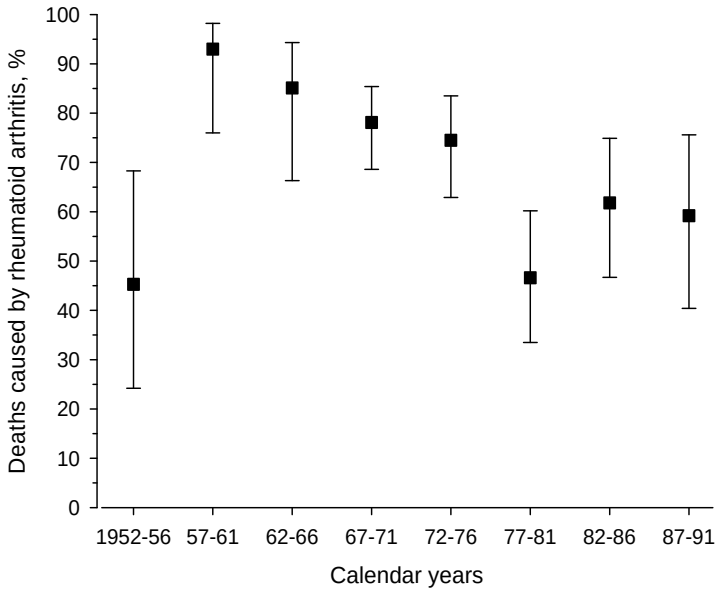

Figure 11. Sex- and age-adjusted deaths caused by rheumatoid arthritis with 95% confidence intervals. Multiple causes of death.

No significant change occurred in Study population B in deaths caused by reactive amyloidosis, CVDs, infections, malignancies, respiratory diseases, GI disorders, endocrinological diseases, and haematological diseases (data not shown).

6.2.3 Contribution of autopsy to cause-of-death diagnoses

RA patients and their controls had one-third of their CoDs undetected before autopsy (mean; 39% vs. 36%, respectively). This is similar to a study that showed that, of 108 autopsied geriatric patients, CoDs were undetected by the clinician in one-third (Zaitoun and Fernandez, 1998). Between clinician-assessed CoD and that determined at autopsy by a pathologist, RA patients had a lower agreement (Kappa reliability test; of various CoDs, mean 0.35) than non-RA patients (mean 0.42). This was true especially with respect to CVDs, including CHD. In the RA patients here, the most inaccurately diagnosed CoDs were GI disorders, renal diseases, respiratory diseases, and CVDs, in this order. Deaths caused by malignancies in RA patients and non-RA patients were diagnosed most accurately, consistent with the findings of others in randomly selected autopsies from the general population (Kircher *et al.*, 1985) and in consecutive autopsies at an adult hospital (Sington and Cottrell, 2002) (Table 18).

Table 18. Agreement between clinical causes of death and those determined at autopsy in Study population B

Multiple causes of death	RA patients Kappa reliability[a]	non-RA patients Kappa reliability
Cardiovascular diseases[b]	0.31	0.51
Coronary heart disease	0.33	0.46
Malignancies	0.58	0.68
Infections	0.34	0.34
Renal diseases	0.29	0.21
Gastrointestinal disorders	0.25	0.33
Respiratory diseases	0.30	0.24
Diabetes[c]	0.48	0.60

[a]Kappa reliability test between the clinical cause of death and that made at autopsy (low agreement: < 0.40, medium: 0.40 – 0.75, high: > 0.75); [b]including cardiac, cerebrovascular, and vascular diseases; [c]unpublished data.

6.2.4 Causes of death and medication

Between RA patients on DMARDs and those not on DMARDs, no significant difference appeared in CoDs (data not shown). DMARDs, therefore, do not seem to predispose to or prevent any CoDs. RA was a CoD in 59 patients on GCs (69%) and in 35 patients not on GCs (47%) (p=0.005). Compared with those not on DMARDs, patients taking DMARDs had a shortened lifespan (71 $\pm$ 8 vs. 75 $\pm$ 8 years; p=0.038), but no such difference was observed with respect to GCs (data not shown). Evidently, these medications had been used in patients with severe RA.

6.2.5 Detection rate of amyloid deposits

Systematic re-evaluation of autopsy tissue samples doubled the prevalence of amyloid compared with routine autopsy, and tripled the prevalence compared with lifetime. Of the RA patients autopsied from 1973 to 1991, amyloidosis had been diagnosed before autopsy in only 16 (37%), resembling the findings of an autopsy-based series reporting pre-mortem diagnosis of amyloidosis in one-third of their 18 patients with chronic inflammatory disease (Wright and Calkins, 1981). In another study, pre-mortem detection

rate of amyloidosis was as high as 81%, but the study was conducted at an amyloid clinic (Browning *et al.*, 1985). In an autopsy study from the 1950s, amyloidosis was diagnosed before autopsy in less than one-tenth of cases with moderate to severe amyloid deposition (Teilum and Lindahl, 1954).

At the original autopsies of the current study, Congo red staining to detect amyloid had been performed on 93 of 369 RA patients (25%) and on 9 of 370 non-RA patients (2%). Of those nine non-RA patients, five had suffered from an infection (three patients) or a malignancy (two patients) during their lifetime. Other such disorders on autopsy referrals included CHD, universal atherosclerosis, stroke, pulmonary embolism, and GI haemorrhagia. Accordingly, amyloid was found in 67 RA patients (18%) and in 7 non-RA patients (2%) ($p<0.001$). Of those non-RA cases in multiple CoD analysis, death was caused by CVDs (nine patients), infection or pulmonary disease (three patients both), GI disorder (two patients), and haematological disorder (one patient).

Autopsy tissue samples of these 739 patients were available for systematic re-evaluation for 328 RA patients (89%) and for 336 non-RA patients (91%) doubling the amyloid detection rate in both RA (97 patients; 30%) and non-RA patients (12 patients; 4%). The number of non-RA patients with cardiac amyloidosis (six patients) was 2-fold higher than the number of those with renal amyloidosis (three patients). In the RA patients, amyloid found at re-evaluation was as frequent in the kidneys as in the heart (Table 19).

Table 19. Amyloid deposits in rheumatoid arthritis patients autopsied from 1952 to 1991

	n/N (%)
Kidney	77/272 (28)
Heart	64/229 (28)
Other organs	48/194 (25)
Liver	14
Spleen	13
Thyroid gland	8
Synovia/joint	8
Total	97/328 (30)

n/N=amyloid-positive finding/tissue samples examined.

The systematic re-evaluation of autopsy tissue samples revealed no sex-related difference in amyloid prevalence. Amyloid was detected in 74 females (30%) and in 23 males (30%). This is contrary to some reports suggesting males to be at higher risk of developing

reactive amyloidosis (Cohen and Comerford, 1968; Gertz and Kyle, 1991; Wiland *et al.*, 2004). However, these studies comprised only a few patients.

RA patients with amyloid at re-evaluation, compared to amyloid-negative RA patients, had had a significantly higher erythrocyte sedimentation rate (ESR) and lower haemoglobin (HB), in accordance with a 15-year follow-up study of RF-positive RA patients (Tiitinen *et al.*, 1993). These laboratory parameters were regarded as reflecting the inflammatory level, although they may also appear in renal failure. The amyloid-positive patients here had longer RA duration, in parallel with the findings of others (Boers *et al.*, 1987; Kobayashi *et al.*, 1996; Kuroda *et al.*, 2002; Wiland *et al.*, 2004). The amyloid-positive RA patients were also more disabled, consistent with other studies in which amyloid-positive RA patients had had more joint erosions (Wiland *et al.*, 2004) or worse functional status (Kobayashi *et al.*, 1996). Clinical manifestations associated with amyloidosis, such as proteinuria or renal failure or both, occurred in only about half of the amyloid-positive RA patients (Table 20). Between amyloid-positive RA patients and those with amyloid-negative findings, no significant difference was detected in the proportion of RA patients on DMARDs or GCs or both (data not shown). Neither were there any significant differences between patient groups in frequency of extra-articular manifestation, RF positivity, or abnormal ECG findings (data not shown).

Table 20. Factors associated with amyloid[a] in autopsied RA patients

	Amyloid +	Amyloid –	p-value
ESR (mm/h); mean±SD	69 ± 26	51 ± 21	<0.001
HB (g/l); mean±SD	107 ± 15	122 ± 14	<0.001
Proteinuria; n (%)	24 (56)	9 (9)	<0.001
Renal failure ± renal amyloidosis; n (%)	43 (56)	17 (9)	<0.001
Heart failure ± cardiac amyloidosis; n (%)	26 (41)	66 (40)	0.958
Steinbrocker class III – IV; n (%)	44 (98)	78 (77)	0.002
Severe joint destruction[b]; n (%)	31 (32)	49 (21)	0.039
Duration of RA (years); mean±SD	21 ± 12	16 ± 11	0.040
Age at death (years); mean±SD	69 ± 10	71± 8	0.052
Age at death with or without renal amyloidosis	69 ± 9	71 ± 8	0.051
Age at death with or without cardiac amyloidosis	69 ± 11	71± 8	0.192

[a]diagnosed at re-examination of autopsy tissue samples; [b]radiographic changes typical of RA in hips, glenohumeral joints, or cervical spine. Data on age at death and renal and heart failure were available between 1952 and 1991; the rest of the data between 1973 and 1991.

Amyloid in kidney samples was of type AA in all but one of the 73 RA patients examined. That RA patient without type AA amyloid had RA and pyelonephritis as a CoD.

In the RA patients, the prevalence of amyloid in re-evaluated tissue samples showed no significant change between 1952 and 1991 (p=0.792), contrary to one Finnish report by Laiho et al (1999) that suggested a declining incidence of amyloidosis in patients with inflammatory joint disease between 1987 and 1997. However, these two studies may not be comparable. The studies comprised different study populations and covered different time periods. The medication of the RA patients in the current study may have been less effective because of the earlier period covered. However, medication in the study by Laiho et al (1999) went unreported. Furthermore, their survey of tissue samples was not systematic and they used fine-needle aspiration of subcutaneous fat, which may be less sensitive than rectal (Klemi *et al.*, 1987; Dhillon *et al.*, 1989) or gastroduodenal biopsies (Kuroda *et al.*, 2002). In addition, their number of samples taken decreased over time. Unlike Laiho et al (1999), who reported new cases with amyloid-positive findings from a cross-sectional study of living patients, the current study reports the lifetime burden of inflammation in RA patients in the final stage of their disease.

7. General discussion

As it appears to be proven that mortality is increased in RA patients, the aim of this study was to evaluate determinants of mortality over a long period. Because diagnosis of CoD may be inaccurate without autopsy, this study aimed to clarify the contribution of autopsy to the diagnosis of CoD. Furthermore, the study investigated the contribution of RA medication to CoDs and the detection rate of amyloidosis.

CoDs in a large RA population were investigated over a long period. In the literature, only a few RA mortality studies have reported mortality changes in specific CoDs over time. This study is strengthened by CoDs being examined in each RA patient treated at Kivelä Municipal Hospital between 1971 and 1991 who died during that period (Study population A). Kivelä Hospital was responsible for primary to tertiary care of all RA patients in the Helsinki area. Furthermore, RA patients were treated by rheumatologists, and standard practice was to start any DMARD in the hospital ward. Thus, the RA population in Study population A is likely to be representative of mild to severe RA.

This study focused on CoDs determined at autopsy. CoDs were studied in RA patients consecutively autopsied from 1952 to 1991, with patients having no rheumatic disease autopsied at the same hospital serving as reference cases (Study population B). The study emphasizes the role of autopsy in determination of CoD. Based on the findings here, autopsy in RA patients is important, especially in the determination of cardiovascular deaths. In the literature, no studies are available on the role of autopsy in CoD determination in RA patients. Only a few studies exist that report on CoDs in autopsied RA patients (Davis and Engleman, 1974; Mutru *et al.*, 1976; Suzuki *et al.*, 1994). However, none of these have investigated the accuracy of CoD determination.

All patients deceased between 1952 and 1991 had not undergone autopsy (Study population B) which is one limitation of this study. This may cause some bias in the patient population. However, the potential bias is reduced by the autopsy rate being high (67%). Furthermore, autopsies over the 40 years had been performed by only a few pathologists.

Autopsy rates have constantly declined over time. In the 1960s, the hospital autopsy rate in Europe and in the USA was approximately 60%, but today it is 10% or less (Roulson *et al.*, 2005). Similarly, the autopsy rate at Kivelä Hospital declined. Because of this decline, the end for the study was set at 1991. The aim in the current study was to collect as many RA patients as possible (Study population B) so that RA patients autopsied each year would represent as closely as possible all RA patients who had died that particular year.

Most RA mortality studies have been based on official death certificates, but only a few have been based on analysis of autopsy reports (Davis and Engleman, 1974; Mutru *et*

al., 1976; Suzuki *et al.*, 1994), as the current study. However, autopsy is regarded as the gold standard for determination of CoD (Goldman *et al.*, 1983; Welsh and Kaplan, 1998). The discrepancy rate between clinical and autopsy-based diagnoses has been high (Goldman *et al.*, 1983; Stevanovic *et al.*, 1986; Landefeld *et al.*, 1988; Zarbo *et al.*, 1999; Roosen *et al.*, 2000; Twigg *et al.*, 2001; Perkins *et al.*, 2003; Combes *et al.*, 2004). New diagnostic techniques, such as ultrasound, computerized tomography, and radionuclide scans, have not reduced the discrepancy rate (Kirch and Schafii, 1996). Furthermore, the clinician's certainty about the diagnosis before autopsy seems to correlate poorly with the final diagnosis determined at autopsy (Cameron *et al.*, 1980; Podbregar *et al.*, 2001).

Most RA mortality studies report only underlying CoD or sometimes underlying and contributory CoDs. However, multiple CoD analysis, used in this study, is recommended in evaluating mortality caused by chronic diseases such as RA (Ziade *et al.*, 2008). An analysis based solely on underlying CoD may underestimate contribution of a disease to mortality (Redelings *et al.*, 2006). Reporting both underlying CoD and multiple CoDs is therefore recommended (Redelings *et al.*, 2006). Furthermore, according to WHO guidelines, reactive amyloidosis should not be recorded as the underlying CoD. Thus, if only underlying CoD is analysed, information about reactive amyloidosis may remain undetected. In addition, use of the ICD coding system may result in losing information about infectious CoDs because several infections are recorded under the organ system that they affect. For that reason, this study was based on diagnoses of CoDs in which infections were classified under their own heading.

To the best of my knowledge, the current study is the first series on the detection rate of amyloidosis at routine autopsy, and one of the few studies reporting lifetime detection rate of amyloidosis. One limitation here is that lifetime detection rate of amyloidosis was only available from 1973 onwards, with 95% of medical records before this having been destroyed. On the other hand, tissue samples taken during routine autopsies were available for as many as 90% of patients. Furthermore, the type of amyloidosis was determined in kidney samples, which confirmed that all but one RA patient had AA amyloidosis.

Only infrequently may RA subside and end up in remission; usually, it leads to joint deformities, functional disability, and premature death. RA medication is nowadays started early in the disease course, and the treatment strategies have become more effective over time. Mortality in RA patients has, however, remained high (Table 1). The mortality gap between RA patients and the general population appears to have become even wider (Gonzalez *et al.*, 2007). More attention should thus be paid to mortality, especially determinants of mortality, as an outcome measure in RA.

In RA patients, CVD is the major determinant of mortality (Allebeck *et al.*, 1981; Allebeck, 1982; Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Björnådal *et al.*, 2002; Goodson *et al.*, 2002; Mikuls *et al.*, 2002; Sihvonen *et al.*, 2004a; Goodson *et al.*, 2005), reflected also in the current study. Only a few studies have reported low proportions of cardiovascular deaths in RA patients. In these studies, cardiovascular death

occurred in 21% of Spanish RA patients (Martinez *et al.*, 2001) and 17% of Japanese RA patients (Suzuki *et al.*, 1994). However, several other series have reported higher cardiovascular death rates, varying from 31% to 53% (Mutru *et al.*, 1976; Allebeck *et al.*, 1981; Allebeck, 1982; Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Sihvonen *et al.*, 2004a; Young *et al.*, 2007) (Table 14). Because many of these studies (Wållberg-Jonsson *et al.*, 1997; Symmons *et al.*, 1998; Sihvonen *et al.*, 2004a; Young *et al.*, 2007) used only underlying CoDs in their analyses, the proportion of RA patients dying of CVDs may be even higher.

RA patients are at increased risk for dying of CHD, which constitutes the majority of cardiovascular deaths. Mortality risk for CHD seems to be more evident in females, in whom the risk, compared with the general population, has been 2-fold (Thomas *et al.*, 2003; Goodson *et al.*, 2005). Furthermore, congestive heart failure, rather than CHD, has been proposed to be an important contributor to the excess mortality in RA (Nicola *et al.*, 2006).

One primary care cohort of recent-onset inflammatory polyarthritis, representing early RA, demonstrated that SMR for cardiovascular death is the highest in patients seropositive for RF who were under 55 years of age at onset of arthritis (Naz *et al.*, 2008). The authors recommended that such patients warrant particular attention in terms of disease and risk factor modification. Although the relative risk for cardiovascular events is higher in young adults, the difference in absolute terms, compared with the general population, is highest in older adults (Solomon *et al.*, 2006). Therefore, both young and old RA patients are at increased risk for cardiovascular events, and both of these subgroups should be included when considering preventive strategies (Solomon *et al.*, 2006).

The reason for increased cardiovascular mortality in RA is likely to be multi-factorial. RA patients not only have an increased risk for developing CHD, but also a higher risk for worse outcome than the general population (Södergren *et al.*, 2007). Systemic inflammation seems to play, via several mediating factors, such as dyslipidaemia, insulin resistance, and endothelial dysfunction, an important role in premature atherogenesis (Van Doornum *et al.*, 2002; Snow and Mikuls, 2005). Accelerated atherosclerosis, reported even in pre-menopausal female RA patients (Pahor *et al.*, 2006), has been proposed to be an extra-articular feature of RA (Van Doornum *et al.*, 2002). RA patients appear to receive, with respect to various diseases, suboptimal health maintenance and preventive care services (Kremers *et al.*, 2003). This may be one factor contributing in these patients to increased cardiovascular mortality. Furthermore, one study has shown that, despite cardiovascular deaths being increased in RA patients, no difference exists, compared with the general population, in CVD admission rates (Goodson *et al.*, 2005). Another factor may be susceptibility to silent coronary events (Maradit-Kremers *et al.*, 2005b; Douglas *et al.*, 2006), as reflected also in this study in which the diagnosis of cardiovascular death in RA patients, compared with non-RA patients, was less accurate. Thus, special attention should be paid to diagnosis and treatment of CVDs in RA patients.

The cardiovascular risk in RA patients has been shown to be comparable with that of patients with diabetes mellitus (van Halm *et al.*, 2008). RA patients with severe disease are especially at risk for cardiovascular death, which is predicted by constantly active disease (Wållberg-Jonsson *et al.*, 1999; Goodson *et al.*, 2005; Maradit-Kremers *et al.*, 2005a), by seropositivity for RF (Goodson *et al.*, 2002, Maradit-Kremers *et al.*, 2005a; Gonzalez *et al.*, 2008b), by functional disability (Farragher *et al.*, 2007), and by extra-articular features, such as rheumatic nodules (Maradit-Kremers *et al.*, 2005a; Naz *et al.*, 2008), vasculitis, or rheumatic lung disease (Maradit-Kremers *et al.*, 2005a). One study suggested that the mechanisms responsible for cardiovascular morbidity and mortality were different in RA patients than in subjects without RA (Aubry *et al.*, 2007). In 41 RA patients autopsied from 1985 to 2003, the authors observed, compared with 82 matched non-RA controls, less histological evidence of atherosclerosis in coronary arteries, but greater evidence of inflammation and instability, i.e. increased frequency of vulnerable plaques. Thus, RA patients may be at higher risk for cardiovascular events than estimated based on the degree of coronary atherosclerosis.

The current study observed in RA patients autopsied during the period from 1952 to 1991 no decline in coronary deaths, contrary to one study covering the period from the 1980s to the 1990s (Krishnan *et al.*, 2004). One explanation for the decline in the latter study may be the frequent use of MTX. The patients in the current study had not used MTX. Use of MTX may increase levels of homocysteine, which is considered to be a risk factor for CVD (Whittle and Hughes, 2004). Folates, i.e. folic or folinic acid, should be supplemented to prevent hyperhomocysteinaemia (Whittle and Hughes, 2004). Chronic inflammation in RA has been shown to be an independent risk factor for cardiovascular mortality (Maradit-Kremers *et al.*, 2005a). RA patients who respond to RA medication, such as anti-TNF alpha therapy, have experienced a reduction in the incidence of myocardial infarction (Dixon *et al.*, 2007). Thus, effective anti-inflammatory treatment in RA seems essential in reducing cardiovascular mortality.

Reports about lipid levels in RA patients are somewhat contradictory, but levels appear to oscillate according to duration and severity of RA. Some studies have shown an inverse association between CRP and high-density lipoprotein (HDL) cholesterol levels. In active RA, concentrations of apolipoprotein A-1, a protein present on HDL cholesterol particles, are decreased. Early untreated RA is associated with declines in HDL, with concomitant elevations in low-density lipoprotein (LDL) and total cholesterol/HDL ratios. On the other hand, a catabolic state in severe and advanced RA may lead to lowering in total cholesterol, LDL, and HDL levels (Snow and Mikuls, 2005; Nurmohamed, 2007). Besides beneficial effects on the lipid profile, statins also have additional properties (Calabro and Yeh, 2005). One of these appears to be the ability to reduce inflammation (Calabro and Yeh, 2005). A study on 116 RA patients showed that atorvastatin can mediate anti-inflammatory effects (McCarey *et al.*, 2004). That study reported the number of swollen joints and inflammatory variables during atorvastatin therapy to decline. Thus, statins may also have beneficial effects on RA activity.

RA patients are, compared with those without RA, more likely to smoke, to be physically inactive, and to have a higher body mass index (Brady *et al.*, 2008). Thus, efforts should be made to influence these life style cardiovascular risk factors. Cessation of smoking is essential in reducing the risk for cardiovascular morbidity and mortality. To prevent cardiovascular morbidity, RA patients should also be encouraged to exercise regularly (Turesson and Matteson, 2007).

Dietary factors in RA patients are also important in reducing cardiovascular risk. The Mediterranean diet has well-documented benefits on CVDs, and may also be advantagious in RA management, given the increased risk of CVDs in RA patients (Choi, 2005). This diet is characterized by less red meat and more fish, olive oil, poultry, and an abundance of plant food (Choi, 2005). Especially, the n-3 fatty acids found in fish and fish oils are beneficial in preventing CVDs and may also provide modest symptom alleviation in RA (Stamp *et al.*, 2005).

One study suggested that some traditional risk factors, i.e. male sex, history of CVD, and even smoking, have in RA patients less impact than in the general population on cardiovascular risk (Gonzalez *et al.*, 2008a). The authors concluded that controlling solely these traditional risk factors may not have the same impact on RA patients as expected based on estimates from the general population. In another study, the risk of CVD in RA patients was comparable with that of patients with diabetes mellitus (van Halm *et al.*, 2008). After adjustment for traditional cardiovascular risk factors, the chance of having CVD was attenuated in these patients, but still significantly increased. Thus, traditional cardiovascular risk factors only partly explained the high cardiovascular risk. Therefore, controlling both inflammation and traditional risk factors in RA patients seems to be important in cardiovascular risk management. It has been proposed that every RA patient be screened for traditional cardiovascular risk factors (Nurmohamed, 2007). For RA patients, similar treatment thresholds of lipids and blood pressure have been suggested as those for patients with diabetes mellitus (Nurmohamed, 2007).

In RA patients, infections are important determinants of mortality (Allebeck, 1982; Prior *et al.*, 1984; Vandenbroucke *et al.*, 1984; Mutru *et al.*, 1985; Wolfe *et al.*, 1994; Symmons *et al.*, 1998; Sokka *et al.*, 1999; Mikuls *et al.*, 2002; Sihvonen *et al.*, 2004a), as also shown here. The most common infectious deaths are due to infections of the respiratory (Thomas *et al.*, 2003; Sihvonen *et al.*, 2004a) and urogenital (Vandenbroucke *et al.*, 1984) tract. Findings of the present study indicate that RA patients, compared with those without RA, may be at similar risk for death due to respiratory infection, but at higher risk for death by urinary tract infection. In the current study, medication for RA, i.e. DMARDs and GCs, seemed not to predispose to or prevent any CoDs. In accordance with this, risk of infections has not been associated with use of DMARDs (Coyne *et al.*, 2007; Lacaille *et al.*, 2008). On the other hand, risk of infections does appear to be associated with use of GCs (Coyne *et al.*, 2007; Lacaille *et al.*, 2008) and anti-TNF therapy (Bongartz *et al.*, 2006), neither of which was available to the RA patients here. The risk of infectious death increases with RA duration (Symmons *et al.*, 1998). Advanced age and

male gender predict infections of the lower respiratory tract, which may have a fatal outcome (Coyne *et al.*, 2007). Active RA should be treated effectively, with careful monitoring of infections, especially in elderly patients, males, and patients with advanced RA.

RA patients have increased risk for dying of lymphoma (Symmons *et al.*, 1998; Sihvonen *et al.*, 2004a), as also observed here. This risk seems to be associated with inflammatory activity of RA, rather than RA medication (Bäcklund *et al.*, 2006). Effective treatment of RA is, therefore, essential in reducing risk of dying from lymphoproliferative disorders. RA patients seem to die frequently of lung cancer (Thomas *et al.*, 2003). The increased risk of dying from lung cancer may be linked to tobacco smoking, which has a causal connection to the development of RA (Heliövaara *et al.*, 1993; Symmons *et al.*, 1997; Uhlig *et al.*, 1999; Albano *et al.*, 2001). Cessation of smoking is important in reducing the risk of development of lung cancer as well as CHD.

Reactive amyloidosis is an important extra-articular manifestation contributing to premature mortality (Lehtinen and Isomäki, 1991; Martinez *et al.*, 2001; Sihvonen *et al.*, 2004a), reflected also in this study. The findings here indicate that amyloidosis frequently remains undetected during the lifetime, in accordance with the findings of other authors (Teilum and Lindahl, 1954; Wright and Calkins, 1981). Furthermore, amyloidosis may remain undiscovered at routine autopsy, too. The impact of amyloidosis on mortality in RA may thus be underestimated. Because even small amyloid deposits have been associated with increased mortality (Kobayashi *et al.*, 1996), amyloidosis should be searched for actively. As demonstrated in the current study, male and female RA patients seem to be at similar risk for development of amyloidosis. Only approximately half of the amyloid-positive RA patients here had had renal failure or proteinuria. In addition, the amyloid-positive RA patients had had, compared with those with amyloid-negative findings, higher inflammatory activity, longer RA duration, and more disabling RA. Therefore, the systematic search for amyloid is important not only in RA patients with renal failure or proteinuria, but also in those with active, long-lasting, and disabling RA.

8. Conclusions

Over this 40-year study period between 1952 and 1991, RA patients died most frequently of CVD, RA, and infections. Deaths caused by RA seemed to be decreasing. The same was not true for CVDs and infections. Despite advances in diagnostic technology, autopsy remains an important tool in CoD determinations. In RA patients, CVDs, especially CHD, may remain undetected during the lifetime. Active search and effective treatment of CHD, as well as RA, are important in reducing cardiovascular mortality. Reactive amyloidosis associated with RA is an important determinant of mortality. Prevalence of amyloid deposits showed from 1952 to 1991 no significant change. In RA patients, amyloidosis appears to be common, but is frequently undetected. Active search is essential for detecting amyloidosis as early as possible. Amyloidosis should be searched for in RA patients with proteinuria or renal failure or both, but also in those with active, long-lasting, and disabling RA. Early detection of amyloid deposits enables the enhancement of immunosuppressive medication, including biologicals, which may prevent development of clinical manifestations and improve survival.

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