Mortality in rheumatoid arthritis: 2008 update

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ABSTRACT

Mortality rates in patients with rheumatoid arthritis (RA) are 1.5-1.6 fold higher than in the general population, with similar patterns over 60 years. The acute attributed causes of death appear overall similar to the general population, with cardiovascular disease the most common attributed cause of death, and with more infection, pulmonary and renal disease in RA than in the general population. All clinical measures indicating more severe clinical status appear prognostic of premature mortality, with rheumatoid factor and the shared epitope significant for progressive RA. Functional and global measures as well as comorbidities generally are the most significant predictors of premature death.

Mortality rates in patients with rheumatoid arthritis (RA) are elevated compared to the general population (1-124) (Table I). Similar standardized mortality ratios (SMRs) of about 1.2-1.3 in inception cohorts and 1.6-1.7 in non-inception cohorts (Table II) have been seen over 60 years (Table III). The acute attributed causes of death in patients with RA appear overall not unlike those in the general population, with cardiovascular disease the most frequent cause of death, though at an earlier age. Infection, pulmonary and renal disease are more common in RA than the general population as attributed causes of death (Table IV). The pattern of causes of death in RA also has remained similar over the years, and RA usually does not appear on death certificates, even in recent years (Table V). All clinical measures indicating more severe clinical status appear prognostic of premature mortality, with rheumatoid factor significant for progressive RA, and functional and global measures as well as comorbidities generally the most significant predictors of premature death (Table VI).

A clinical rheumatologist with 300 RA patients would see one patient die every 6 weeks, or 8 per year (125), with causes of death seen in Table IV. Evidence of higher mortality rates would not be apparent, unless longitudinal data over 5-20 years were available for comparison to the general population. Such data are not available at most treatment centers, even at this time.

People with RA have higher levels of comorbidities than seen in the general population. Higher rates of infectious, pulmonary and renal disease have been recognized in the pathophysiology of inflammatory rheumatic diseases, and inflammation is now recognized in the pathogenesis of cardiovascular disease (126). When an individual with RA (or any inflammatory rheumatic disease) dies of any cause 5-15 years prior to expected according to that person's age and sex, the death appears in some way related to the inflammatory disease. Therefore, it does not appear informative to attempt to classify causes of death in patients with RA as "related to RA" or "not related to RA."

This review is based on a PubMed search in May 2008, which identified 193 papers for "rheumatoid arthritis" + "mortality," an additional 13 for "rheumatoid arthritis" + "survival" and 25 other reports which were identified from cited reports, for a total of 231 reports (Fig. 1). Among these reports, 124 concerned 84 unique cohorts, which are included in this review. Excluded manuscripts included 7 in languages other than English, 49 addressing outcomes other than mortality and survival in adult RA (laboratory studies without clinical data, drug continuation, surgery results, work disability outcomes, juvenile RA, economic outcomes, family history/cardiovascular outcomes in RA, non-Hodgkin's lymphoma in RA), 14 editorials, 13 letters without data, and 24 reviews.

Fifteen key points concerning mortality in RA

Extensive data concerning mortality in RA is summarized, as 15 key points.

Supporting evidence is found in the text and tables.

1. RA is associated with increased mortality rates compared to the general population in 78 of 84 cohorts studied; the exceptions may be explained on the basis of a short observation period, inception cohorts with possible inclusion of a higher proportion of individuals with self-limited inflammatory arthritis who met criteria for RA, and/or simple random variation.
2. Median standard mortality ratios (SMRs) for RA compared to the general population have been remarkably similar in the aggregate over the last 60 years, in the range of 1.5-1.6 overall, 1.2-1.3 in inception cohorts and 1.6-1.7 in non-inception cohorts. This observation may be compatible with some improvement in absolute RA mortality outcomes, as survival is greater in the general population, although a widening gap in mortality between patients with RA and the general population has been reported in some locales.
3. Many complexities are seen in analysis of mortality in RA, including the absence of a "gold standard" for diagnosis, and similar clinical findings, including meeting RA classification criteria, in individuals with self-limited polyarthritis and those with progressive RA. Variation in patient populations is seen in different sites, and baseline patient status appears considerably improved at this time compared to previous decades at some sites.
4. Mortality is a lagging indicator, and most published reports necessarily have enrolled patients before the 1990s, prior to early aggressive treatment with methotrexate as a usual practice in many settings, and later availability of biologic agents, so improved mortality outcomes may be anticipated, but only a few reports are available at this time.
5. The attributed causes of death in patients with RA also show remarkably similar patterns in the aggregate over 60 years, both to one another and to the general population. Cardiovascular disease is the most common cause of death, in 40-50% of patients, as in the general population. However, pulmonary, gastrointestinal, renal diseases, and especially infection, are more common as acute attributed causes of death in patients with RA than in the general population.
6. RA is included on the death certificate in fewer than 25% of deaths. Mortality attributable to therapies is seen in fewer than 2% of deaths, although therapies for RA can lead to fatal consequences.
7. Many apparent differences in interpretation of mortality outcomes, rates and predictors may emerge as much from recognized and unrecognized methodological differences as from actual differences. For example, absolute mortality rates generally are higher in men and older patients, while relative mortality rates are generally higher in women and younger patients, in whom the normal population is less likely to experience mortality. Cardiovascular disease is the most common acute cause of death, but infection and pulmonary disease are the causes of death substantially higher in patients with RA than in the general population. As noted, standardized mortality ratios (SMRs) are lower in inception cohorts (both community/population-based and clinic-based) than in non-inception cohorts.
8. Long-term monitoring of patient cohorts is required to recognize possible shortening of lifespan in patients with RA, for comparison with expected survival for individuals matched for age and sex in the general population. However, most rheumatology sites do not collect these data, as important as they may be to justify expensive therapies, document improved outcomes, and raise awareness of RA among health professionals and the general public for greater research support.
9. Premature mortality in patients with RA is predicted by poor status according to almost all measures of clinical status, reflecting an obvious phenomenon that "sicker people are more likely to die." However, depiction of severity in quantitative rather than simple descriptive terms provides more accurate information concerning the risk of mortality for patients and providers of medical care. Quantitative data also allow analyses of whether a change in a measure indicating clinical improvement is associated with improvement in mortality outcomes (as in hypertension).
10. The most significant predictors of premature mortality in patients with RA are older age, male sex, comorbidities, patient and physician global estimates, and poor functional status assessed by physical measures and patient questionnaires. These measures are almost always prognostic of RA mortality at higher levels of significance than radiographs and laboratory tests. However, data concerning functional status have not been included in most reports, even in recent reports.
11. Poor status according to traditional measures, including radiographic scores, ESR, CRP and rheumatoid factor, predicts mortality significantly in many cohorts, although the level of significance generally is lower than for questionnaire measures of physical function and global measures in multivariate analyses. These findings do not reduce the importance of traditional measures to identify individuals with progressive RA and in patient management, but emphasize the greater significance of measures of functional status to predict mortality.
12. Recent reports concerning associations of cardiovascular diseases and mortality in patients with RA with TNF receptors and with the shared epitope at the major histocompatibility locus may provide valuable clues regarding pathogenesis and mechanisms of cardiovascular comorbidity.
13. Socioeconomic status remains a significant indicator of clinical status in RA (and most diseases) and predicts premature mortality in many databases in which a socioeconomic variable is available. However, variables describing socioeconomic status are

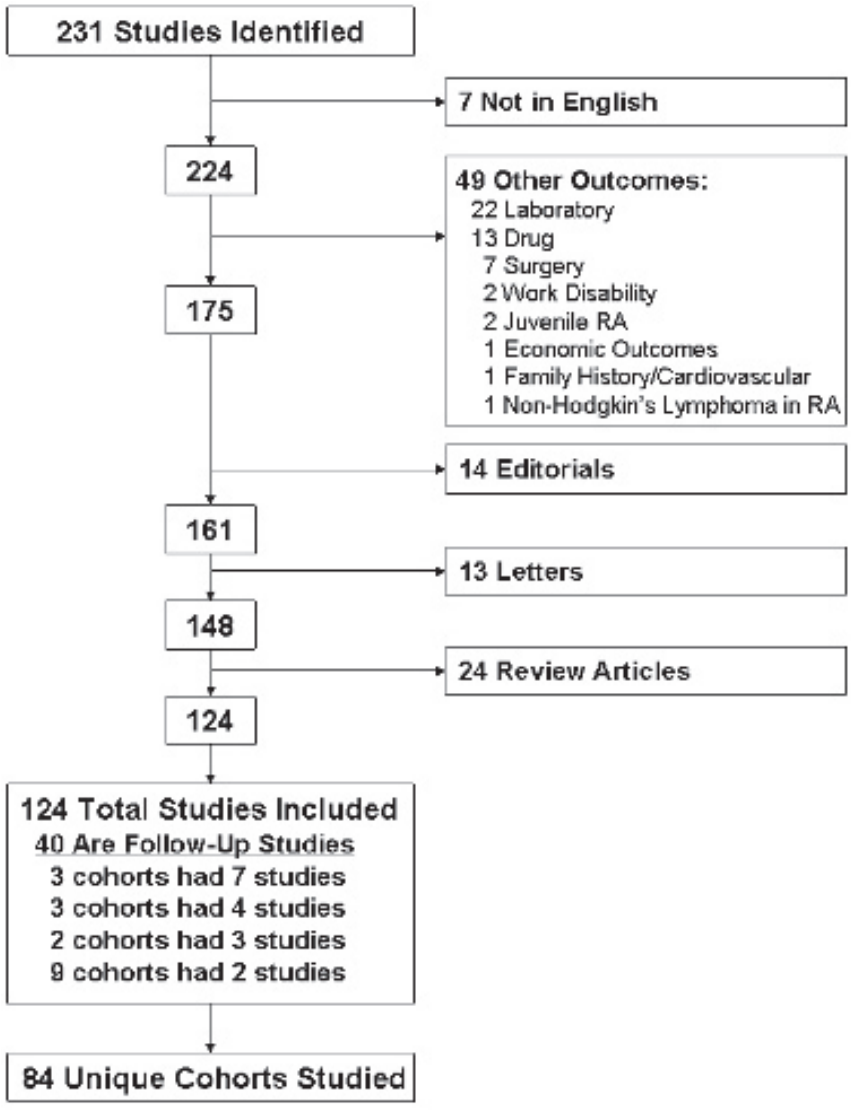

Fig. 1. Flow diagram of published reports identified and reviewed.

not included in most reports concerning patients with RA.

14. Therapies for RA, including gold salts, methotrexate and biologic agents, have been reported to be associated with reduced mortality rates in patients with RA, as might be expected, as these therapies are associated with improved values for quantitative prognostic indicators of premature mortality. However, some of these reports involve short-term observations in inception cohorts, in which standard mortality ratios are lower than in non-inception cohorts.
15. Although mortality outcomes do not appear essential to usual patient care, information concerning mortality, and possibly its reduction through aggressive therapy, may not only improve quality and years of life for current patients with RA, but also promote future advances, as well as interest among the general medical community and general public in further clinical and basic research for people with RA.

This review updates earlier reviews by ourselves (127-132) and others (27,133-139) concerning mortality in RA, and is divided into 5 sections:

1) *Rationale to study mortality in RA*
2) *Mortality rates in patients with RA*
3) *Acute causes of death in RA*
4) *Risk factors and predictive markers for mortality in RA*
5) *Therapies and mortality in RA*

1) Rationale to study mortality in RA

Premature mortality may not appear a primary outcome of interest in care of patients with RA. However, important reasons to study this subject beyond the value for general knowledge and more accurate information for patients and providers of medical care may be cited, including:

a) Predictors of mortality are also predictors of most long-term outcomes, including work disability, functional declines and costs (140, 141). Therefore, identified markers provide useful targets for therapeutic interventions to improve most outcomes. Many outcomes, such as work disability, joint replacement, costs, etc., may depend to a large extent on societal, economic and medical system variables, rather than effects of disease on a patient. Mortality clearly presents an unequivocally undesirable outcome in any society.

b) The possibility of identifying "target values" such as a blood pressure of 140/90 in hypertension (142) or a hemoglobin A_{1C} level of 7.0% in diabetes (143), which are not necessarily "normal" but "near normal" goals of therapy, might be applied to RA markers (131). Recent emphasis in treatment of RA has appropriately shifted from improvement compared with a placebo to a goal of remission (144), based on a number of clinical trials which documented the value of "tight control" (144-152). Improvement at 20% or 50% ("ACR20" or "ACR50") (153-156) is not acceptable (145). However, the remission criteria of the American Rheumatism Association (ARA) (157) appear overly stringent (158), as total remission is unusual (159; 160), even with new DMARDs and biologic agents. Efforts to attain complete remission may require unnecessary risks of adverse events in therapy.

New definitions of low disease activity and remission in RA according to indices of 3 or 4 measures, including disease activity score 28 (DAS28) (161-163), clinical disease activity index (CDAI) (164, 165) and routine assessment of patient index data 3 (RAPID3) (166, 167),

Table Ia. 1953-1980: Studies in rheumatoid arthritis and mortality.

Study	Ref.	Year of study	Location	Study focus	Mean duration of follow-up (years)	Number of patients with RA	Source	Mean age at baseline (years)	Mean disease duration at baseline (years)	SMR (95% CI)
Cobb *et al.*	(1)	1953	MA, USA	All RA	9.5	583	Clinic	--	--	1.29 (No CI)
Reah	(2)	1963	UK	All RA	13	185	Clinic	--	--	--
Duthie *et al.*	(3)	1964	UK	All RA	9	307	Rheum Hospital	--	--	2.14 (No CI)
Uddin *et al.*	(4)	1970	Canada	All RA	10	475	Registry (Queens University, Ontario)	--	--	1.29
Jacoby *et al.*	(5)	1973	UK	All RA	11 (8-14)	100	Rheum Hospital	51	3 months	1.4 (No CI)
• Rasker and Cosh	(6)	1981		All RA	18					
• Cosh and Rasker	(7)	1982		All RA	20					
• Rasker and Cosh	(8)	1984		All RA	14.6					
• Rasker and Cosh	(9)	1987		All RA	20					
• Reilly *et al.*	(10)	1990		All RA	25					1.4 (No CI)
• Minaur *et al.*	(11)	2004		All RA	40					2.13 (1.26-3.60)
Gordon *et al.*	(12)	1973	Canada	Extraarticular disease	5	127	Clinic	55	11.5	--
Isomäki *et al.*	(13)	1975	Finland	All RA	3	1000	Rheum Hospital	M: 54.5 F: 55.5	--	--
• Koota *et al.*	(14)	1977		All RA	5					
• Mutru, *et al.*	(15)	1985		All RA	10					1.73 (p<0.0001)
• Laakso *et al.*	(16)	1986		Cancer	10					
• Laakso *et al.*	(17)	1986		Death certificates	10					
• Laakso *et al.*	(18)	1986		Renal	10					
• Mutru *et al.*	(19)	1989		Cardiovascular	10					
Monson and Hall	(20)	1976	MA, USA	All RA	M: 11.4 F: 12.6 (up to 42)	1035	Rheum Hospital	--	--	1.86 (No CI)
Fleming *et al.*	(21)	1976	UK	All RA	4.5 (up to 15)	102	Clinic	50.5	<1	--
• Corbett *et al.*	(22)	1993		All RA	12					--
Lewis *et al.*	(23)	1980	UK	Azathioprine	11	311	Clinic	--	--	1.13 (No CI)
Linos *et al.*	(24)	1980	MN, USA	All RA	25	521	Population	--	--	1.16 (No CI)

Table Ib. 1981-1994: Studies in rheumatoid arthritis and mortality.

Study	Ref.	Year of study	Location	Study focus	Mean duration of follow-up (years)	Number of Patients with RA	Source	Mean age at baseline (years)	Mean disease duration at baseline (3 years)	SMR (95% CI)
Allebeck *et al.*	(25)	1981	Sweden	All RA	11	293	Population	--	--	M: 1.92 (p=.0003) F: 1.18 (p=0.11)
• Allebeck *et al.*	(26)	1985		All RA	13					--
Allebeck *et al.*	(27)	1982	Sweden	All RA	7	1165	Population	--	--	2.48 (p<.001)
Scott *et al.*	(28)	1983	UK	All RA	10	112	Rheum Hospital	--	--	--
Foster *et al.*	(29)	1984	MA, GA & CO, USA	Scleritis and Keratitis	10	34	Clinic	61.5	12	--
Pincus *et al.*	(30)	1984	TN, USA	All RA	9	75	Clinic	54.7	11.2	1.92 (1.21-2.78)
• Pincus *et al.*	(31)	1985		All RA	9					
• Pincus *et al.*	(32)	1987		All RA	9					
• Pincus *et al.*	(33)	1994		All RA	15					1.62 (1.12-2.21)
Prior *et al.*	(34)	1984	UK	All RA	11.2 (3-18)	448	Clinic	43.9	--	199 (No CI)
• Symmons *et al.*	(35)	1986		All RA	17					2.5 (p<0.001)
• Symmons *et al.*	(36)	1998		All RA	21.5					2.7 (2.4-3.1)
Vandenbroucke *et al.*	(37)	1984	Netherlands	All RA	25	209	Clinic	53.5	8	--
Mitchell *et al.*	(38)	1986	Canada	All RA	12 (8-16)	805	Clinic	51.8	10	1.51 (No CI)
• Fries *et al.*	(39)	1985		Cancer	12					
Wicks *et al.*	(40)	1988	Australia	All RA	32	--	Population	--	--	--
Wolfe *et al.*	(41)	1988	KS, USA	All RA	3.1	400	Clinic	54.8	9.5	--
Erhardt *et al.*	(42)	1989	UK	All RA	8 (6-9)	107	Clinic	--	--	--
Saway *et al.*	(43)	1989	AL, USA	Cervical spine surgery	--	113	Clinic	60	13.9	-
Kazis *et al.*	(44)	1990	MA, USA	All RA	5	279	Clinic	58	14	--
Lehtinen and Isomäki	(45)	1991	Finland	Intramuscular Gold Therapy	28	573	Rheum Hospital	39.5	2.8	--
Leigh and Fries	(46)	1991	CA, USA	All RA	8	263	Registry	55	13	--
Jacobsson *et al.*	(47)	1993	AZ, USA	All RA	24	172	Registry	43.8	--	1.28 (1.01-1.62) [a]
Wolfe *et al.* [includes Wolfe *et al.* 1988 cohort (41)]	(48)	1994	CA & KS, USA, Canada	All RA	35	3501	Registry (ARAMIS)	53.3	9	2.26 (SEM = 0.05)
Coste and Jougla	(49)	1994	France	All RA	20	1159	Population	--	--	--

[a] given as mortality rate ratio (MRR).

Table Ic. 1995-2000: Studies in rheumatoid arthritis and mortality.

Study	Ref.	Year of study	Location	Study focus	Mean duration of follow-up (years)	Number of patients with RA	Source	Mean age at baseline (years)	Mean disease duration at baseline (years)	SMR (95% CI)
Radis *et al.*	(50)	1995	PA, USA	Cancer – follow-up study of cyclophosphamide therapy	13.1	a-119 b-119	Clinic	a-54.7 b-55.3	a-9.2 b-9.0	--
Myllykangas-Luosujärvi *et al.*	(51)	1995	Finland	All RA	--	1666	Population	--	M: 14.0 F:17.4	1.37 (1.35-1.40)
• Myllykangas-Luosujärvi *et al.*	(52)	1995		Cardiovascular						--
• Myllykangas-Luosujärvi *et al.*	(53)	1995		Cancer						--
• Neva *et al.*	(54)	2001		Cervical spine disorders						--
Heliövaara *et al.*	(55)	1995	Finland	All RA	--	175	Population	--	--	--
Jones *et al.*	(56)	1996	UK	Immuno-suppressive therapy	10	259	Registry	58.6 (median)	--	--
Voskuyl *et al.*	(57)	1996	Netherlands	Rheumatoid vasculitis	--	244	Clinic	62 (median)	9 (median)	--
Callahan *et al.*	(58)	1996	CA, FL, ID, PA, TN, MN and DC, USA	All RA	5	Registry (15 private practice) 1378	Clinic	56.6	11.7	1.54 (p<0.001)
• Pincus *et al.*	(59)	2004		All RA	10					1.6 (p<0.001)
Swinson *et al.*	(60)	1997	UK	Bronchiectasis	5	32	Registry	59.5	10.7	0.9 (0.1-2.5)
Callahan *et al.*	(61)	1997	TN, USA	All RA	5	210	Clinic	56.6	9.7	1.61 (No CI)
Kremer, Joel	(62)	1997	--	Methotrexate	13.3	29	Clinic	60.6	31.4	--
Wallberg-Jonsson *et al.*	(63)	1997	Sweden	All RA	15	606	Clinic	M: 56 F: 54	12.5	1.57 (p<0.001)
Soderlin *et al.*	(64)	1998	Finland	All RA	5	103	Registry	59.5	18.4	--
van den Borne *et al.*	(65)	1998	Netherlands	Cyclosporine-A	4.7	208	Registry	55	5.7	--
Lindqvist and Eberhardt	(66)	1999	Sweden	All RA	5	183	Clinic	51	11 months	0.87 (0.53-1.36)
Turesson *et al.*	(67)	1999	Sweden	Extraarticular disease	--	489	Clinic	68.4	14.2	1.82 (1.48-2.16)
Sokka *et al.*	(68)	1999	Finland	All RA	11 (8-14)	135	Clinic	50.5	6.5 months	1.28 (.83-1.89)
Gabriel *et al.*	(69)	1999	MN, USA	All RA	15.1	425	Population	60.2	--	1.38 (1.22-1.55)
Maiden *et al.*	(70)	1999	UK	All RA	12	200	Clinic	57 (median)	7 (median)	--
Wallberg-Jonsson *et al.*	(71)	1999	Sweden	All RA	21	211	Clinic	51.9	≤1	--
Krause *et al.*	(72)	2000	Germany	Methotrexate	10	256	Clinic	64.3	8.5	2.60 (2.05-3.15)
Kvalvik *et al.*	(73)	2000	Norway	All RA	16	147	Rheum Hospital	58	4.1	149 (1.15-1.88)
Kroot *et al.*	(74)	2000	Netherlands	All RA	10	622	Clinic	53.3	--	--

Table Id. 2001-2002: Studies in rheumatoid arthritis and mortality.

Study	Ref.	Year of study	Location	Study focus	Mean duration of follow-up (years)	Number of patients with RA	Source	Mean age at baseline (years)	Mean disease duration at baseline (years)	SMR (95% CI)
Riise *et al.*	(75)	2001	Norway	Atlantoaxial subluxation	17	187	Clinic	56.9	10.3	2.00[a] (1.6-2.5)
Chehata *et al.*	(76)	2001	UK	All RA	14	309	Rheum Hospital	53	2.5 (median)	1.65 (1.34-1.98)
Isaacs *et al.*	(77)	2001	UK	Lymphopenia	5.9	53	Clinic	54	9 (median)	1.45 (0.65-3.13) [a]
• Lorenzi *et al.*	(78)	2008	UK	Lymphopenia	11.8					1.20 (0.72-1.98) [a]
Martínez *et al.*	(79)	2001	Spain	All RA	9	182	Clinic	M: 57.7 F: 55.8	--	1.85 (No CI)
Riise *et al.*	(80)	2001	Norway	All RA	6.1	241	Clinic	62.3	--	8 (3-25) [a]
Uhrin *et al.*	(81)	2001	CA, USA	Lymphoid irradiation	a-11.2 b -9.2	a-53 b-106	a-Clinic b-Registry	a-61.9 b-62.0	a-21.1 b-20.4	--
Chevrel *et al.*	(82)	2001	France	All RA	--	15	Clinic	41	--	--
Doran *et al.*	(83)	2002	MN, USA	All RA	14.2	609	Population	58	--	1.27 (1.13-1.41)
• Gabriel *et al.*	(84)	2003		All RA	14.2	609		58	--	1.27 (1.13-1.41)
• Turesson *et al.*	(85)	2002		All RA	14.8	424		60	--	--
• Maradit Kremers *et al.*	(86)	2004		Cardiovascular/ BMI	14.7	603		58	--	--
• Maradit Kremers *et al.*	(87)	2005		Cardiovascular	15.0	603		58	--	--
• Maradit Kremers *et al.*	(88)	2005		Sudden death	14.7	603		58	--	--
• Nicola *et al.*	(89)	2006		Comorbidities	12.7	603		58	--	--
Yelin *et al.*	(90)	2002	CA, USA	All RA	8.4	1269	Registry	56.7	11.1	1.32
Choi *et al.*	(91)	2002	KS, USA	Methotrexate	6	1240	Clinic	--	--	--
Bjornadal *et al.*	(92)	2002	Sweden	All RA	31	46,917	Population	--	--	2.03 (2.00-2.05)
Mikuls *et al.*	(93)	2002	IA, USA	All RA	13.4	158	Population	67.8	13.4 months	1.52 (1.05-2.20) [b]
Peltomaa *et al.*	(94)	2002	Finland	All RA	a-12.2 b-7.7	150 a-87 b-63	Clinic	a-46.5 b-59.0	a-7.6 b-5.7 months	1.33 (0.85-1.98) a-0.93 (0.37-1.92) b-1.62 (0.95-2.60)
Goodson *et al.*	(95)	2002	UK	All RA	6.9	575	Registry (Norfolk Arthritis Registry)	57	6.6 months	M: 1.08 (0.78-1.47) F: 0.99 (0.71-1.33)
• Farragher *et al.*	(96)	2007	UK	Cardiovascular	10.3	1098				
• Farragher *et al.*	(97)	2008		HLA	11.4	751		55	5	--
• Naz *et al.*	(98)	2008		All RA	11.4	499		55	5	1.06 (0.93 - 1.21)

[a]given as mortality rate (MRR); [b]given as hazard ratio (HR).

Table Ie. 2003-2005: Studies in rheumatoid arthritis and mortality.

Study	Ref.	Year of study	Location	Study focus	Mean duration of follow-up (years)	Number of patients with RA	Source	Mean age at baseline (years)	Mean disease duration at baseline (years)	SMR (95% CI)
Watson *et al.*	(99)	2003	UK	Cardiovascular	M: 4.7 F: 4.8	11,633	Registry (General Practice Research Database)	54.5 (m) 57.2 (f)	--	1.6 (1.6-1.6) [a]
Navarro-Cano *et al.*	(100)	2003	TX, USA	All RA	6.3	779	Clinic	54 (living); 67 (dead)	11 (living); 16 (dead)	--
Thomas *et al.*	(101)	2003	UK	All RA	19	20,875	Population	58.1	--	M: 2.07 (2.01-2.13) F: 1.97(1.93-2.01)
Wolfe *et al.*	(102)	2003	KS, USA	All RA	15	1387	Clinic	55.5	7.1	--
• Ang *et al.*	(103)	2005	--	Depression	18	1290	Rheum Hospital	55.3	6.6	--
Solomon *et al.*	(104)	2003	MA, USA	Cardiovascular	21	2170 (all women)	Registry (Nurses' Health Study)	58	--	--
Sihvonen *et al.*	(105)	2004	Finland	All RA	11	604	Population	59	15	1.78 (1.34-2.31) [b]
• Sihvonen *et al.*	(106)	2005			12					--
• Sihvonen *et al.*	(107)	2006			12					--
Krishnan *et al.*	(108)	2004	CA, USA	Cardiovascular	17	3862	Registry (ARAMIS)	56	9.7	--
Sokka *et al.*	(109)	2004	Finland	All RA	2	1095	Clinic	62.4	11.3	--
• Kauppi *et al.*	(110)	2005		All RA						

[a]given as given as mortality rate ratio (MRR), [b]given as hazard ratio (HR).

may provide realistic therapeutic targets (168). Long-term observations regarding values for these indices and individual clinical variables, including joint counts, radiographs, laboratory tests and patient questionnaire measures that are not necessarily totally normal, but result in a prognosis for long-term mortality outcomes similar to the general population, would be informative. These data would help the clinician to balance "tight control" to provide pragmatic target values for therapeutic goals toward improved mortality outcomes.

c) Information concerning mortality outcomes and possible improvement with treatment of RA may provide an important impetus to increase interest of primary care physicians and the general public. Even today, most health professionals are unaware that the natural history of RA (and other rheumatic diseases) includes premature mortality. Interest in treatment of hypertension, diabetes and hypercholesterolemia was advanced greatly by documentation that treatment not only improved measures indicating a dysregulation (blood pressure, cholesterol), but also improved mortality outcomes. Similar data for RA could raise the profile for treatment in the medical community and the general public.

2) Mortality rates in patients with RA

Eighty-four cohorts of patients with RA have been reported with analyses of mortality outcomes (1-124), including 40 reported more than once (Table I, organized according to 84 cohorts) (Fig. 1). The median standardized mortality ratio (SMR) of 57 reports from 1953-2008 was 1.54, including 1.62 in 15 reports from 1953-1989, compared to 1.52 in 14 reports from 1990-2000, and 1.54 in 28 reports from 2001-2008 (Table II).

The median SMR was 1.31 (mean 1.29) in 6 community/population-based inception cohorts and 1.28 (mean 1.23) in 5 clinic-based inception cohorts, compared to 1.63 (mean 1.72) in 12 community/population-based non-inception cohorts and 1.65 (mean 1.74) in 19 clinic-based non-inception cohorts (Table II). The median SMR in inception cohorts remained remarkably stable at 1.28 (mean 1.25) from 1953-2008, and in non-inception cohorts fell slightly from 1.86 in 1953-1994, to 1.61 in

Table If. 2005-2008: Studies in rheumatoid arthritis and mortality.

Study	Ref,	Year of study	Location	Study focus	Mean duration of follow-up (years)	Number of patients with RA	Source	Mean age at baseline (yr)	Mean disease duration at baseline (yr)	SMR (95% CI)
Book *et al.*	(111)	2005	Sweden	All RA	20	152	Clinic	61	12	1.56 (128-188)
Goodson *et al.*	(112)	2005	UK	Cardiovascular	11.4	1010	Registry (Stockport Rheumatology Clinic, Office for National Statistics)	60.4	--	M: 1.45 (1.22-1.71); F: 1.84 (1.64-2.05)
Hakoda *et al.*	(113)	2005	Japan	All RA	17.8	91	Registry (Radiation Effects Research Foundation)	56.8	8.8	1.6 (1.29-1.99) [b]
Escalante *et al.*	(114)	2005	TX, USA	Body mass index	7	779	Clinic	55.6	11.06	--
Ronkainen *et al.*	(115)	2006	Finland	Cervical spine disorders	7.5	86	Clinic	61.8	23.6	--
Carmona *et al.*	(116)	2007	Spain	Anti-TNF	5	B-789 E-789	Drug Registry (BIOBADASER) Clinic (EMECAR)	B-59 E-61	10 10	B-0.516 (0.315-0.797)[c] E-1.493 (1.174-1.872)
• Abasolo *et al.*	(117)	2007		Cancer	5	E-789	Clinic (EMECAR)	E-61	10	1.00 (0.50–1.70) [d]
Jacobsson *et al.*	(118)	2007	Sweden	Anti-TNF	4	1430	Registry (South Swedish Arthritis Treatment Group)	57.8	13.2	1.56 (1.26-1.86)
Gonzalez *et al.*	(119)	2007	MN, USA	All RA	11.7	822	Population	57.6	--	1.35 (1.23-1.49)
Gonzalez-Gay *et al.*	(120)	2007	Spain	Cardiovascular /HLA	13.4	182	Clinic	59.7	10.5	--
Young *et al.*	(121)	2007	UK	Cardiovascular	9.1	1429	Clinic	55.2	6 months	1.27 (1.04-1.46)
• Mattey *et al.*	(122)	2007	UK	All RA	18	767	Clinic	--	6 months	--
Mattey *et al.*	(123)	2007	UK	All RA	13	401	Clinic	59.4	9.5	--
Nikolaisen *et al.*	(124)	2008	Norway	Anemia	6.2	111	Clinic	61 (median)	4.5 (median)	--

[b]given as hazard ratio (HR); [c]all patients on biologics; [d]SMR for cancer.

1995-2001, and 1.61 in 2002-2008. The median SMR in inception cohorts was 1.28 in those maintained over 6-12 years compared to 1.39 in those maintained over >12 years, while the SMR was at similar levels, 1.59-1.82, according to period of observation in the 32 non-inception cohorts (Table III). These data extend the observations of Ward (136), who concluded that the primary basis for suggestions of improved mortality outcomes in RA in some recent reports was based on their being inception cohorts rather than non-inception cohorts. Six reports (24, 60, 66, 74, 94, 95) indicated that mortality rates were not increased compared to the general population. Two were based on a mean of 5 years of observation (60, 66). Another was based on median 5.8 years observation (although the title states "up to 10 years") (74). A fourth study was based on a mean of 6.9 years of observation and included all patients from an early arthritis clinic with inflammatory polyarthritis, of whom only 29% were positive for rheumatoid factor (95). A fifth was a population-based study indicating an SMR of 1.16 (24), interpreted as not significant, but later recalculated and interpreted as significant (84). The sixth study indicated an increase in mortality rates that was not statistically significant: an SMR of 1.62 in one of two cohorts was balanced by an SMR of 0.93 in the second cohort (94). Several reports from other cohorts suggested that mortality rates in RA were not increased until after 8-10 years (84) and

were increased with increasing duration of disease (36, 48, 92), although excess mortality within 3 years (22) and 7 years (121) has been reported. While variation in certain settings may be seen, overall SMR levels do not differ substantially according to the period of observation (Table III).

Forty-four specialized studies have been focused on three domains: 18 focused on specific causes of death, including 11 on cardiovascular death (19, 52, 86, 87, 96, 99, 104, 108, 112, 120, 121), 4 on cancer (16, 39, 50, 117), and 1 each on renal death (18), sudden death (88), and death certificates (17); 16 focused on comorbidities and disease features, including 4 on cervical spine disorders (43, 54, 115, 169), 2 on extraarticular disease (12, 67), 2 on lymphopenia (77; 78), 2 on body mass index (114, 119), and 1 each on general comorbidities (89), depression (103), vasculitis (57), scleritis/keratitis (29), anemia (124), and bronchiectasis (60); and 10 focused on therapies, including 3 on methotrexate (62, 72, 91), 2 on anti-TNF biological agents (116, 118), and 1 each on intramuscular gold (45), azathioprine (23), cyclosporine-A (65), immunosuppressive therapy (56), and follow-up of lymphoid irradiation (81).

Some variation has been seen among different cohorts, explained in part by different patient populations, different treatment philosophies at different sites, and many other factors. Although SMR levels have not changed substantially over half a century of observation, most patients were entered into these databases prior to modern early aggressive therapy with methotrexate. In one report suggesting a widening gap in mortality rates between people with RA and the general population (119), all patients were entered prior to 1995, with hydroxychloroquine reported in 2004 as a mainstay of therapy (170), and may not reflect advances in therapy with methotrexate, and later biological agents. Considering differences in populations in severity, duration at baseline, treatments and other variables, the authors would interpret data concerning the 84 cohorts as showing relatively similar patterns, suggesting a shortening of lifespan of 4-10 years relative to expected mortality according to age and sex (51, 171).

Several important limitations are seen in the analysis of mortality in RA (Table VII):

a) No "gold standard" for diagnosis. Analysis of mortality in RA is similar in some respects to analyses in other chronic diseases such as hypertension or hyperlipidemia (172). Each of these diseases is characterized by a dysregulation, which in itself is not necessarily harmful to the patient, but a natural history in which the dysregulation leads to long-term damage. Excellent therapies have been developed for these diseases, which do not "cure" the dysregulation but "control" its consequences and prevent organ damage, such as vascular disease or joint destruction. Without a "cure," generally there is a need for ongoing (often lifetime) medication, which may improve mortality outcomes.

However, unlike hypertension or hypercholesterolemia, no single "gold standard" is available in RA for diagnosis, monitoring and prognosis. Markers such as rheumatoid factor and antibodies to cyclic citrullinated peptides (CCP) are positive in a majority, but only two-thirds of patients with RA (173). Furthermore, 40% of patients have a normal erythrocyte sedimentation rate (ESR) on presentation (174). Classification criteria for RA have been invaluable to provide relatively uniform cohorts for clinical trials and clinical research. However, a diagnosis of RA remains based primarily on the judgment of a physician, hardly as precise as a single diagnostic marker. This matter complicates analyses of mortality in RA and most rheumatic diseases.

b) Self-limited early inflammatory arthritis. One consequence of complexity in the diagnosis of RA is that many people with signs of early inflammatory arthritis have a self-limited rather than progressive disease. This matter further complicates efforts to analyze populations for the incidence, prevalence, long-term course, morbidity and mortality in RA. This phenomenon was documented in the 1960s and 1970s, in population-based studies in which all individuals in an area were analyzed to recognize those who met ARA criteria for RA (175). In longitudinal studies in Massachusetts and Michigan, only 25% who initially met RA criteria still had evidence of RA 3-5 years later (176-178). Furthermore, in population-based studies in Wensleydale, England (179), Tecumseh, Michigan (180), Jerusalem, Israel (181), Montana and Arizona in the U.S. (182), and Heinola, Finland (183), only about 25% of individuals among all who met RA criteria had rheumatoid factor [summarized in (184)].

Similar data have emerged more recently from early arthritis clinics, in which about 50% of people with early inflammatory arthritis are found to have a progressive disease (185-187). Although anti-CCP and rheumatoid factor identify a high likelihood of progressive RA, about one-third of patients with progressive disease are negative for these markers, as noted above (173). Therefore, all series of patients with RA are "contaminated" in part with some proportion of patients who do not have a progressive inflammatory arthritis. Probably many people with an early self-limited transient polyarthritis never see a physician before the problem is resolved. This phenomenon may explain why the median SMR in inception cohorts is 1.31 compared to 1.63 in non-inception cohorts (Tables II and III).

c) Patient characteristics vary considerably in different cohorts.

Patients with RA differ considerably in clinical manifestations and severity, both within clinical settings and between different settings, in part due to uncertainty concerning diagnosis, but also even in "classical" presentations. Variation may be seen in many characteristics, including whether patients present in early arthritis clinics versus usual clinical settings, tertiary care centers that serve an entire region versus limited areas, severity of clinical status at baseline observation,

Table II. Standard mortality ratios (SMR) in 18 community/population-based cohorts and 24 clinic-based cohorts of patients with rheumatoid arthritis.

COMMUNITY/POPULATION-BASED COHORTS Study	Ref.	no.	SMR	CLINIC-BASED COHORTS Study	Ref.	no.	SMR
INCEPTION COHORTS (n=6)				INCEPTION COHORTS (n=5)			
Linos *et al*. 1980	(24)	521	1.16	Jacoby *et al*. 1973	(5)	100	1.4
Gabriel *et al*. 1999	(69)	425	1.38	Lindqvist & Eberhardt 1999	(66)	183	0.87
Mikuls *et al*. 2002	(93)	158	1.52	Sokka *et al*. 1999	(68)	135	1.28
Goodson *et al*. 2002	(95)	575	1.06	Peltomaa *et al*. 2002	(94)	150	1.33
Doran *et al*. 2002	(83)	609	1.27	Young *et al*. 2007	(121)	1429	1.27
Gonzalez *et al*. 2007	(119)	822	1.35				
			Median 1.31 Mean 1.29				Median 1.28 Mean 1.23
NON-INCEPTION COHORTS (n=12)				NON-INCEPTION COHORTS (n=19)			
Uddin *et al*. 1970	(4)	475	1.29	Cobb *et al*. 1953	(1)	583	1.29
Allebeck *et al*. 1981	(25)	193	1.92	Duthie *et al*. 1964	(3)	307	2.14
Allebeck *et al*. 1982	(27)	1165	2.48	Isomäki *et al*. 1975	(13)	1000	1.73
Jacobsson *et al*. 1993	(47)	172	1.28	Monson & Hall 1976	(20)	1035	1.86
Myllykangas-Luosujärvi *et al*. 1995	(51)	1666	1.37	Lewis *et al*. 1980	(23)	311	1.13
Bjornadal *et al*. 2002	(92)	46917	2.03	Pincus *et al*. 1984	(30)	75	1.92
Watson *et al*. 2003	(99)	11633	1.6	Prior *et al*. 1984	(34)	448	1.99
Thomas *et al*. 2003	(101)	2003	2.02	Mitchell *et al*. 1986	(38)	805	1.51
Sihvonen *et al*. 2004	(105)	604	1.78	Wolfe *et al*. 1994	(48)	3501	2.26
Goodson *et al*. 2005	(112)	1010	1.65	Callahan *et al*. 1996	(58)	1416	1.54
Hakoda *et al*. 2005	(113)	91	1.6	Callahan *et al*. 1997	(61)	210	1.61
Jacobsson *et al*. 2007	(118)	1430		Wallberg-Jonsson *et al*. 1997	(63)	606	1.57
				Krause *et al*. 2000	(72)	256	2.6
				Kvalvik *et al*. 2000	(73)	147	1.49
				Riise *et al*. 2001	(75)	187	2
				Chehata *et al*. 2001	(76)	309	1.65
				Martínez *et al*. 2001	(79)	182	1.85
				Yelin *et al*. 2002	(90)	1269	1.32
				Book *et al*. 2005	(111)	152	1.56
			Median 1.63 Mean 1.72				Median 1.65 Mean 1.74

Table III. Standard mortality ratios (SMRs), in rheumatoid arthritis cohorts according to community or clinic, period of observation, and year of report, classified for inception cohorts and non-inception cohorts.

	INCEPTION COHORTS			NON-INCEPTION COHORTS		
	no.	Median	Mean	no.	Median	Mean
Source of patients						
Community/population-based	6	1.31	1.29	14	1.63	1.73
Clinic-based	5	1.28	1.23	17	1.65	1.73
Period of Observation						
< 6 years	1	0.87	0.87	5	1.60	1.66
6 - 12 years	6	1.28	1.26	16	1.82	1.78
> 12	4	1.39	1.37	10	1.59	1.68
Year of Report						
1953-1994	2	1.28	1.28	13	1.86	1.75
1995-2001	3	1.28	1.18	9	1.61	1.74
2002-2008	6	1.30	1.30	9	1.61	1.68
Total	11	1.31	1.30	31	1.63	1.73

and many others. Wide variations in DAS and HAQ scores in different countries have been reported in the multinational QUEST-RA database (188), with mean low disease activity levels in such countries as the Netherlands, Finland and the U.S., but high activity in such countries as Serbia, Poland, Latvia. Furthermore, formal education level has been found in several settings to be a more significant identifier of good versus poor clinical status than age or duration of disease (189).

d) Different reference mortality rates. Differences in SMRs across studies may result from the choice of reference mortality rates. For example, if observed RA deaths were ascertained between 1960-2000, and expected deaths were derived using mortality rates between 1980-2000, then SMR may appear worse than using rates derived from 1960-2000 (assuming that mortality improved over time).

e) Changing natural history of RA. A number of reports suggest that the status of patients with RA is considerably improved in recent years compared to 2–3 decades earlier, in terms of functional status, radiographic scores, level of erythrocyte sedimentation rate (ESR), number of swollen joints, and other variables (190). Improved clinical status may have many bases, including a change in treatment philosophy from relatively indolent to aggressive early therapy, use of methotrexate and other DMARDs early in disease (191). In addition, some reports suggest that RA may be becoming a milder disease in general (192), similar to cardiovascular disease (193). The improved clinical status of patients according to measures associated with a higher likelihood of premature mortality might be anticipated to be translated into improved mortality outcomes, which have been reported in some locales (62, 72, 91, 116, 193, 194), but not in others (119).

f) Period of observation. As noted above, increased mortality rates were seen in some studies after 3 or 7 years of disease (22, 121), while other reports suggest that highest increased mortality rates are seen after 8-10 years (84), and even later in disease course (36, 48, 92). Overall, median SMR appear similar according to the period of observation. The influence of RA variables on mortality in general is most marked in periods of 5-20 years. After 15-20 years, the impact of age and gender become predominant, and ultimately SMR approaches 1.0 (as everyone ultimately dies).

g) Limited resources for study. Resources for studies of mortality in RA are considerably less than support for studies of mortality associated with hypertension and hyperlipidemia, based on higher prevalence and recognized pathophysiologic consequences of possible sudden cardiac death not seen in RA. Incentives in RA (and other rheumatic diseases) are lesser than in cardiovascular and neoplastic diseases to support large-scale studies to document favorable mortality effects of therapies by publicly funded agencies and/or pharmaceutical companies. Therefore, cost-effective strategies to study mortality outcomes, risk factors, and possible benefits of interventions in RA are needed, through data collected at many clinical settings (195).

h) Absence of long-term clinical trials. RA is a symptomatic disease, in contrast to hypertension and hyperlipidemia, which generally are asymptomatic. In asymptomatic diseases, it was reasonable to conduct randomized controlled clinical trials to determine whether a therapy (which could lead to adverse events) may or may not favorably affect long-term mortality outcomes. Such trials have indicated that "tight control" of hypertension, hyperlipidemia or diabetes results in improved mortality outcomes (196-198).

In a symptomatic disease such as RA, it is ethically and logistically impossible to conduct long-term randomized controlled clinical trials of mortality outcomes (199), particularly with evidence over the last two decades that "tight control" with methotrexate and other DMARDs as well as biologic agents is associated with prevention of long-term joint damage (144-152). Therefore, possible evidence of improved mortality outcomes must necessarily be derived from longitudinal databases rather than randomized trials, which lead to intrinsically less precise estimates than in hypertension or hyperlipidemia.

i) Numbers used to describe risk. Several complexities in the literature used to describe mortality rates in different cohorts remain incompletely understood by health professionals. For example, the absolute risk of death in almost all series of patients with RA is greater in older people and in males. However, the relative risk of death generally is higher in younger people and females (who have a lower absolute risk of death in the general population). Thus, the same data can be interpreted as indicating greater mortality rates in men or women, or younger or older individuals, depending on whether absolute or relative risk is reported. The SMR differs substantially in inception cohorts versus non-inception cohorts (Tables II and III), but conclusions again may appear superficially conflicting, or consistent, depending on the analyses chosen.

Despite these complexities, the similarity of patterns of increased mortality rates over the years provides rather robust conclusions concerning premature mortality in RA.

3) Acute causes of death in RA

The acute attributed causes of 33,250 deaths in 50 published reports (of 54 cohorts) of patients with RA in the United States and Western European countries, in which most series were compiled, indicate quite similar patterns (Tables IV and V). Cardiovascular disease was the acute attributed cause of death in 39.6% of patients, compared to cancer in 16.8%, renal disease in 5.8%, respiratory disease in 9.0%, infection in 14.3%, gastrointestinal disease in 5.1%, sudden death in 3.1%, accidents/intoxication in 4.2%, musculoskeletal disease or rheumatoid arthritis in 9.4%, and

"other causes" in 12.9%. These proportions also appear similar over the years, including 14 reports/cohorts from 1953-1989, 9 reports/cohorts from 1990-2000, 10 reports of 11 cohorts from 2001-2008, as well as 10 reports of 13 specialized cohorts involving results of particular therapies or a focus on a specific outcome, and 7 studies of population cohorts (Table V). The data appear quite similar to a compilation prepared 22 years ago in 1986 (127).

RA or musculoskeletal disease was included as an acute attributed cause of death or listed on death certificates in 12.9% of patients in 1953-1989, 8.3% in 1990-2000, 6.5% in 2001-2008, 4.1% in specialized studies, and 9.2% in population studies (Table V). These data may be explained in part on whether cause of death data were derived from death certificates, which has been more likely in recent years, or from review of a medical record, which was more common in earlier years. Nonetheless, these data suggest that the increased mortality rates in RA remain at least as underrecognized in the medical community as two decades earlier (127).

Cardiovascular disease. Cardiovascular disease was the most common cause of death, listed as the cause of 39.6% of all 33,250 deaths, including 39.6% in 1953-89, 46.7% in 1990-2000, 38.6% in 2001-08, 33.5 in specialized studies (some of which were focused on cancer or renal disease) and 43.5% in population studies. These data are similar to the general population, in which 41.0% of deaths in 1977 (127) and 38.3% in 2005 (http://www.cdc.gov/nchs/data/dvs/LCWK9_2005.pdf) were attributed to cardiovascular disease (Table V). Therefore, the proportion of cardiovascular deaths among RA patients is not substantially higher than in the general population, but patients die at an earlier age, indicating that RA may be regarded as a risk factor for premature cardiovascular disease and cardiovascular death.

As noted above, the relative risk of cardiovascular death is highest in younger patients under the age of 50, whereas the highest absolute risk is seen older patients over the age of 75 (104). Nicola *et al*. (89) reported that congestive heart failure, rather than ischemic heart disease, is an important contributor to excess mortality in patients with RA, not because of greater severity, but higher frequency.

As discussed in greater detail in the chapter on cardiovascular disease in RA (126), traditional cardiovascular risk factors are increased in patients with RA, including hypertension and smoking. Non-traditional risk factors related to inflammation, including C-reactive protein (CRP) (200) and persistently high disease activity (88), also are associated with cardiovascular mortality in patients with RA. One study indicated that 30-day mortality following myocardial infarction was higher in RA patients than in the general population (88). Krishnan *et al*. describe declines in mortality from myocardial infarction in patients with RA (108), although Naz and Symmons suggested that RA patients do not appear to enjoy the benefits of decreased mortality from cardiovascular disease in the general population (139). Some improvement in mortality is not necessarily incompatible with a widening mortality gap between people with RA and the general population (119).

Infection. Infection is the acute cause of death with highest increased frequency in RA patients compared to the general population (Tables IV and V): 14.3% in patients with RA compared to 1.0% in the U.S. population in 1977 and 4.4% in 2005 (suggesting an older population and/or more accurate reporting in 2005). The proportion of deaths attributed to infection has not changed substantially over the years, and was similar to recent years in the era prior to treatment with methotrexate and biologic agents.

Other causes of death. Higher mortality rates are also seen for pulmonary, renal and gastrointestinal diseases in patients with RA compared to the general population (Tables IV and V). The proportion of deaths attributed to renal disease was due in large part to high levels of amyloidosis in Finland (18, 45), and fell in recent years. A concomitant lesser likelihood of most cancers is seen, but not of lymphoma and lung cancer, which appear increased as attributable causes of death in patients with RA (201-203). A lower proportion of deaths is attributed to accidents, presumably as patients with RA are less likely to engage in activities posing a danger to life.

Complexities in analysis. Complexities in the analysis of causes of death in RA (Table VII) include:

a) *Source of information: death certificate or medical record*. The source of information may be a death certificate or a medical record. A death certificate is often completed by a non-rheumatologist attending the patient's demise and may omit mention of RA, whereas an analytic review of a medical record by a rheumatologist may more likely include mention of RA. These differences may lead to different estimates of causes of deaths.
b) *Underestimation of RA as associated with premature mortality.* Limited knowledge of RA as associated with premature mortality may result in underestimation of RA on a death certificate. For example, a patient with RA who dies of myocardial infarction is less likely than someone known to have suffered from hypertension or diabetes to have their chronic condition listed as "contributory" to cardiovascular death.
c) *Differences in reporting in different series*. Classification is complicated by differences in reporting in different series. For example, cardiovascular deaths are subclassified as myocardial infarction or stroke in some studies but not others. Certain studies report pneumonia as a pulmonary death, and others as an infection. Given these possibilities for differences, simply on the basis of different classification systems or sources of information, similarity in attributed causes of death in the different series is remarkable.

4) Risk factors and predictive markers for mortality in RA

Predictive markers for mortality in patients with RA indicate unequivocally that mortality 5-15 years after baseline is predicted by almost all quantitative baseline measures indicating more severe clinical status. Mortality, therefore,

Table IVa. 1953-1984: Percentage of various acute attributed causes of death in rheumatoid arthritis.

	Cobb *et al.* 1953	Duthie *et al.* 1964	Uddin *et al.* 1970	Gordon *et al.* 1973	Isomaki *et al.* 1975	Monson and Hall 1976	Fleming *et al.* 1976	Lewis *et al.* 1980	Allebeck *et al.* 1981	Scott *et al.* 1983	Pincus *et al.* 1984	Prior *et al.* 1984	Vanden-broucke *et al.* 1984
Ref. no.	(1)	(3)	(4)	(12)	(13)	(20)	(21)	(23)	(25)	(28)	(30)	(34)	(37)
Specialized or Population study?	--	--	--	--	--	--	--	--	Population	--	--	--	--
Total no. of patients	583	307	475	127	1000	1035	102	311	293	112	75	448	209
Total no. of deaths	137	75	94	23	122	570	10	46	84	17	20	199	165
Source of data*	DC+MR	Unknown	DC+MR	MR	DC	Unknown	MR	DC	DC+MR	DC	DC+MR	DC	MR
Cardiovascular	33.8	41.3	54.3	13	46.7	54.5	30	41.3	54.8	35.3	40	39.2	43
Cancer	11.5	13.3	7.4	4.3	9	12.6	10	28.3	23.8	5.9	25	15.1	19.4
Renal	13.1	17.3	4.3	--	22.1	4.4	--	4.3	--	11.8	--	3	5.5
Respiratory	3.1	4	4.3	--	--	10	10	6.5	1.2	5.9	--	0.5	12.1
Infection	24.6	14.7	19.1	43.5	15.6	--	20	13	2.4	35.3	20	16.1	2.4
Gastrointestinal	6.2	8	2.1	--	--	4	--	4.3	6	--	--	5.5	5.5
Sudden death	--	--	--	--	--	--	--	--	--	--	--	--	--
Accidents or intoxication	--	0.5	--	--	0.8	--	--	--	--	--	--	--	0.6
Musculoskeletal diseases	--	--	--	--	--	6.7	20	--	4.8	5.9	--	17.1	10.3
Other	7.7	--	8.5	39.1	5.7	7.7	10	2.2	7	--	15	3.5	2.4

*DC: death certificates; MR: medical records.

Table IVb. 1985-1998: Percentage of various acute attributed causes of death in rheumatoid arthritis.

	Mitchell *et al.* 1986	Erhardt *et al.* 1989	Saway *et al.* 1989	Lehtinen & Isomäki 1991	Jacobsson *et al.* 1993	Wolfe *et al.* 1994	Myllykangas-Luosujärvi *et al.* 1995	Jones *et al.* 1996		Wallberg-Jonsson *et al.* 1997	Soderlin *et al.* 1998	van den Borne *et al.* 1998	
Ref. no.	(38)	(42)	(43)	(45)	(47)	(48)	(55)	(56)		(63)	(64)	(65)	
Specialized or population study?	--	--	Focused	Focused	Population	--	Population	Focused		--	--	Focused	
Total no. of patients	805	107	113	573	172	3501	1666	518	604	606	103	208	415
Total no. of deaths	251	50	28	251	79	922	1186	193	201	265	22	16	57
Source of data*	DC+MR	DC	DC+MR	DC	DC	DC	DC	DC		DC+MR	DC	DC+MR	
Cardiovascular	42.6	40	25	16.9	25.3	47.1	50	49.7	49.2	53	45	25	38.6
Cancer	13.2	12	14.3	2.6	11.4	11.3	14	16.1	15.9	14	18	18.8	14
Renal	3.2	2	--	12.6	8.9	1.2	2.1	3.1	3	2	4.5	6.3	5.3
Respiratory	4.8	18	7.2	--	7.6	5	8	13	11.9	9	0	6.3	10.5
Infection	13.6	2	35.7	6.3	--	20.1	1.3	4.1	3.5	2	4.5	31.3	21.1
Gastrointestinal	6	4	3.6	--	7.6	5.7	4.4	4.1	4	6	4.5	--	1.8
Sudden death	--	--	--	--	--	--	--	--	--	--	--	--	--
Accidents or intoxication	4	--	--	--	10.1	2.6	3	--	--	--	9	6.3	--
Musculoskeletal diseases	10	20	--	--	--	1.3	12.1	3.6	4.5	9	14	--	--
Other	2.6	2	14.3	56.2	29.1	5.7	5.1	6.3	8	--	0	6.3	5.3

*DC: death certificates; MR: medical records.

Table IVc. 1999-2001: Percentage of various acute attributed causes of death in rheumatoid arthritis.

	Lindqvist & Eberhardt 1999	Turesson *et al.* 1999	Sokka *et al.* 1999	Maiden *et al.* 1999	Krause *et al.* 2000	Kvalvik *et al.* 2000	Kroot *et al.* 2000	Riise *et al.* 2001	Isaacs *et al.* 2001	Martínez *et al.* 2001	Uhrin *et al.* 2001		Chevrel *et al.* 2001
Ref. no.	(66)	(67)	(68)	(70)	(72)	(73)	(74)	(75)	(77)	(79)	(81)		(82)
Specialized or Population study?	--	--	--	--	Focused	--	--	--	--	--	Focused		--
Total no. of patients	183	489	135	200	256	147	622	187	53	182	53	106	15
Total no. of deaths	18	119	25	95	88	68	55	91	13	23	25	45	11
Source of data*	DC	DC	DC+MR	DC+MR	MR	DC	MR	DC	DC	DC+MR	DC		DC
Cardiovascular	50	52.9	40	42	28.4	42.6	47.3	38.5	46.2	21.7	28	30	54.5
Cancer	38.8	8.4	12	21	14.8	23.5	30.9	13.2	30.8	8.7	28	25	--
Renal	--	--	4	4	4.5	1.5	5.5	--	--	17.4	4	--	--
Respiratory	--	--	4	15	--	1.5	10.9	--	--	--	12	5	--
Infection	5.5	--	8	1.1	7.9	8.8	1.8	7.7	23.1	21.7	24	30	27.3
Gastrointestinal	--	--	8	5	8	--	--	--	--	4.3	--	5	--
Sudden death	--	--	--	--	--	2.9	--	3.3	--	--	--	--	--
Accidents or intoxication	5.5	--	8	2	--	--	--	4.4	--	4.3	--	--	--
Musculoskeletal diseases	--	--	4	5	--	16.7	--	--	--	--	--	--	--
Other	--	38.7	12	4	35.2	2.5	3.6	33.3	--	21.7	4	5	18.2

*DCM: death certificates; MR: medical records.

Table IVd. 2002-2008: Percentage of various acute attributed causes of death in rheumatoid arthritis.

	Doran *et al.* 2002	Bjornadal *et al.* 2002	Mikuls *et al.* 2002	Peltomaa *et al.* 2002	Goodson *et al.* 2002	Thomas *et al.* 2003	Minaur *et al.* 2004	Book *et al.* 2005	Goodson *et al.* 2005	Hakoda *et al.* 2005	Carmona *et al.* 2007		Young *et al.* 2007	Mattey *et al.* 2007	Nikolaisen *et al.* 2008
Ref. no.	(83)	(92)	(93)	(94)	(95)	(101)	(11)	(111)	(112)	(113)	(116)		(121)	(122)	(124)
Specialized or Population study?	Population	Population	Population	--	--	Population	--	--	Focused	--	--		Focused	Focused	Focused
Total no. of patients	609	46917	158	150	575	20875	100	152	1010	91	789	789	1429	767	111
Total no. of deaths	334	25353	30	24	84	158	84	111	470	83	20	75	459	186	20
Source of data*	DC	DC	DC	DC+MR	DC	DC	MR	DC	DC	DC	DC		DC	DC	MR
Cardiovascular	46.8	50.6	32	41.7	38.1	45.2	45.2	45.9	46.8	34.9	35	22.7	41	37.1	20
Cancer	10.3	12	28.6	33.3	32	14.3	14.3	8.1	18.7	14.5	15	17.3	24	24.7	5
Renal	--	3.2	--	--	--	2.8	2.8	--	--	2.4	--	--	2	2.2	--
Respiratory	10	4.2	--	8.3	11.9	15.7	15.7	--	16.4	15.7	--	--	22	13.4	--
Infection	15.2	7.4	7.1	12.5	--	1.1	1.1	18.9	--	4.8	35	18.7	5	15.6	20
Gastrointestinal	--	5.6	--	--	--	5.4	5.4	--	--	6	--	--	3	4.3	--
Sudden death	--	--	--	--	--										
Accidents or intoxication	--	2.4	--	--	--	--	--	--	--	--	--	--	--	--	--
Musculoskeletal diseases	--	11	--	4.2	--	8.8	8.8	--	--		--	--	--	--	--
Other	17.6	3.6	32.1	--	18	6.3	6.3	26.1	18.1	21.7	--	18.7	3	2.7	55

*DC: death certificates; MR: medical records.

Table V. Summary of causes of death – Percentages of death due to various causes according to period and type of study.

	1953-1989	1990-2000	2001-2008	Specialized studies	Population studies	Total*	U.S. Averages 1977	U.S. Averages 2005
No. of reports (cohorts)	14 (14)	9 (9)	10 (11)	10 (13)	7 (7)	50 (54)	--	--
Total no. of patients	5696	5986	3083	6163	70690	91618	--	--
Total no. of deaths	1779	1589	619	2039	27224	33250	--	--
Cardiovascular	39.6	46.7	38.6	33.5	43.5	39.6	41.0	38.3†
Cancer	13.4	19.8	18.7	17.1	16.3	16.8	20.4	22.8
Renal	8.3	3.2	7.5	4.8	4.3	5.8	1.1	1.8
Respiratory	7.2	6.5	12.9	11.8	7.8	9.0	3.9	5.3
Infection	18.5	6.5	17.1	17.0	5.8	14.3	1.0	4.4
Gastrointestinal	5.1	5.8	5.2	4.2	5.8	5.1	2.4	1.1
Sudden Death	--	2.9	3.3	0.0	--	3.1	--	--
Accidents or intoxication	1.5	5.4	4.4	6.3	5.2	4.2	5.4	6.9
RA/Musculoskeletal diseases	12.9	8.3	6.5	4.1	9.2	9.4	--	--
Other	8.9	9.5	20.5	13.0	14.4	12.9	24.8	21.4

* The total of these percentages exceeds 100%, as each value is based on the mean of percentage of deaths attributed to each cause in each of the 50 reports, so as to weight all studies equally, rather than to weight studies according to the number of included patients.
† includes cerebrovascular and diabetes.
US averages 1977 from Vital statistics of the United States 1977 (127).
US averages 2005 from CDC/NCHS National Vital Statistics System (http://www.cdc.gov/nchs/data/dvs/LCWK9_2005.pdf).

is not simply a random event in people with RA, and secondary to drug toxicities in only 2% of patients.

Predictive markers for mortality were reported for 53 of the 84 cohorts, and may be classified in 4 categories: *a)* non-modifiable variables, including demographic variables (age, sex, socioeconomic status), duration of disease, and major histocompatibility and other genes; *b)* traditional clinical measures, including joint counts, radiographs, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor and disease activity score (DAS); *c)* modifiable functional and global measures, including physical functional assessed by performance measures, physical function assessed by patient questionnaires, physician global estimate of status, and patient global estimate of status; *d)* other potentially modifiable measures not specific to RA but important for outcomes, including extra-articular disease, comorbidities, pain, psychological status, and body mass index.

The observation that poor clinical status according to all these variables predicts a higher risk of mortality may be viewed as essentially confirming a rather trivial truism: that people who have more severe illness are more likely to die. At the same time, description of "severe illness" according to quantitative measures rather than clinical impressions would appear a real advance to better estimate mortality risk, and determine whether improvements in these measures toward normal values are associated with improved long-term survival. Furthermore, long-term observational studies could be performed to recognize possible target values for prognostic variables, which may not require complete remission toward favorable mortality outcomes.

Analyses of predictive markers for premature mortality in RA in various reports are described according to the number of reports in which each is included. Obviously, it is not possible to assess a measure as a possible risk factor for mortality if baseline data concerning the variable are not available or reported. The estimates presented may not be entirely accurate, as certain variables might not have been reported, either because they were presumed significant in the prognosis of mortality (*e.g.*, age, male sex) or as they were found not significant in the prognosis of mortality. Nevertheless, a "best effort" to compile available data appears informative.

Possible risk factors for premature mortality in RA are further classified into 5 categories (Table VI): reported as not statistically significant (although poorer status usually indicated a greater risk for mortality); statistically significant only in univariate analyses, without report of multivariate analyses, generally prior to 1985-1990; statistically significant only in univariate analyses, but not significant in multivariate analyses which include other possible predictive markers in addition to age and sex; statistically significant in both univariate and multivariate analyses that did not include a functional status questionnaire; statistically significant in both univariate and multivariate analyses that included a functional status questionnaire. The rationale for these categories of statistical significance includes that multivariate analyses of mortality in RA were not reported until the mid-1980s (31, 32, 38, 41), so it is not possible to assess whether variables might be significant in such analyses in earlier reports. Furthermore, the highest level of significance in the prognosis of mortality in RA in most studies is physical function on a patient questionnaire (Fig. 2); therefore, studies were classified regarding whether or not a measure of physical function was included.

Non-modifiable risk factors for mortality

Age. Age was a statistically significant predictor of mortality in all 33 cohorts in which it was reported, including in 27 multivariate analyses, 15 of which included a functional status questionnaire (Table VI). As noted above, absolute mortality rates are almost invariably greater in older people, whereas relative mortality rates are generally greater in younger people.

Sex. Male sex was a significant predictor of mortality in 27 of 30 studies, including 19 multivariate analyses, 10 of which included a functional status questionnaire (Table VI). The absolute and relative mortality rates differ in two groups – absolute mortality rates are higher in males, but relative mortality rates are higher in females, in whom absolute mortality rates in the general population are lower than in males.

Socioeconomic status. A measure of socioeconomic status was included in 13 reports as a possible predictor of mortality, primarily formal education level in the U.S. and the Carstairs index of social deprivation in the U.K. (204). In 10 of these analyses, socioeconomic status was a significant predictor of mortality in univariate analyses, including 4 in which this measure was also significant in multivariate analyses that included a functional status questionnaire (Table VI) (Fig. 2). These data suggest that an indicator of socioeconomic status might be included in all long-term databases to better characterize prediction of mortality and other clinical outcomes in RA. Socioeconomic status is an important indicator of clinical status, not only in RA and other rheumatic diseases (189), but also in most diseases, as discussed elsewhere in this Supplement (205).

Duration of disease. Duration of disease was a significant predictor of mortality in 9 of 21 reports, including only 1 in multivariate analyses (107) (Table VI). In many reports, the prognostic significance of duration of disease for mortality is explained by age, since individuals with longer duration tend to be older. These findings are consistent with different rates of disease progression in different individual patients, as duration of disease is often correlated only weakly with measures of clinical status, other than radiographic scores, which present cumulative, irreversible damage (206).

Major histocompatibility locus – shared epitope. The major histocompatibility locus was analyzed as a possible predictor of mortality in 5 cohorts, and indicated a significantly higher risk of mortality in 3 reports, one in univariate analysis where multivariate analysis was not reported (120), one in univariate but not multivariate analyses (122), and one in both univariate and multivariate analyses (97) (Table VI). In one report, there was not a significant increase in mortality in the entire cohort compared to the general population (74). In a second cohort, HLA DR4 was not a significant predictor of mortality, though HLA B27, curiously, predicted both cardiovascular events and mortality (71).

Gonzalez-Gay (120) found increased risk of cardiovascular mortality according to the HLA shared epitopes 04 and 0404; 0404 was also prognostic of increased cardiovascular events. Information concerning overall mortality in the cohort from causes other than cardiovascular disease was not presented. In multivariate analyses, CRP and ESR also were significant, but not rheumatoid factor. These regressions did not include any of the other Core Data Set measures based on a joint count or patient questionnaire.

In the Norfolk Arthritis Register (NOAR) early arthritis cohort, significant risk of mortality was seen in individuals with 2 copies of the shared epitope alleles, particularly 0101/0401, compared to individuals with one copy or no copies of the shared epitope alleles. Again, rheumatoid factor was found to add to the risk in individuals who did not have shared epitope, but not anti-CCP (97).

In 767 patients in the Early RA Study (ERAS) cohort recruited in 1987, the genotypes 0101/0401 and 0404/0404, which were found in 37 (4.8%) and 10 (1.3%) of 767 patients in the entire cohort, were significant predictors of ischemic heart disease (122). HLA DR4 was not predictive of mortality for the entire cohort, but the higher risk of mortality from ischemic heart disease is similar to 2 of the other studies (97, 120).

HLA DR4 may serve as a marker for progressive RA versus self-limited polyarthritis in inception cohorts. Early studies indicated that HLA haplotype, rheumatoid factor, ESR, and radiographic changes were associated with one another at higher levels than with joint count or patient questionnaire measures (207), and similar associations have been described in many studies (208, 209) (Fig. 3). Although this cluster of measures may appear the more substantial measures in RA, including for the prognosis of mortality, the patient questionnaire measures generally have greater significance to predict mortality. Nonetheless, these studies may provide important long-term clues concerning mechanisms of cardiovascular comorbidity and mortality in patients with RA.

Traditional measures of RA clinical status as predictors of mortality

Joint count. Swollen and tender joint counts were reported in 18 cohorts, and were statistically significant in the prediction of mortality in 9 (50%) (Table VI) (Fig. 2), including 5 (38%) in univariate analyses only (without multivariate analyses), and 4 (22%) in multivariate analyses, 3 of which included a functional status questionnaire. In 2 additional studies (61, 100), the swollen and tender joint count were not significant in prediction of mortality, while joint count data concerning deformity or limited motion were significant in univariate but not multivariate analyses. These data suggest that it may be desirable for long-term longitudinal analyses to assess joints at baseline not only for tenderness and swelling, but also for deformity or limited motion (210). A swollen and tender joint count may not be sufficient for long-term studies, as swollen joints may improve over 5-6 years, while joint deformity and radiographic changes may progress (211). One study suggested that large joints appeared far more significant in the prognosis of mortality than small joints, and a reduced "joint count" including only 6 joints – shoulders, hips and knees – was as informative to identify the likelihood

Table VI. Numbers of possible predictive markers of mortality classified into 5 categories according to non-significance and significance in univariate and multivariate analyses.

Variable, number of studies that report this variable	Not Significant	Significant in univariate analysis		Significant in univariate and multivariate analyses	
		No multivariate analysis available	NOT significant in multivariate analysis	No functional status questionnaires	Functional status questionnaires INCLUDED
Age, 33	0	5 (36;45;64;79;113)	1 (55)	12 (38;42;47;48;63;66; 68;69;71;74;76;85)	15 (33;41;46;58;61;70; 90;94;95;100;102; 105;109;121;123)
Sex, 30	3 (6;80;113)	4 (14;25;36;79),	4 (33;55;68;100)	9 (38;47;48;63;66; 71; 74;81;85)	10 (41;46;58;90;94;102; 105;109;121;123)
Disease duration, 21	12 (33;38; 47;58;64;75; 87;90;94;94;109;118)	2 (36;45)	6 (41;46;48;61;100;111)	0	1 (107)
Major Histocompatibility Locus, 5	2 (71;74)	1 (120)	1 (122)	1 (97)	0
Socioeconomic Status, 13	3 (44;46;64)	0	6 (61;68;70;71;90;100)	0	4 (33;48;58;121)
Swollen and Tender Joint Count, 18	9 (10;61; 62;64;66;76; 80;100;121)	0	5 (33;42;46;102;111)	1 (38)	3 (48;94;105)
Deformity or Limited Motion Joint Count, 2	0	0	2 (61;100)	0	0
Radiographs, 18	7 (22;32;38; 61;64; 66; 120)	1 (3)	8 (48;76;80;87;94; 111; 113;121)	1 (55)	1 (102)
ESR, 19	6 (10;42;64; 66;76;80)	2 (3;120)	4 (61;94;113;123)	4 (71;87;111;114)	3 (48;102;121)
Rheumatoid Factor, 29	10 (10;61;64; 66;75; 94; 100;110-112)	2 (25;45)	4 (68;74;113;121)	8 (38;47;55;69;76; 80; 85;93)	5 (48;95;102;106;109)
DAS, 3	0	0	2 (76;121)	0	1 (96)
Function: Physical Measure, 6	0	1 (64)	5 (33;48;61;102;121)	0	0
Function: Questionnaire, 18	1 (95)	1 (64)	3 (70;94;100)	NA	13 (32;41;46;48;58;61; 90;96;102;105; 109; 118;121)
MD Global, 10	0	4 (3;6;22;25)	3 (61;100;121)	2 (38;111)	1(48)
Patient Global, 6	0	0	3 (46;61;111)	2 (43;44)	1 (118)
Extra-articular Disease, 18	3 (6;22;120)	3 (12;29;64)	4 (38;94;107;121)	5 (42;43;76;87;123)	3 (48;95;102)
Co-morbidities, 23	1 (46)	3 (19;44;64)	4 (33;38;94;111)	8 (47;63;69;71;87; 93; 100;114)	7 (48;61;90;107;109; 118;121)
Pain, 6	4 (44;61;76; 90)	0	1 (46)	0	1 (118)
Psychological Status, 5	2 (44;61)	0	1 (113)	0	2 (58;102)
Body Mass Index, 2	0	0	2 (86;114)	0	0
Glucorticoids, 11	2 (26;118)	2 (22;46)	3 (105;111;121)	2 (71;84)	2 (31;48)

of mortality as a complete joint count (33).

Radiographs. Radiographs were significant predictors of mortality in 11 (61%) of 18 reported cohorts, including 9 in univariate analysis and 2 in multivariate analyses, one of which included a patient questionnaire (102) (Table VI) (Fig. 2). This was a large study of 1387 patients from the Wichita Arthritis Center, illustrating that most available baseline indicators of severe disease status are significant predictors of mortality in univariate as well as multivariate analyses in large databases, but not in smaller databases. All published analyses of radiographs in the prediction of mortality are based on hand joints, which explain in part the lower significance than other variables, including physical function questionnaires, in the prognosis of mortality.

Erythrocyte sedimentation rate. ESR was a significant predictor of mortality in 13 (68%) of 19 reported cohorts, including 7 in multivariate analyses, 3 of which also included a functional status

questionnaire (Table VI) (Fig. 2). This finding may reflect the fact that ESR has been found to be normal at presentation in 40% of patients with RA (174). Furthermore, a similar proportion of patients with normal or abnormal ESR were treated with methotrexate or biological agents (Sokka and Pincus, unpublished data). A high ESR may identify patients with a likelihood of progressive RA versus self-limited inflammatory polyarthritis in inception cohorts.

Rheumatoid factor. Rheumatoid factor was a significant predictor of mortality in 19 (66%) of 29 reported cohorts, 6 in univariate analysis only, and 13 in multivariate analyses, 5 of which also included a functional status questionnaire (Table VI) (Fig. 2). These 5 cohorts included 2 very large databases (48, 102), and 2 inception cohorts (95, 109) in which rheumatoid factor may serve to identify a higher likelihood of progressive RA versus self-limited polyarthritis.

The relatively limited significance of rheumatoid factor as a predictor of mortality may be unexpected by most rheumatologists, as textbooks have emphasized for many years that seropositive individuals have more severe disease than individuals who are not seropositive. Rheumatoid factor does serve as a marker for progressive RA versus self-limited inflammatory polyarthritis which may even meet classification criteria for RA, as discussed above, and may be a more significant predictor in inception cohorts versus cohorts of established patients. As noted above, HLA haplotype, rheumatoid factor, ESR, CRP and radiographs tend to be associated with one another more than with patient and joint count measures (Fig. 3), while the latter measures tend to be more significant predictors of mortality (207).

Disease activity score (DAS). A DAS28 was included in only 3 cohorts, all after 2000, and was a significant predictor of mortality in univariate but not multivariate analyses in 2 reports, and significant in multivariate analysis that included a functional status questionnaire in 1 report (96) (Table VI). This was an inception cohort in which DAS28 may also have served in part as a marker of progressive rather than self-limited disease (96).

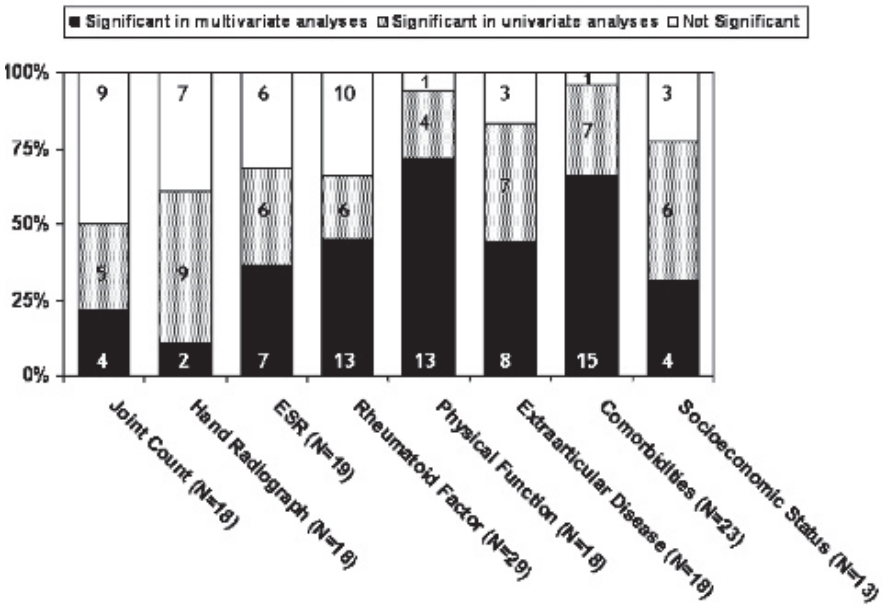

Fig. 2. Significance of 8 variables as possible predictors of mortality. Bars indicate, for each variable, percentage of reports that included the variable in which it was significant in multivariate analyses (black), significant in univariate analyses (gray), or not significant (white).

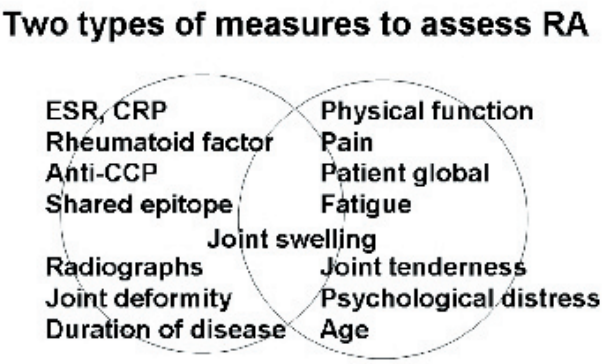

Fig. 3. Two types of measures to assess RA. Almost all measures are correlated significantly in most cohorts. ESR, CRP, rheumatoid factor, anti-CCP and shared epitope in the left circle are correlated at higher levels with one another and with radiographic changes, joint deformity and duration of disease than with swollen joint count, and at even lower levels with measures in the right circle. Measures in the right circle are correlated with one another at higher levels than with swollen joint count, and at even lower levels with measures in the left circle. The left cluster of measures is more important in pathogenesis of RA, while physical function on a patient questionnaire generally has greater significance to predict severe outcomes, including work disability and mortality.

Physical function and global measures

Physical function assessed by performance measures. A measure of physical performance was a significant predictor of mortality in univariate analyses in all 6 reported cohorts, but not significant in any multivariate analyses (Table VI). Specific cutpoints for physical measures of grip strength, walking time and button test were identified to recognize levels of survival over 5, 10 or 15 years (33). The rheumatology community has largely abandoned the use of these measures in clinical research and clinical care, possibly because of a perception that they are poorly reliable. However, they may be quite reliable when performed according to a standard protocol (212, 213). Furthermore, these measures overcome cultural limitations of patient questionnaires.

Physician global estimate of status. Physician global estimate of status was recognized initially in 1981 by Rasker

and Cosh as a predictor of mortality (6), and was significant in all 10 cohorts reported, 7 in univariate analyses, 4 of which had no available multivariate analyses, and in 3 multivariate analyses, one of which included a functional status questionnaire. American Rheumatism Association (ARA) functional class, the primary physician global estimate reported prior to 2000, measured one year after baseline, had greater significance in the prediction of mortality than the baseline value (6).

Patient global estimate of status. Patient global estimate of status was a significant predictor of mortality in all 6 cohorts in which it was reported, including 3 in univariate analyses only, and 3 in multivariate analyses, one of which included a functional status questionnaire. These data indicate that global measures are quite robust, as these measures also were the most significant of all RA Core Data Set measures (153) to distinguish active from placebo treatment in several randomized controlled clinical trials (214, 215).

Physical function assessed by patient questionnaires. A functional status questionnaire, generally a health assessment questionnaire (HAQ) or multidimensional HAQ (MDHAQ), was a significant predictor of mortality in 17 of 18 reports, including 4 in univariate analyses only (1 with no available multivariate analyses and 3 which included multivariate analyses) and 13 in multivariate analyses (Table VI) (Fig. 2). The one study in which a functional status questionnaire was not a significant predictor (95) was an inception cohort in which rheumatoid factor had the highest level of significance to predict mortality, possibly in part as a marker to identify individuals with progressive RA versus self-limited disease.

Several reports have documented that patient HAQ score at 1 year is substantially more prognostic of mortality than the baseline HAQ (96, 121), similar to observations of global status estimates. It is possible that similar observations might be seen for swollen joints, ESR, or other modifiable measures of clinical status. The data indicate the value of ongoing periodic quantitative assessment of patient status.

Other variables that may be significant in the prognosis of mortality

Extra-articular disease. Extra-articular disease was reported as a significant predictor of mortality in 15 (83%) of 18 cohorts (Table VI) (Fig. 2), including 7 in univariate analyses, 3 of which did not include multivariate analyses, 4 in which it was not significant in multivariate analyses, and 8 in multivariate analyses, 3 of which included functional status questionnaires. Extra-articular disease provides an important marker for severity of RA.

Comorbidities. Comorbidities were significant in 22 of 23 cohorts in which a comorbidity variable was reported (Table VI) (Fig. 2), 7 in univariate analyses, 3 of which did not have multivariate analyses available, and 15 in multivariate analyses, 7 of which included a functional status questionnaire. Comorbidities appear comparable to functional status and global measures as highly significant predictors of mortality in patients with RA.

Pain. Pain was included in 6 cohorts, and curiously was a significant predictor of mortality in only 2 studies, including one in univariate but not multivariate analysis (46), and one in multivariate analysis, which included a functional status questionnaire (118) (Table VI). In one report, patients who died had somewhat lower, not significant, pain scores than those who survived (61). A pain score appears far less prognostic of mortality than a physical function score, possibly reflecting patients with RA and concomitant fibromyalgia, seen in 20-30% of RA patients (216).

Body mass index. Two recent reports (86, 114) indicate a very interesting observation that a low body mass index was curiously found to be a significant risk factor for mortality in RA patients, unlike in the general population. This observation may be interpreted that cachexia serves as a marker of severe RA.

TNF receptors. In a cohort of 401 patients with RA seen initially between 1993 and 1998 at Staffordshire, England, circulating levels of tumor necrosis factor (TNF) receptors predicted mortality significantly (123). The soluble TNF receptor 1 was a significant predictor of mortality in multivariate analyses adjusted for age, sex, disease duration, ESR, CRP, rheumatoid factor, nodules, MHAQ score, and smoking. These data may be interpreted to suggest that anti-TNF therapies may reduce overall mortality in RA, as documented in recent reports presented below.

Complexities in analyses. Complexities in analyses of risk factors for premature mortality (Table VII) include:

a) *Only variables that are included can be analyzed*. It is axiomatic that variables that are not available cannot be analyzed as potential risk factors for premature mortality. For example, if a patient questionnaire score for physical function or marker of socioeconomic status is not included in a baseline database, it could not be assessed as a possible independent variable in mortality outcomes. The available data suggest that the four most important variables for prediction of mortality are age, sex, comorbidities, and functional status, all of which should be included in long-term longitudinal databases to analyze mortality in RA.

b) *Absolute risk versus relative risk may differ substantially.* As noted above, the absolute risk of mortality is greater for males and older individuals, but the relative risk is higher for females in younger individuals. Therefore, different reports might suggest that males versus females or younger versus older people might have better or worse outcomes without specifying how these outcomes are defined.

5) Therapies and mortality in RA

Nonsteroidal anti-inflammatory drugs (NSAIDs). Among 1666 Finnish patients with RA who died in 1989, NSAIDs contributed to 30 deaths (1.8%), while disease-modifying antirheumatic drugs (DMARDs) contributed to only 6 deaths (0.3%) (217). Therefore, more severe disease was the primary basis for premature mortality over the subsequent 5-20 years, but treatments did account for 2% of deaths.

Glucocorticoids. Glucocorticoids have been reported as a predictor of mortality in 9 (82%) of 11 cohorts, including

2 in univariate analyses with no available multivariate analyses (22, 46), 3 in univariate but not multivariate analyses (105, 111, 121), and 4 in multivariate analyses (31, 48, 71, 84), 2 of which included functional status questionnaires (31, 48). There is relatively little information concerning the dose of glucocorticoids, and one interpretation of the data is that glucocorticoid use is a marker for more severe clinical status. In one study (71), early glucocorticoid treatment was a significant predictor of mortality in multivariate analyses, while long-term treatment was associated with reduced risk of mortality. Most of the glucocorticoid use prior to the mid-1990s regarded "low-dose" as 10 mg/day, whereas at this time many suggest that low-dose involves 5 mg/day or even less with relatively little toxicity (218-220).

Gold salts. Lehtinen and Isomaki reported improvement in mortality outcomes associated with the use of therapeutic gold salts in 1991 (45), echoing previous observations indicating that morbidity, including radiographic progression, was favorably affected by intramuscular gold salts (221). Although gold salts have been supplanted largely by methotrexate, sulfasalazine, hydroxychloroquine, and biologic agents, this study established a principle that control of inflammation by any agent might be associated with better mortality outcomes.

Methotrexate. Krause, Herborn, Rau and colleagues (72) reported in 2000 that patients who responded to methotrexate had substantially lower mortality than patients who did not respond to methotrexate. Choi, Wolfe and colleagues (91) reported in 2002 that methotrexate treatment results in improved survival for patients with RA, based on a sophisticated statistical model that adjusted for confounding by indication, *i.e.*, that patients with more severe disease were more likely to receive methotrexate. As noted, long-term clinical trials cannot be performed in patients with RA (199), and those data are encouraging that reduction of premature mortality in RA is possible.

Biologic agents. Carmona *et al*. reported a standard mortality ratio of 0.32 in 4,459 patients treated with anti-TNF agents in Spain compared to a control cohort of 789 RA patients (116). SMR were 0.58 for cardiovascular events, 0.52 for infection, and 0.36 for cancer-related deaths – although confidence intervals crossed one, due to small numbers of patients. The authors concluded that morbidity (other than infection) and mortality (including infection) were lower in patients treated with anti-TNF antagonists than in a standard observational cohort of RA patients. Jacobsson *et al*. (118) reported a hazard ratio for mortality of 0.65 for patients treated with anti-TNF agents, compared to those not treated, adjusted for age, sex, disability and baseline comorbidity, significant in women but not in men. Taken together, these reports suggest improved mortality outcomes associated with anti-TNF therapies, but require confirmation in other sites over longer periods.

Table VII. LIMITATIONS: Complexities in the analysis of mortality in rheumatoid arthritis (and possibly other rheumatic diseases).

1. Mortality rates
   a) No "gold standard" for diagnosis.
   b) Self-limited early inflammatory arthritis included in early RA cohorts.
   c) Patient characteristics vary considerably in different cohorts.
   d) Different reference mortality rates.
   e) Changing natural history of RA.
   f) Period of observation.
   g) Limited resources for study.
   h) Absence of long-term clinical trials.
   i) Numbers used to describe risk.
2. Causes of death
   a) Source of information – death certificate or medical record.
   b) Underestimation of RA as associated with premature mortality.
   c) Differences in reporting in different series.
3. Markers for premature mortality
   a) Only variables that are included can be analyzed.
   b) Absolute risk versus relative risk may differ substantially.
4. Possible favorable benefits of therapies on mortality rates
   a) No long-term randomized controlled clinical trials.
   b) Mortality is a "lagging indicator".
   c) Similarity of disease effects and adverse events.

Complexities in analyses. Complexities in analyses of therapies in premature mortality of RA (Table VII) include:

a) No long-term randomized controlled clinical trials. As discussed above, it is not possible to conduct long-term randomized controlled clinical trials in symptomatic diseases such as RA. Reliance on long-term databases is always affected by "confounding by indication," *i.e.*, patients with more severe disease are more likely to be treated more aggressively, leaving greater risks of therapies. For example, associations of higher mortality rates with glucocorticoids may be explained in part by glucocorticoids being a marker for more severe disease.

b) Mortality is a "lagging indicator." Mortality outcomes are seen at least 3-10 years after baseline. Therefore, a study of mortality at this time may include many patients treated prior to the biological era. Studies focused only on patients who receive biological therapy suggest better mortality outcomes, but longer observations are needed. Possible advances may require years for documentation.

c) Similarity of disease effects and adverse events. Infections are increased significantly in people with RA, but also may be a serious adverse event of therapy with biological agents. Therefore, a higher level of infection in people treated with biological agents might reflect higher disease severity and/or an adverse event associated with the therapy. Without a randomized trial it may be difficult to sort this out. Higher mortality rates from infection in people who take biological therapies may nonetheless be lower than expected in people with severe disease.

Conclusions

Analysis of mortality in RA over the past 60 years has provided considerable impetus to recognition of RA as a serious chronic disease. Certain complexities, including the absence of a "gold standard" for diagnosis, patient heterogeneity, and limited resources, have complicated analyses of mortality. The causes of death overall are similar to those in the general population, with earlier cardiovascular disease and a higher level of infection, pulmonary, gastrointestinal and renal disease. Increased mortality rates can be recognized only with long-term longitudinal data for comparison with the general population. All clinical markers that indicate more severe clinical status are associated with a higher risk of death. The highest levels of prognostic significance are seen for higher age, male sex, poorer functional status, and comorbidities. Several reports suggest improved mortality outcomes associated with effective therapies, but these remain to be confirmed in longitudinal analyses.

In a presidential address to the U.K. Royal College of Physicians in 1963 (2), Reah commented on his earlier impression of RA as a mild disease: *"I now believe that my earlier impression was based on patients, certainly impressive when we see them, who do remain otherwise well for many years …. Those who develop other disorders or become more or less completely incapacitated no longer come to our clinics and they are thus forgotten unless we keep in touch with them…I cannot now fully agree with the folk lore of America nor with the opinion that rheumatism is a good healthy complaint. It may be, however, that from the study of groups of patients for many years and observations on the natural history of the disease, with its remissions and exacerbations, inevitably modified by therapy, there may yet be derived knowledge of its causation and its more effective treatment*."

Dr. Reah's recognition of comorbidities and poor function as primary predictors of mortality, and his hope that longitudinal data will lead to improved outcomes, remain as valid today as 45 years ago. Further research might focus more on target values associated with a favorable prognosis, rather than regressions to determine the statistical significance of a variable in the prognosis of mortality. In clinical settings, it might be considerably more informative to know whether a specific number of swollen joints, or a specific HAQ or MDHAQ score, might be associated with similar levels of survival as no swollen joints, or HAQ or MDHAQ scores of 0, or that DAS28 levels of 3.2, CDAI levels of 10, or RAPID3 levels of 2 (on a 0-10 scale), might be associated with mortality outcomes comparable to entirely normal values. Such data would provide clinicians with targets for therapy based on prevention of mortality.

All rheumatology sites are encouraged to develop clinical databases, remembering that a clinical tool which calculates and records disease activity variables only, or an electronic medical record with lengthy texts but no option to analyze collected material, is not a database for long-term longitudinal observations. A database is required to analyze mortality outcomes, causes of death, comparison with the general population, and risk factors for mortality. Further studies of these matters should lead to improved outcomes for people with RA.

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