Early intensive treatment normalises excess mortality in ACPA-negative RA but not in ACPA-positive RA

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With great interest, we read the recently published report by Poppelaars *et al* in which no excess mortality was observed in 155 patients with rheumatoid arthritis (RA) from the COmbinatie therapie Bij Rheumatoide Artritis (COBRA)-trial, who received early intensive treatment, compared with the general population (Standardised mortality rate (SMR) 0.80 (0.59–1.06)).[1] The question whether mortality in RA has normalised is debated, as contradicting results have been published.[2–8] In many of the studies on mortality, two important factors are not sufficiently taken into account: follow-up duration and disease subtypes. This might explain the conflicting results. Because thus far none of the reported studies incorporated both factors in the analyses, it is too soon to conclude that mortality is 'normal' again, as we will show here.

We compliment the authors on emphasising the importance of a long follow-up duration by showing in their meta-analysis that excess mortality in RA becomes fully apparent after >10 years. This implies that previous studies that reported on normalisation of mortality had insufficient follow-up to reach this conclusion.[2–5] Some studies with a short follow-up duration even showed a seemingly decreased mortality in RA, which may be due to a healthy inclusion bias.[3–5]

RA consists of two subtypes that are characterised by the presence or absence of RA-related autoantibodies, of which the presence of anti-citrullinated protein antibodies (ACPA) is most specific for RA. Both subtypes have known differences in the severity of the disease course. The study of Poppelaars *et al* did not stratify for ACPA, which is due to a small sample size (n=155), leaving the question unanswered if mortality has normalised in both subsets of RA.

To assess the true impact of early intensive treatment on mortality, we performed a large study with up to 25 years of follow-up and sufficient power to stratify for ACPA. One thousand two hundred and eighty-eight patients with RA fulfilling the 1987 criteria, who were consecutively included in the Leiden Early Arthritis Clinic, were studied. According to treatment in routine care, patients included between 1993 and 2000 received initial treatment with only non-steroidal anti-inflammatory drugs or mild disease-modifying antirheumatic drugs (eg, penicillamine, gold, hydroxychloroquine). Patients included between 2001 and 2016 were treated with early intensive treatment with methotrexate as first-line treatment. Treat-to-target became routine during this period as well. Mortality data were obtained from the civic registries on 1 June 2018. Mortality was compared with the general population in the Netherlands with SMRs adjusted for birth year, gender and calendar year. SMRs were determined for both treatment strategies, after stratification for follow-up duration (0–5 years, 5–10 years, >10 years) and disease subset (ACPA status).

Table 1 Baseline characteristics of patients with RA treated without and with early intensive treatment

	No early intensive treatment	Early intensive treatment
	(n=353)	(n=945)
Inclusion period	1993–2000	2001–2016
Women, n (%)	238 (67)	620 (66)
Age in years, mean (SD)	56 (16)	58 (15)
Symptom duration, days median (IQR)	136 (75–279)	117 (58–234)
Current smoker, n (%)	98 (30)	211 (25)
ESR, median (IQR)	37 (21–58)	29 (14–45)
66-SJC, median (IQR)	10 (5–16)	6 (3–11)
RF-positive, n (%)	193 (55)	543 (59)
ACPA-positive, n (%)	199 (56)	456 (51)

ACPA, anti-citrullinated peptide antibody; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SJC, swollen joint count.

Baseline characteristics are shown in table 1. Two hundred and forty-eight patients died during follow-up. SMRs increased during follow-up and excess mortality became evident after 10 years of disease (0–5 years SMR 0.55 (0.41–0.73); 5–10 years 1.08 (0.87–1.33) and >10 years 1.39 (1.15–1.66); figure 1A). Stratification for disease subset revealed that a decreased mortality was observed within ACPA-negative RA (SMR 0.80 (0.67–0.96)) and an increased mortality within ACPA-positivity

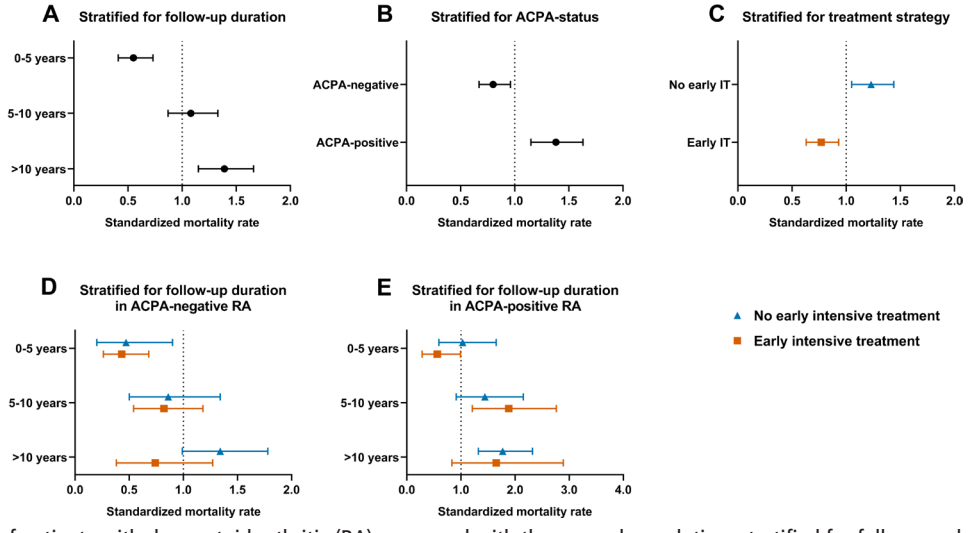

Figure 1 Mortality of patients with rheumatoid arthritis (RA) compared with the general population, stratified for follow-up duration (A), disease subset characterised by anticitrullinated protein antibody (ACPA) status (B), early intensive treatment (IT) (C) and these variables combined (D and E), showing that excess mortality has normalised by early intensive treatment in ACPA-negative RA but not in ACPA-positive RA.

RA (SMR 1.38 (1.15–1.63); figure 1B). Comparing the two treatment strategies without considering follow-up duration and ACPA status revealed that early intensive treatment was associated with a decrease in mortality compared with the general population (SMR 0.77 (0.63–0.93)), in contrast to group without early intensive treatment (SMR 1.23 (1.05–1.44); figure 1C). This is concordance with the findings from Poppelaars *et al*. Subsequent stratification for follow-up duration and ACPA-status showed that excess mortality became apparent after 10 years of disease in ACPA-negative RA without early intensive treatment and that early intensive treatment had normalised this excess mortality. In ACPA-positive RA, in contrast, excess mortality emerged after 5 years of follow-up and was not influenced by early intensive treatment.

In conclusion, sufficient follow-up duration and stratification for relevant disease subsets are important to disentangle the effects of treatment on mortality. Our data from a large cohort of patients with RA with up to 25 years follow-up showed that excess mortality has resolved since the introduction of early intensive treatment in ACPA-negative RA, but excess mortality remains an issue in ACPA-positive RA. This underlines that RA consists of two types with differences in treatment response and long-term outcome and that additional efforts are still needed to reduce the increased risk of early death in ACPA-positive RA.

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