Differences and similarities of autoantibody-positive and autoantibody-negative rheumatoid arthritis during the disease course: on our way to personalized medicine

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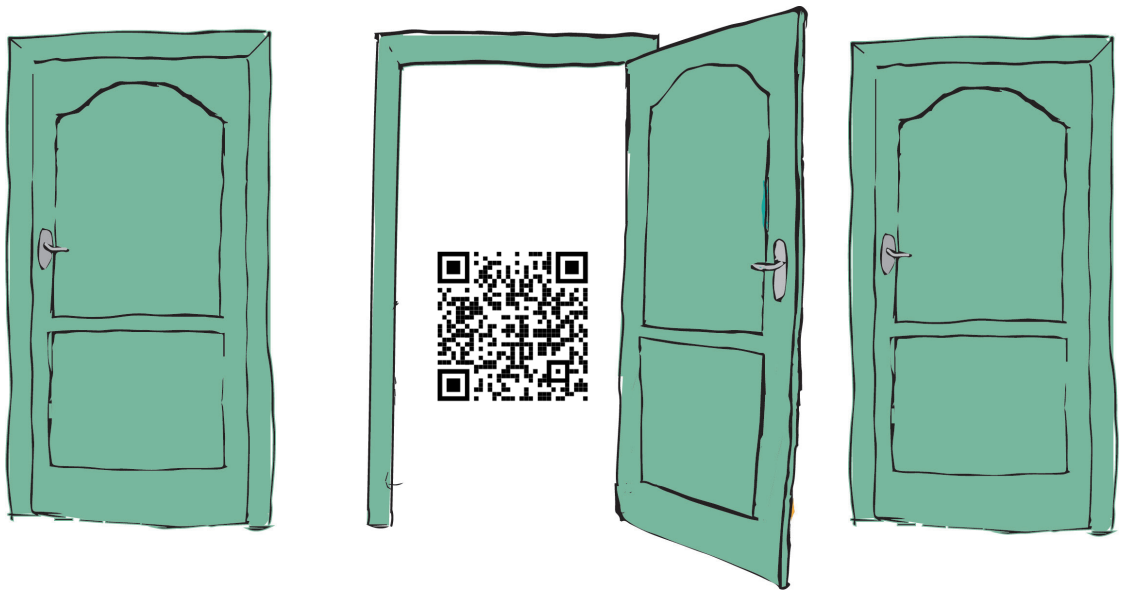

CHAPTER 8

Early intensive treatment normalizes 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 rheumatoid arthritis (RA) patients from the COBRA-trial, who received early intensive treatment, compared to the general population (Standardized mortality rate (SMR) 0.80 (0.59-1.06)).[1] The question whether mortality in RA has normalized 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 emphasizing 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 normalization 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 characterized 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 normalized 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. 1288 RA-patients 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 1993-2000 received initial treatment with only NSAIDs or mild DMARDs (e.g. penicillamine, gold, hydroxychloroquine). Patients included between 2001-2016 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 June 1, 2018. Mortality was compared to 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).

Baseline characteristics are shown in Table 1. 248 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 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 to 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 normalized 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.

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

	No early intensive treatment (n = 353)	Early intensive treatment (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)

Legend: N, number of patients; SD, standard deviation; IQR, inter quartile range; ESR, Erythrocyte sedimentation rate; SJC, swollen joint count; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody;

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 RA patients 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.

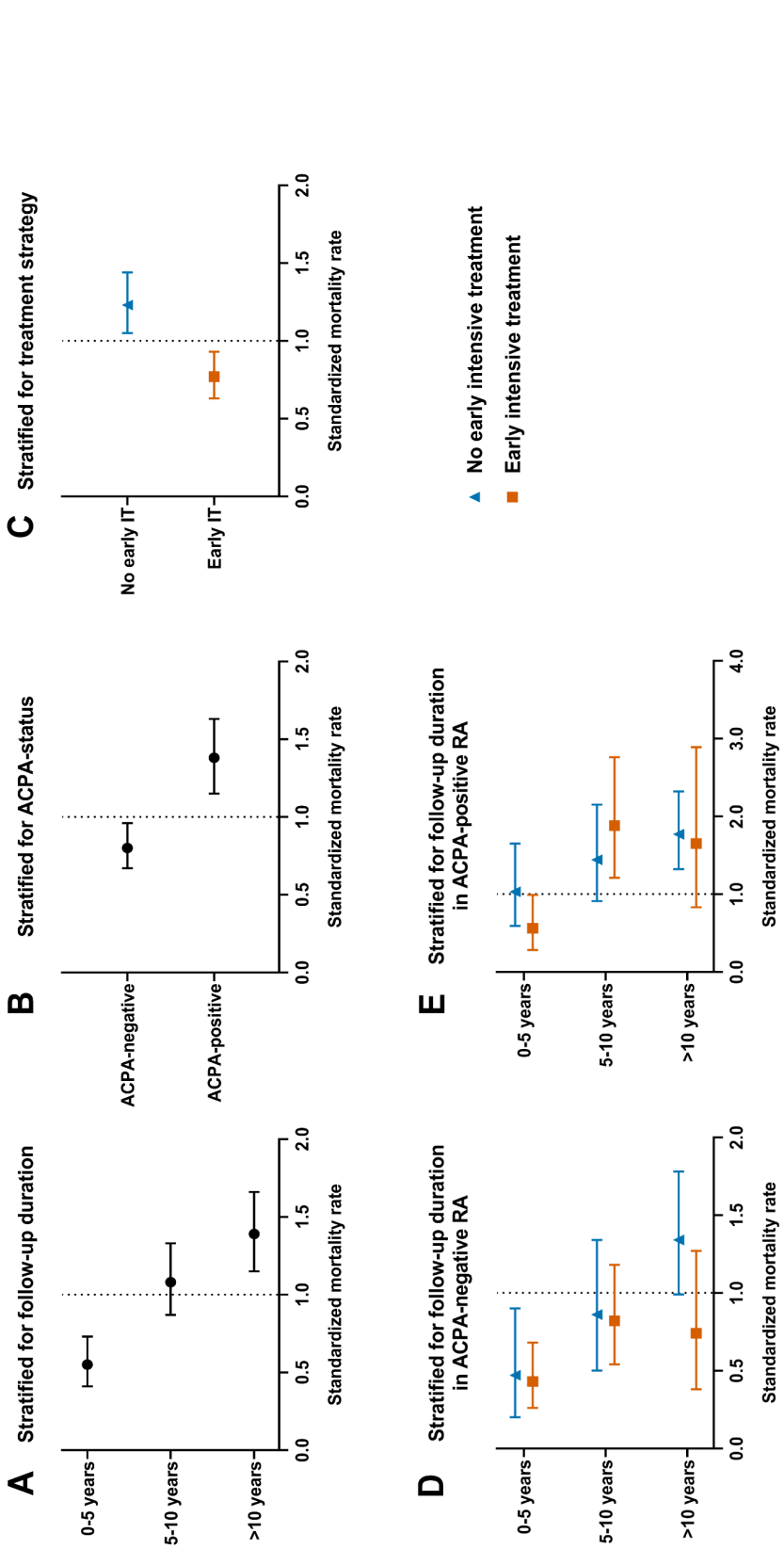

Figure 1: Mortality of patients with RA compared to the general population, stratified for follow-up duration (A), disease subset characterized by ACPA-status (B), early intensive treatment (IT) (C) and these variables combined (D&E), showing that excess mortality has normalized by early intensive treatment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

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