No excess mortality in contemporary undifferentiated arthritis, in contrast to rheumatoid arthritis: a study with a follow-up of at least 10 years

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Two decades ago, the terminology of undifferentiated arthritis (UA) was proposed with the hypothesis that UA is an earlier phase of rheumatoid arthritis (RA).[1] Consequently, management strategies of RA are often transferred to UA-patients, assuming outcomes are comparable. Mortality is a long-term outcome that is unknown in UA, but widely studied in RA.

In RA, excess mortality becomes apparent after 10 years of follow-up in both anticitrullinated protein antibody (ACPA)-negative and ACPA-positive RA, and is presumably mediated by long-term, insufficiently suppressed inflammation.[2–4] Recently, it has been shown that early and treat-to-target treatment resolved excess mortality in ACPA-negative-RA, but not in ACPA-positive-RA.[5] In UA, mortality rates are unknown. Moreover, the UA-population has changed during the last decade.[1] Conventionally, UA was defined as not fulfilling the 1987 RA-critera and absence of another clinical diagnosis. With the introduction of the 2010 RA-criteria, part of the conventional UA- population became classified as RA. The remaining contemporary UA-population (not fulfilling the 1987/2010 RA-criteria) is largely autoantibody-negative, presents with monoarthritis or oligoarthritis and progresses less frequently to RA.[6] Thus, this population of contemporary UA may no longer represent a group of patients in an early phase of RA, but a population with intrinsically different characteristics than RA. We, therefore, hypothesised that there is no excess mortality in contemporary UA, in contrast to RA. This prompted us to assess mortality-rates in contemporary UA-patients, and compare this to conventional UA and RA, all during at least 10 years of follow-up.

We studied 860 conventional UA-patients (no 1987 RA-criteria or other diagnosis at baseline) and 561 contemporary UA-patients (no 1987 and 2010-RA-criteria or other diagnosis at baseline), included in the Leiden Early-Arthritis-Clinic (EAC) between 1993 and 2008 to ascertain minimally 10 years of follow-up after inclusion. Patients who were included between 1993 and 2008, but deceased within 10 years were included. Mortality data were obtained from the civic registries (June–2018). Mortality rates were compared with the general Dutch population using standardised mortality ratios (SMRs) adjusted for age at time of death, gender and calendar-year. SMRs were additionally stratified for ACPA-positivity (anti-CCP2, Euro diagnostica, cut-off>10 mg/L) and autoantibody-positivity (ACPA-positivity and/or rheumatoid-factor-positivity (in-house ELISA)). Mortality rates in RA, which have been previously studied for 1987-RA,[5] were included for comparison. For this, all patients with a clinical RA-diagnosis and fulfilling the 1987/2010-RA-criteria (n=762/828), included between 1993 and 2008 in the Leiden-EAC, were studied. Stratification was applied for early, treat-to-target disease-modifying antirheumatic drug (DMARD)-therapy, as described previously.[5]

The contemporary UA-population was predominantly autoantibody-negative; median swollen joint count was 1 and tender joint count 2, which presentation was milder than conventional-UA (table 1). The contemporary UA-population was also

Table 1 Characteristics of patients studied

	Contemporary UA N=561	Conventional UA N=860	RA according to 1987 RA-criteria N=762	RA according to 2010 RA-criteria N=828
Age (years), mean (SD)	49 (17)	51 (17)	56 (16)	56 (16)
Gender (female), %	54	59	67	68
Symptom duration (weeks), median (IQR)	13 (5–29)	17 (7–33)	19 (10–37)	20 (11–36)
ACPA-positive, %	7	19	52	54
RF-positive, %	9	21	59	61
Swollen joint count (0–28), median (IQR)	1 (1–2)	2 (1–3)	7 (4–12)	7 (4–12)
Tender joint count (0–28), median (IQR)	2 (1–4)	3 (1–7)	13 (7–21)	14 (8–21)
VAS (0–100), median (IQR)	28 (12–50)	31 (13–52)	44 (20–60)	40 (20–59)
CRP (ug/mL), median (IQR)	8 (3–22)	8 (3–23)	17 (7–38)	15 (6–37)
DAS28CRP, median (IQR)	3.2 (2.6–3.9)	3.7 (2.9–4.5)	4.8 (4.1–5.7)	4.7 (4.0–56)
HAQ-DI, median (IQR)	0.5 (0.1–1.0)	0.6 (0.2–1.1)	1.0 (0.6–1.5)	1.0 (0.5–1.5)
DMARD-therapy during follow-up	39%	57%	100%	100%
RA-progression* after 1-year follow-up	20%	44%	–	–

Characteristics of the conventional and contemporary UA-population and the RA-populations. Compared with conventional UA, contemporary UA patients were largely autoantibody negative and presented with lower disease activity at baseline. In conventional UA, more patients progressed to RA after 1 year of follow-up and DMARD-treatment was more frequently required.
*RA-progression was defined as clinical diagnosis of RA and fulfillment of the 1987 and/or 2010-criteria for RA.
ACPA, anticitrullinated autoantibody protein; CRP, C reactive protein; DAS, Disease Activity Score; DMARD, Disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; UA, undifferentiated arthritis; VAS, Visual Analogue Scale.

smaller than conventional-UA (figure 1) and progressed less frequently to RA (online supplemental file 1). Median follow-up for conventional UA-patients was 17.2 years (IQR 13.0–22.1), for contemporary UA 17.3 years (IQR 12.7–22.3), for 1987 RA patients 16.0 years (12.8–20.4) and for 2010 RA patients 16.2 years (IQR 13.0–20.8). Mortality rates were increased in RA, both when defined according to the 1987-criteria or 2010-criteria. Additionally, ACPA-stratification revealed that early initiation of DMARD-treatment and treat-to-target-strategies did not resolve excess mortality in ACPA-positive-RA (figure 1).[5] In conventional-UA, a trend towards excess mortality was observed: SMR 1.11 (95% CI 0.96 to 1.27). However, part of this UA-population is

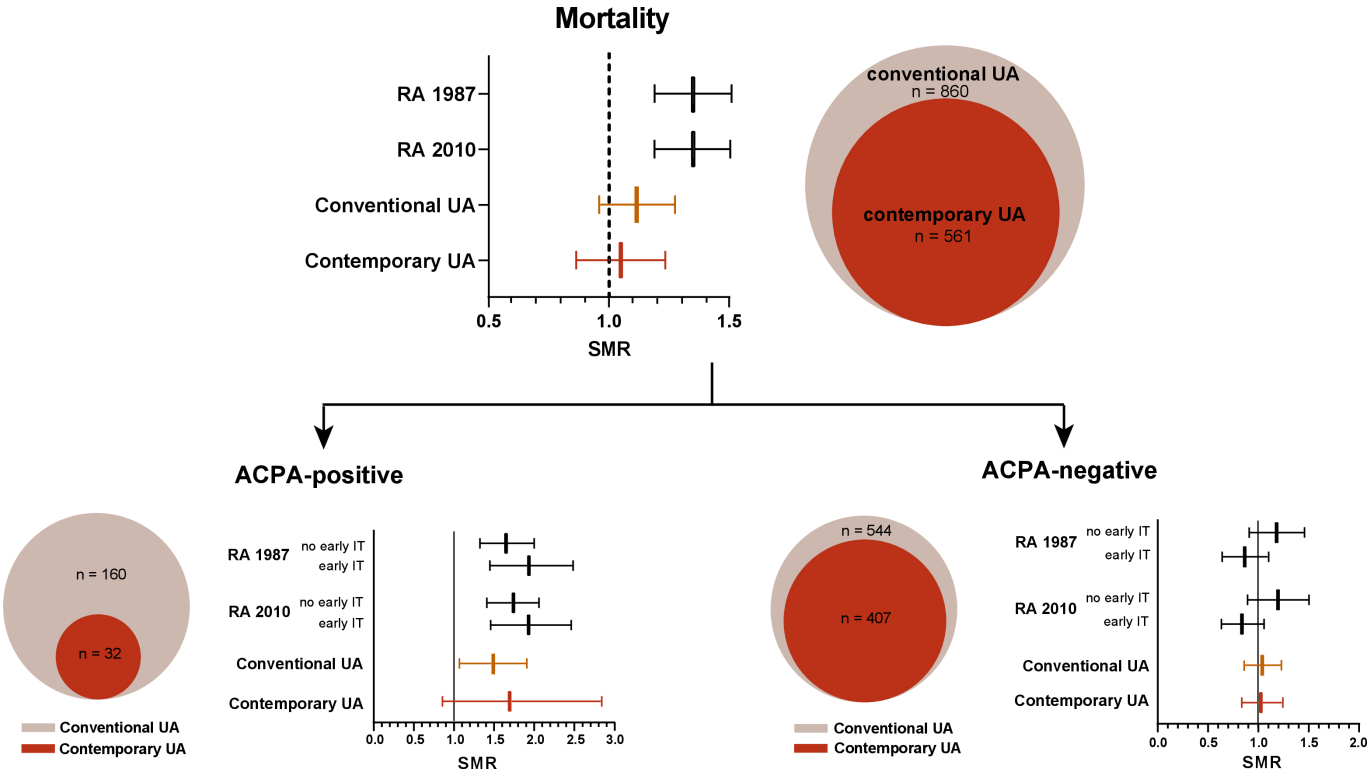

Figure 1 Standardised mortality ratios in undifferentiated and rheumatoid arthritis. Standardised mortality ratios in undifferentiated arthritis and rheumatoid arthritis patients with minimally 10 years of follow-up. Additionally, mortality was stratified for ACPA-status. In RA, SMRs were also stratified for early treat-to-target DMARD-therapy, which has been shown to be relevant for mortality analysis in RA.[5] ACPA, anticitrullinated-protein-antibody; DMARD, disease-modifying antirheumatic drugs, IT, intensive treatment; RA, rheumatoid arthritis; SMR, standardised mortality rate; UA, undifferentiated arthritis.

currently classified as 2010-RA. Subsequently, in contemporary-UA no excess mortality was observed: SMR 1.05 (95% CI 0.87 to 1.26; figure 1). ACPA-stratification provided data suggestive for excess mortality in ACPA-positive contemporary UA, although this group was small. No excess mortality was present in ACPA-negative contemporary UA (figure 1). Results were similar when stratification was performed for autoantibody-status (online supplemental file 1). Mortality rates in contemporary UA patients who did and did not receive DMARD-treatment were comparable (SMR 0.93 (95% CI 0.66 to 1.24) and SMR 1.08 (95% CI 0.82 to 1.36), respectively).

In conclusion, contemporary UA has no excess mortality, which is in contrast to RA. Only a few per cent of patients presenting with contemporary UA are autoantibody-positive; these patients may be considered at increased risk to progress to RA. Interestingly, the estimate of the SMR of this subgroup resembled that of RA, but the confidence interval was broad. The large majority of contemporary UA- patients, in contrast, is autoantibody-negative and presents with few inflamed joints. This is the first large study on mortality in UA. Differences between conventional UA and RA have been shown in the past for other outcomes. This study on mortality suggests that the differences have increased for contemporary UA and RA. These results should be considered together with results from other studies and other outcomes in contemporary UA.[6] Further research and discussions are needed as to whether the management of contemporary UA should be similar to or different from that of RA.

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