A joint evaluation of local and systemic disease activity in treated-to-target rheumatoid arthritis

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Chapter 5

Long-term mortality in treated-to-target RA and UA: results of the BeSt and IMPROVED cohort

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Ann Rheum Dis; 2023 Nov

Abstract

Objectives
To study long-term (up to 20-year) mortality of two treat-to-target trial cohorts in undifferentiated arthritis (UA) and early rheumatoid arthritis (RA).

Methods
The BeSt (BehandelStrategieën) study (n=508, early RA) was performed between 2000 and 2012. For 10 years, patients were treated to target disease activity score (DAS) ≤2.4.

The IMPROVED (Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) study (n=610, early RA/UA) was performed between 2007 and 2015. For 5 years, patients were treated to target DAS<1.6.

Vital status of BeSt/IMPROVED participants was assessed up to and including 31 December 2021. Standardized mortality ratios (SMRs) were calculated. Stratified analyses for anticitrullinated protein antibody (ACPA) and smoking status were performed. Death causes and the potential effect of disease activity during the trial period on late mortality were assessed.

Results
Excess mortality was found in both BeSt (SMR 1.32, 95% CI 1.14 to 1.53) and IMPROVED (SMR 1.33, 95% CI 1.10 to 1.63) and became manifest after 10 years. Excess mortality was statistically significant in ACPA+ patients who smoked (BeSt: SMR 2.80, 95% CI 2.16 to 3.64 ; IMPROVED: 2.14, 95% CI 1.33 to 3.45). Mean survival time was 10 (95% CI 5 to 16) months shorter than expected in BeSt and 13 (95% CI 11 to 16) months in IMPROVED. The HR for mortality was 1.34 (95% CI 0.96 to 1.86; BeSt) / 1.13 (95% CI 0.67 to 1.91; IMPROVED) per 1 point increase in mean DAS during the trial. The main cause of death was malignancy.

Conclusions
After long-term treatment to target, excess mortality occurred in patients with RA after >10 years since treatment start, with smoking as an important risk factor.

Introduction

In the previous century, life expectancy of patients with rheumatoid arthritis (RA) was lower than that of the general population, with standardized mortality ratios (SMRs) up to 2.03 measured over 10 years.[1, 2] In recent years, results from observational cohorts suggest that survival has improved.[3, 4] However, excess mortality may appear later than 10 years.[5] Therefore, our aim is to study long-term mortality in two cohorts of treat-to-target trials: the BeSt study (10-year protocolized treat-to-target therapy followed by 10-year treat-to-target therapy in clinical practice follow-up) and IMPROVED study (5-year protocolized treat-to-target therapy followed by 8-year treat-to-target therapy in clinical practice). We report causes of death and investigate mortality in the allocated treatment arms within the studies, in anti-citrullinated protein antibody (ACPA) positive and negative patients and in RA versus undifferentiated arthritis (UA). We also study the association of disease activity over time with late mortality. Because in previous studies, disease activity has been found to be associated with mortality, we hypothesized that survival in our study had improved compared to survival reported in pre-treat-to-target studies.

Methods

Patients

We performed this analysis in two Dutch trial cohorts. In BeSt (*BehandelStrategieen*, i.e. treatment strategies), 508 patients with disease modifying antirheumatic drugs (DMARD) naive newly diagnosed RA (1987 American College of Rheumatology (ACR) classification criteria; symptom duration ≤2 years) were included between 2000 and 2002 and randomised between 4 treatment strategy arms: 1) sequential monotherapy starting with methotrexate (MTX), 2) step-up combination therapy starting with MTX, 3) initial combination therapy with MTX, sulfasalazine and prednisone or 4) initial combination therapy with infliximab and MTX. For 10 years, patients were treated-to-target and clinically assessed every 3 months. In case of a disease activity score (DAS) >2.4, treatment was intensified (online supplemental table 1). In case of sustained low disease activity (DAS ≤2.4 for ≥6 months) treatment was tapered to monotherapy at a maintenance dose and discontinued when sustained remission (DAS ≤1.6 for ≥6 months) was achieved afterwards. More details of the BeSt study have previously been described.[6, 7]

In IMPROVED (*Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease*), 610 patients with newly diagnosed

RA or UA suspected for early RA (symptom duration ≤2 years) were included between 2007 and 2010. RA was defined by 2010 ACR/European League Against Rheumatism (EULAR) criteria. All patients started treatment with MTX therapy and prednisone. Patients in early remission (DAS <1.6 at 4 months) tapered medication to stop, if possible. Patients not in early remission were randomised between two treatment arms: 1) combination of MTX, sulfasalazine, hydroxychloroquine and prednisone or 2) MTX and adalimumab. At 4 months, 50 patients had a DAS ≥1.6 but were not randomized (out-of-protocol group). For 5 years, all patients were treated-to-target and were clinically assessed every 4 months. In case of DAS ≥1.6, treatment was intensified (see online supplemental figure 1). If remission was achieved during follow-up, treatment was tapered to stop. More details of IMPROVED have been previously described.[8, 9]

After the trial periods, patients were treated according to daily practice. All participating hospitals followed the Dutch guidelines, based on EULAR recommendations, in which a treatment target of DAS remission or low disease activity was advised.[10]

Patient and public involvement

During and after BeSt and IMPROVED, patient information meetings were arranged to inform participants on previous study results and consult them about follow-up investigations.

Data collection

The vital status of patients was assessed up to and including 31 December 2021 . Mortality (date and cause of death) and emigration data of patients were obtained from the database of Statistics Netherlands (CBS), which includes data of people in the Personal Records Database in the Netherlands. 92% of the BeSt/IMPROVED participants could be identified in the CBS database based on sex, date of birth and last available home address. The vital status of patients that could not be linked to CBS data was based on previously acquired information (online supplemental figure 2). The remaining 21 patients were censored at the last available BeSt/IMPROVED study visit.

Causes of death

Main underlying causes of death were reported based on CBS methodology, based on cause-of-death certificates completed by medical practitioners. We categorized causes of death in predefined categories: cardiovascular disease (including stroke), malignancy, infection (including respiratory tract infection), other and 'unknown'. Results with <10 individuals per group are reported as '<10', adhering to the policy of CBS to warrant patient anonymity. No additional

categories containing ≥10 individuals could be defined.

For patients who died during BeSt or IMPROVED and could not be identified in the CBS database, causes of death as reported during the study were used or reported as 'unknown'.

Statistical analysis

For each study, we performed two sets of analyses: in the first set, the follow-up period started at baseline of BeSt/IMPROVED and ended at 31 December 2021, that is median 20 and 13 years, respectively. In the second set, the follow-up period started at the end of BeSt/IMPROVED, spanning median 10 years for BeSt and 8 for IMPROVED, until December 31st 2021 (landmark analysis[11]).

Analyses from baseline

The main outcome is the SMR from start of BeSt/IMPROVED to 31 December 2021. As a reference, mortality hazards of the general Dutch population were used, matched based on a period life table stratified for age, sex and calendar year.[12] Mortality in the BeSt/IMPROVED population was also compared to this age-, sex- and calendar year-matched reference with Kaplan-Meier curves. The difference in survival between study group and reference population was also expressed in life years lost, calculated as the difference between restricted mean survival times (RMST) of the study population and the reference population.

SMRs were also reported per treatment arm. Since previous studies reported differences in mortality between patients with and without anti-citrullinated protein antibodies (ACPA), we also stratified the analysis for ACPA status.[13, 14] Because ACPA-positivity is associated with smoking, we additionally stratified for both ACPA status and history of smoking.[15] For IMPROVED, we also investigated the difference between patients with RA and UA.

As an exploratory analysis, based on biological plausibility and previous research, we assessed whether the following patient characteristics at treatment start were predictive for mortality: randomisation arm, ACPA, a history of cardiovascular disease, previous history of malignancy (>5 years ago, as specified in the exclusion criteria), ever smoking, body mass index (BMI), health assessment questionnaire (HAQ) score, erosive disease, DAS and symptom duration.[4, 13, 16-19] For this analysis we used a multivariable Cox regression model. Because of assumed non-linear associations between BMI/age and mortality, a categorical term was used for BMI and a quadratic term for age was added as a sensitivity analysis in a second model. All variables

satisfied the proportional hazards assumption, as checked by assessing Schoenfeld residuals, parallelism of log-minus-log plots and comparison of Kaplan Meier observed survival curves and Cox predicted curves for each variable (continuous variables were dichotomized).

Landmark analysis

We additionally performed the analyses mentioned above using as start of follow-up the end of the BeSt/IMPROVED trial period (including every patient who was not deceased or censored at that time point). Furthermore, Cox regression models were used to assess the associations between average disease activity during the BeSt/IMPROVED trial period and mortality after the end of the trial period. Disease activity during the trial period was defined as mean DAS during BeSt/IMPROVED, in patients with at least 4 (BeSt) or 3 study visits (IMPROVED) available, corresponding with at least 1 year of follow-up. The analysis was adjusted for potential confounders: age, randomisation arm, ACPA, sex, ever smoking (as recorded until the end of follow-up of BeSt/IMPROVED) and BMI (at baseline, follow-up BMI was not available).[13, 17-23] As sensitivity analyses, different summary measures of disease activity over time were used: whether the patient was in early DAS-remission (DAS<1.6 at second study visit), or ever in sustained (≥1 year) or drug-free DAS-remission, the percentage of visits with moderate to high disease activity (DAS>2.4) and the mean erythrocyte sedimentation rate (ESR) during the trial period (at least 4 ESR measurements).

We exploratively assessed whether patient characteristics (age, treatment arm, RF, ACPA, sex, cardiovascular disease (including BeSt/IMPROVED study period), malignancy (idem), ever smoking (idem), BMI, and mean HAQ and mean DAS during at least 1 year of follow-up) were predictive for late mortality, with a multivariable Cox regression model. Rapid radiological progression was omitted from the originally planned model because of >10% missing data. Al other variables had ≤5% missingness and available case analysis was used for the models with these variables.

All analyses were performed in Stata V.SE 16.1.

Results

Best – from baseline

At baseline of BeSt (N=508), symptom duration of RA was median 23 weeks (IQR 14-53), mean age was 54±14 years and mean DAS was 4.4±0.9. Of the participants, 68% were women and 35% (ever) smoked. Between the start of BeSt (2000-2002) and 31 December 2021, 174 patients died and 25 were lost to follow-up (incl. emigration) before the end of follow-up and therefore censored during the follow-up period (characteristics: online supplemental table 2) After median 20 years of follow-up, mortality was significantly higher in the BeSt study population than in the reference population, with an SMR of 1.32 (95% CI 1.14 to 1.53). Mean age of death was 77±10 years. Over 20 years of follow-up, the survival time was 10 (95% CI 5 to 16) months shorter than expected (RMST BeSt population: 17.0 years (95% CI 16.5 to 17.4), RMST expected: 17.8 years)

Kaplan Meier curves comparing the mortality rate of BeSt participants and the general Dutch population are displayed in figure 1.

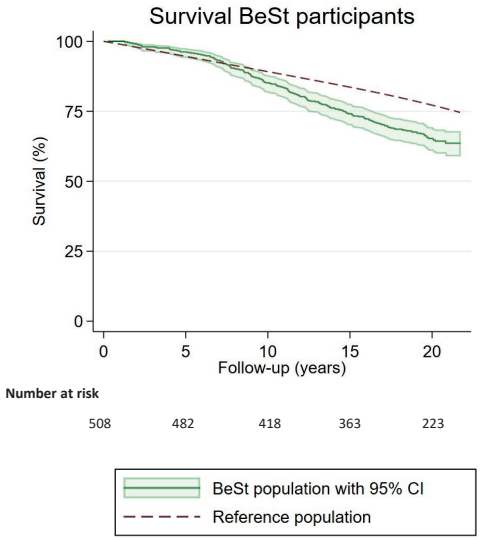

Figure 1. 20-year survival of BeSt study participants (from baseline until end of 2021) compared to the age- and sex matched reference population

Malignancies were the cause of death in 52 patients (30%), of which <10 haematological malignancies (<6%). Cardiovascular disease was the cause of death in 41 patients (24%) and infection in 10 patients (6%). Forty-seven (27%) patients had another cause of death, and for 24 (14%) the cause was unknown.

SMRs per treatment arm are depicted in figure 2. Excess mortality was found in in treatment strategy arm 1 (sequential monotherapy), 2 (step-up combination therapy) and arm 3 (initial MTX + sulfasalazine + prednisone), compared to the reference population (figure 2).

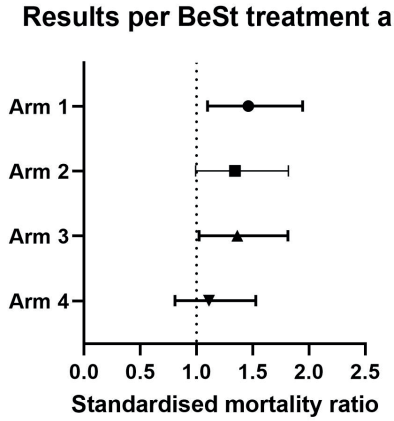

Figure 2. Standardized mortality ratios (20-year follow-up) per treatment strategy arm of BeSt
Arm 1: sequential monotherapy (n=126), SMR 1.46 (95% CI 1.10 to 1.95); arm 2: step-up combination therapy (n=121), SMR 1.34 (95% CI 0.99 to 1.82); arm 3: initial combination with MTX + sulfasalazine + prednisone (n=133), SMR 1.36 (95% CI 1.02 to 1.81); arm 4: initial combination with MTX + infliximab (n=128), SMR 1.11 (95% CI 0.81 to 1.53). SMR is based on a sex and age matched reference population.

Survival curves of the 4 treatment arms were not statistically significantly different from each other (log rank test: p=0.70; online supplemental figure 3).

Mortality in ACPA-positive patients (n=300), but not in ACPA-negative patients (n=184), was higher than in the reference population (SMR 1.49, 95% CI 1.23 to 1.81 and 0.97, 95% CI 0.75 to 1.26, respectively; online supplemental figure 4).

The log rank test did not show a statistically significant difference between the survival curves of ACPA-positive and ACPA-negative patients (p=0.32; online supplemental figure 5).

When stratifying for both ACPA status and smoking history, we only found statistically significant excess mortality in patients who smoked (ACPA-positive: SMR 2.80, 95% CI 2.16 to 3.64; ACPA-negative: 2.55, 95% CI 1.63 to 4.00). SMRs for patients who never smoked were 0.95, 95% CI 0.72 to 1.27 (ACPA-positive); 0.74, 95% CI 0.53 to 1.02 (ACPA-negative).

In the multivariable Cox model evaluating baseline characteristics, the most important independent predictors for mortality were age, male sex, and a history of smoking (table 1). Adding a quadratic term for age did not change the results (online supplemental table 3)

Table 1. Results of the multivariable Cox regression model evaluating characteristics at baseline of BeSt possibly predictive for mortality.

	HR (95% CI)	p-value
Age (years)	1.14 (1.12 to 1.16)	<0.001
Male sex	1.51 (1.07 to 2.14)	0.021
Ever smoker	3.87 (2.71 to 5.55)	<0.001
BMI (<25 = reference)		
25-30	0.94 (0.66 to 1.33)	0.72
≥30	1.39 (0.83 to 2.34)	0.21
Disease activity score (DAS)	0.98 (0.79 to 1.21)	0.85
Health Assessment Questionnaire (HAQ) score (0-3)	1.29 (0.98 to 1.68)	0.07
ACPA positivity	1.36 (0.96 to 1.94)	0.09
Presence of erosions	1.42 (0.90 to 2.24)	0.13
Randomisation arm (arm 1 = reference)		
Arm 2: step-up combination therapy	0.90 (0.57 to 1.41)	0.64
Arm 3: initial combination with MTX + sulfasalazine + prednisone	0.91 (0.59 to 1.42)	0.72
arm 4: initial combination with MTX + infliximab	0.69 (0.44 to 1.08)	0.11
History of cardiovascular disease	1.03 (0.70 to 1.51)	0.88
History of malignancy	0.97 (0.44 to 2.12)	0.94
Symptom duration (weeks)	1.000 (0.997 to 1.002)	0.80

The estimates are the hazard ratios for each characteristic, adjusted for all other baseline characteristics in the table.

IMPROVED – from baseline

At baseline of IMPROVED, symptom duration of RA/UA was median 18 weeks (IQR 9-32) and mean age was 52±14 years . Mean DAS was 3.2±0.9. Of the participants, 68% were women and 29% were (former) smokers. At baseline, 40% of the patients were diagnosed with UA (n=146), of whom 43% (n=105) were ACPA positive. From the start of IMPROVED (2007-2010) until 31 December 2021, 99 patients died and 22 patients were censored from the survival analysis before the end of follow-up (characteristics: online supplemental table 4). Follow-up duration was median 13 years (IQR 12-14). The SMR was 1.33 (95% CI 1.10 to 1.63), indicating excess mortality in IMPROVED patients compared to the general Dutch population. Mean age of death was 74±11 years. Figure 3 shows the survival curves of the IMPROVED study participants compared to the reference population. Over 13 years of follow-up, the observed survival time was 13 (95% CI 11 to 16) months shorter than expected (RMST IMPROVED: 12.2 years, 95% CI 12.0 to 12.4, RMST expected: 13.3 years).

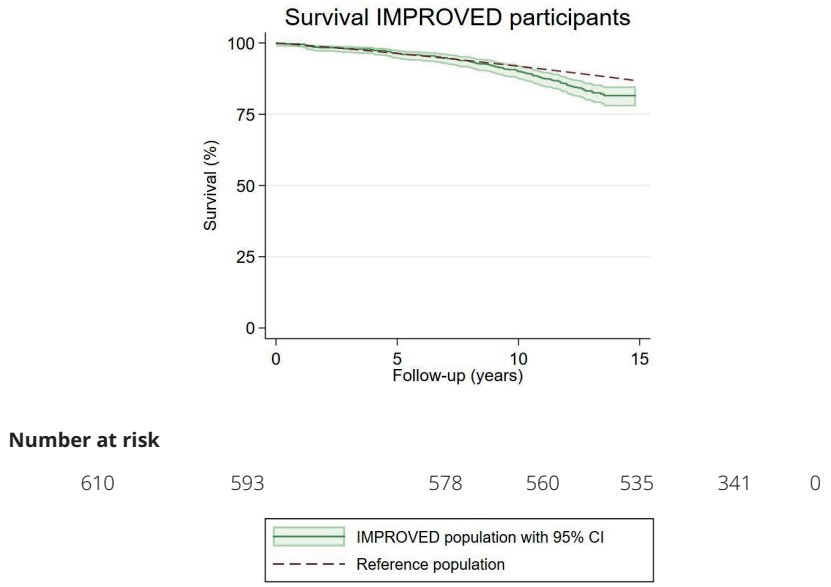

Figure 3. Survival curve of IMPROVED study participants compared to the reference population

Malignancy was the most frequently reported cause of death (n=39 (39%), of which <10 haematological, followed by cardiovascular disease (n=21 (21%)). Infection was the cause of death in <10 patients. Twenty-four (24%) patients had another cause of death and for 15 (15%) the cause of death was unknown. SMRs per treatment arm are depicted in figure 4. Excess mortality was found

in arm 2 (not in early remission, randomized to early MTX + adalimumab) and patients treated out-of-protocol (not in early remission, but not randomized). Survival curves were statistically significantly different between arm 1 and 2 (log rank test: p=0.02; online supplemental figure 6).

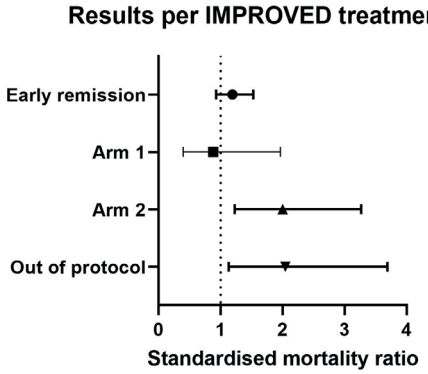

Figure 4. Standardized mortality ratios (13-year follow-up) per treatment strategy arm of IMPROVED
Early remission: patients in remission after 4 months (n=387), SMR 1.19 (95% CI 0.93 to 1.53); arm 1: not in remission at 4 months, escalating to MTX + hydroxychloroquine + sulfasalazine (n=83), SMR 0.88, 95% CI 0.40 to 1.97); arm 2: not in remission at 4 months, escalating to MTX + adalimumab (n=78), SMR 2.00 (95% CI 1.23 to 3.27); out of protocol: not in remission at 4 months but not randomized (n=50), SMR 2.05 (95% CI 1.13 to 3.69).

In IMPROVED we also found excess mortality in ACPA-positive patients (n=332, SMR 1.56, 95% CI 1.18 to 2.06). In ACPA-negative patients (n=262) the SMR was 1.07, 95% CI 0.79 to 1.44 (online supplemental figure 7).

There was no statistically significant difference in survival between ACPA-positive and ACPA-negative patients assessed with a log rank test (p=0.32; online supplemental figure 8).

After stratification for both ACPA and smoking, we only found statistically significant excess mortality in ACPA-positive smokers (SMR 2.14, 95% CI 1.33 to 3.45). SMRs: ACPA-negative/non-smoker 1.00 (95% CI 0.71 to 1.41), ACPA-negative/smoker 1.38 (95% CI 0.74 to 2.6), ACPA-positive/non-smoker 1.32 (95% CI 0.93 to 1.88).

We found statistically significant excess mortality in the RA population (SMR 1.39, 95% CI 1.09 to 1.76). In UA patients, SMR was 1.24 (95% CI 0.87 to 1.75). The RA/UA survival curves were not statistically significantly different (log rank: p=0.065; online supplemental figure 10).

In the multivariable Cox model evaluating baseline characteristics, age and male sex were statistically significantly associated with mortality (table 2). Adding a quadratic term for age did not change the results (online supplemental table 5)

Table 2. Results of the multivariable Cox regression model evaluating characteristics at baseline of IMPROVED possibly associated with mortality.

	HR (95% CI)	p-value
Age (years)	1.14 (1.10 to 1.17)	<0.001
Male sex	1.82 (1.15 to 2.89)	0.011
Ever smoker	1.64 (0.97 to 2.76)	0.063
BMI (<25 = reference)		
25-30	1.04 (0.63 to 1.71)	0.88
≥30	1.31 (0.69 to 2.48)	0.41
Disease activity score (DAS)	0.87 (0.63 to 1.22)	0.40
Health Assessment Questionnaire (HAQ) score (0-3)	0.91 (0.59 to 1.42)	0.68
ACPA positivity	1.54 (0.95 to 2.51)	0.080
Presence of erosions	1.15 (0.65 to 2.05)	0.62
Treatment arm IMPROVED (reference = early remission)		
Arm 1: MTX + hydroxychloroquine + sulfasalazine	0.88 (0.3 to 2.13)	0.78
Arm 2: MTX + adalimumab	2.07 (1.08 to 3.98)	0.029
Out of protocol	2.05 (0.96 to 4.38)	0.062
History of cardiovascular disease	1.13 (0.71 to 1.81)	0.60
History of malignancy	1.17 (0.28 to 4.92)	0.83
Symptom duration (weeks)	1.004 (0.99 to 1.01)	0.38
RA diagnosis (reference = UA)	0.98 (0.578to 1.65)	0.91

The estimates are the hazard ratios for each characteristic, adjusted for all other baseline characteristics in the table.

Landmark analyses BeSt

At the end of BeSt (10 years after baseline), 418 of the patients of whom the vital status could be assessed were alive and were included in the landmark analysis (see online supplemental table 6 for patient characteristics at BeSt baseline). The SMR from end of BeSt to 31 December 2021 (median 10 years), compared to the matched reference population, was 1.41 (95% CI 1.16 to

1.72). Results of the stratified analyses are described in online supplemental tables 7-9.

A one point higher mean DAS during the 10-year trial period was associated with a 1.34 higher hazard for mortality over the second decade (95% CI 0.96 to 1.86). Results for the other summary measures of disease activity are shown in table 3. Effects of all disease activity measures were in the same direction, but only the effect of achievement of drug free remission and mean ESR during the trial period were statistically significant.

Table 3. Results of analyses for associations between disease activity measures during the 10-year trial period of BeSt and mortality in the decade following the end of BeSt

	HR (95% CI)
Mean DAS*	1.34 (0.96 to 1.86)
Early remission (DAS <1.6 at second study visit)	0.89 (0.45 to 1.78)
Ever sustained remission (min. 1 year)	0.69 (0.44 to 1.06)
Ever drug free remission	0.42 (0.24 to 0.73)
Percentage of study visits with DAS >2.4†	1.01 (0.998 to 1.02)
Mean ESR	1.02 (1.01 to 1.03)

* Primary measure of disease activity. The HR indicates the increase in mortality risk for each point in mean DAS increase during the trial period.
† The HR represents the mortality risk increase for each percent of study visits in high disease activity (in case of complete follow-up, 1 study visit corresponds with 2% of the study visits)
All disease activity measures were tested in separate Cox analyses and adjusted for potential confounders (age, randomisation arm, ACPA, sex, ever smoking (until the end of follow-up of BeSt) and BMI). DAS measurement was available at median 35 (IQR 23 to 38) out of 41 study visits.

Results from this landmark analysis and the multivariable Cox model for the full follow-up period were comparable (online supplemental table 10).

Landmark analyses IMPROVED

At the end of IMPROVED (5 years after baseline), 578 of the patients of whom the vital status could be assessed were alive and were included in the landmark analysis (see online supplemental table 11 for patient characteristics at IMPROVED baseline). The SMR was 1.51 (95% CI 1.20 to 1.88). For patients with RA, the SMR was 1.51 (95% CI 1.14 to 1.99) and for UA patients 1.50 (95% CI 1.03 to 2.18). Other results of stratified analyses are reported in online supplemental tables 12-14. Mean DAS during the 5-year trial period of IMPROVED was not statistically significantly associated with mortality in the 8 years after the end of IMPROVED (6th-13th year of total follow-up) (HR

1.15, 95% CI 0.67 to 1.97). Results for other measures of disease activity are reported in table 4. Effects of all disease activity measures were in the same direction, but only the effect of mean ESR during the trial period was statistically significant.

Table 4. Associations between disease activity during the 5-year trial period and late (>5 year) mortality in IMPROVED

	HR (95% CI)
Mean DAS*	1.13 (0.67 to 1.91)
Early remission (DAS <1.6 at second study visit)	0.80 (0.47 to 1.35)
Ever sustained remission (min. 1 year)	0.71 (0.42 to 1.20)
Ever drug free remission	0.70 (0.41 to 1.20)
Percentage of study visits with DAS >2.4[†]	1.00 (0.99 to 1.01)
Mean ESR	1.02 (1.002 to 1.04)

* Primary measure of disease activity. The HR indicates the increase in mortality risk for each point in mean DAS increase during the trial period.
[†] The HR represents the mortality risk increase for each percent of study visits in high disease activity (in case of complete follow-up, 1 study visit corresponds with 6% of the study visits)
All disease activity measures were tested in separate Cox analyses and adjusted for potential confounders (age, randomisation arm, ACPA, sex, ever smoking (until the end of follow-up of IMPROVED) and BMI). DAS measurement was available at median 15 (IQR 13 to 16) out of 16 study visits.

No additional factors associated with mortality were found in the landmark multivariable Cox model compared to the full follow-up period model (online supplemental table 15).

Discussion

In this study we assessed long-term mortality of patients with early RA or UA suspected for very early RA, who participated in the BeSt or IMPROVED study, both treat-to-target trials, targeted at DAS≤2.4 and DAS<1.6, respectively. Although previously no excess mortality was found after 10 years in BeSt, we now found that after longer follow-up (median 20 years in the BeSt study and median 13 years in the IMPROVED study) mortality is higher than in the general Dutch population. Older patients, men, and smokers, in particular if they were ACPA-positive, were more at risk for overall mortality, and high disease activity during the trial showed a trend for increased mortality. The main cause of death across both cohorts was malignancy.

Given that treatment outcomes of RA have greatly improved in the past decades,[24-26] it is disappointing that we observed excess mortality in patients who were treated to a DAS≤2.4 target for 10 years (SMR 1.32, 95% CI 1.14 to 1.53) and even in patients who were treated with a stricter treatment target (DAS<1.6) who had milder disease at the start of treatment (1.33, 95% CI 1.10 to 1.63). The reduction in life expectancy over the follow-up period was approximately a year, which is smaller than reported in older cohorts.[27, 28]

To our knowledge, this is the first study to investigate mortality on very long-term follow-up (up to median 20 years) in cohorts of which all patients were treated-to-target from the beginning of treatment. In comparison to cohorts in which patients with RA received early DMARD treatment, but without strictly targeted treatment protocols, we did not find significantly better relative survival rates.[5, 29] Only in the COBRA trial after 23 years of treatment, no increased mortality was found (SMR 0.80, 95% CI 0.59 to 1.06), although initial treatment in COBRA was similar to that in BeSt (arm 3, initial MTX + sulfasalazine + prednisone arm).[30] However, confidence intervals of the SMRs of the BeSt and COBRA csDMARD combination therapy arms overlapped (SMR BeSt arm 3: 1.36 [95% CI 1.02 to 1.81); COBRA arm 2: 0.75 [0.47 to 1,14]). Additional differences might have been caused by selection of healthier patients in COBRA (age restriction, less comorbidities allowed) and a different source of mortality data (current study: data from Statistics Netherlands in which also the alive status and emigration can be assessed in BeSt, vs COBRA: data from CBG Centre for family history in which only deaths can be confirmed, which might result in underestimation of mortality).[30] Also in the FIN-RACo trial, after 11 years no statistically significant excess mortality was found (SMR 1.13, 95%CI 0.64 to 1.87).[31] However, this might still become apparent after longer follow-up.

After stratifying for ACPA, we only observed statistically significant excess mortality in ACPA-positive patients. This effect seems to be largely explained by smoking. Previously, it was reported that in the Dutch Leiden Early Arthritis Cohort during 25 years of follow-up only ACPA-positive RA-patients had excess mortality, but the effect of smoking was not tested.[14] In a large observational study, smoking cessation was associated with a lower mortality risk compared to continued smoking.[32]

In both BeSt and IMPROVED the main cause of death was malignancy (30 and 39%, respectively). This is comparable with the percentage in the general Dutch population between 2000 and 2021 (30%)[33], and similar to what was recently found in a population of whom 33% were treated to target where there was statistically significant cause-specific excess mortality for

malignancy, and not for cardiovascular disease.[29] In three other studies in RA, the reported percentages of malignancy as the cause of death were slightly lower ranging from 23 to 29%.[5, 34, 35] In these studies, the main cause of death was cardiovascular disease, with higher percentages than in our study (30 to 35% vs. 21 in BeSt and 24% in IMPROVED).[5, 34, 35] However, these were different study populations with other treatment strategies[5, 34, 35] and more smokers[5, 34] or only men included.[34] Between 2000 and 2021, cardiovascular disease was the cause of death in 28% in the general Dutch population.[33] Infection was the primary cause of mortality in 6% in BeSt and <10% in IMPROVED, with similar percentages in other studies (4-10%) and the general Dutch population (6%).[5, 33, 35]

We did not find a clear association between disease activity during the trial (10 and 5 years respectively) and long-term mortality, although all measures followed the same trend. In previous studies, with shorter follow-up and/or without treatment-to-target, associations between RA disease activity and mortality have been found.[5, 7, 16, 36]

In both BeSt and IMPROVED, the treat-to-target dictated treatment adjustments over time make it difficult to link survival data to individual therapies. In IMPROVED, we found that mortality was higher in the treatment arm escalating from initial MTX with prednisone to combination therapy with adalimumab than in the arm escalating to csDMARD combination therapy. In contrast, in the BeSt study, the arm with initial infliximab combination therapy had the lowest SMR, although there was no statistically significant difference in survival between the treatment arms of the BeSt study. In observational data it has been described that exposure to biological DMARDs (bDMARDs) was associated with lower mortality compared to treatment with csDMARDs but these analyses were not adjusted for confounding by indication.[16] A study combining data of different adalimumab trials showed no excess mortality in patients treated with adalimumab.[37] However, the follow-up period for this analysis was not reported.

Strengths of this study are the long follow-up, systematic collection of DAS measures during long-term treatment-to-target, resulting in patients having well suppressed disease activity, and use of reliable mortality and migration data provided by CBS (based on the Personal Records Database of the Netherlands). A limitation is that the original studies were not powered for survival analyses and stratification of these analyses, and therefore the results of the analyses should be interpreted with caution. Also, the mortality reference rates were only based on age, sex an calendar year, but not on other characteristics, such as smoking. Therefore, SMRs for smokers are

likely overestimated (and SMRs for non-smokers underestimated), since the reference population consists of both smokers and non-smokers. Additionally, our outcomes may not translate to outcomes in the general RA/UA population, because of selection of relatively healthy patients. We speculate that, due to patient selection and strict treatment to target, our outcomes may represent an underestimation of excess mortality in unselected patients not treated to target. No control group without treat-to-target strategy was available in our study, so a direct comparison between patients treated with and without a treat-to-target strategy is not possible. Also, we cannot determine the effect of the post-trial period on the results, since no data on disease activity after the end of the trial period currently could be assessed. Death certificates may not always give a comprehensive representation of all factors contributing to death. Finally, we cannot state whether RA/UA is the cause of excess mortality, or that mutual risk factors for RA and for mortality, such as smoking, increase the risk of death. Although we found statistically significant excess mortality in different subgroups (ACPA-positive patients, smokers, patients in BeSt arm 1, patients in IMPROVED arm 2 and the out-of-protocol group) and not in the other subgroups, SMR confidence intervals between groups within stratified analyses often overlapped. Moreover, most survival curves of the compared subgroups were not statistically significantly different from each other. This could either mean that survival in the subgroups is similar, or that there is a difference but the sample size was too low to demonstrate statistical significance. Previously reported studies suggest the latter.[14, 38]

Excess mortality appeared only after approximately 10 years. This might be explained by a protective effect of monitoring of patient health during the trial period, or by selection of patients at study onset who are at that moment relatively healthy (selection bias). However, the same trend was found in observational studies.[5, 29] The suppression of RA disease activity may have contributed to relatively less cardiovascular deaths than in previous studies.[39] Unidentified potential risk factors, such as genetic factors that are unaffected by treatment, may be relevant for late excess mortality. It can also not be ruled out that treatment itself may have had a negative effect on late mortality.

In conclusion, we observed excess mortality in patients with RA in two treat-to-target cohorts (BeSt and IMPROVED) compared to the general Dutch population, that became manifest after more than 10 years of follow-up, in particular in ACPA-positive patients who smoked and with a trend towards an effect of disease activity on late mortality. Reduction of life expectancy was approximately 1 year. Causes of death were similar to that in the general population. Future research should focus on the underlying reasons for excess mortality in order to improve survival of patients with RA.

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