

Progression independent of relapse activity in a population with relapse-onset multiple sclerosis

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Key conclusions

RAW and PIRA are clinically distinct but interrelated. PIRA is more common than RAW, particularly on high-efficacy therapy. High-efficacy therapy was associated with lower risk of relapse, RAW and CDW. Effects on PIRA are more modest. PIRA remains linked to prior relapses, suggesting a potentially modifiable inflammatory contribution. PIRA should not be confused with a progressive MS phenotype, particularly during high-efficacy therapy.

70.3%

of confirmed worsening was PIRA

Persistent disability despite relapse control calls for targeted therapies and imaging/fluid biomarkers of inflammation and neurodegeneration.

Study population & aim

44,757 people with relapse-onset MS
From the international MSBase registry

166 centres · 43 countries · Median follow-up 5.1 years

Aim: quantify the absolute and relative contributions of RAW and PIRA across treatment classes and eras, and assess whether relapse suppression with high-efficacy therapy unmasks ongoing disability worsening outside clinical relapses.

Methods

Adults with ≥3 EDSS assessments and ≥12 months between the second and final assessment.

CDW (MSOutcomes²): EDSS increase ≥1.5 points from 0, ≥1.0 from 1.0–5.5, or ≥0.5 from >5.5; re-baselined after relapse/worsening, confirmed ≥12 months and sustained through follow-up.

RAW (relapse-associated worsening): CDW with a relapse between the EDSS immediately preceding worsening and the index EDSS.

PIRA (progression independent of relapse activity): CDW without a relapse in that interval.¹

*Recurrent-event Cox proportional hazards models: treatment epochs as start–stop intervals (including untreated), stratified by era. Adjusted for age, sex, disease duration, EDSS (cubic spline), prior DMT count and region. Disability models also included cumulative prior relapses and EDSS visit density.

Bayesian joint models: shared patient effects link recurrent relapse and disability trajectories to estimate the association between underlying relapse propensity and CDW/PIRA hazard.

¹ Müller J, Sharmin S, Lorscheider J, et al. Standardized definition of PIRA in relapsing-remitting MS. JAMA Neurol. 2025;82:614–625. doi:10.1001/jamaneurol.2025.0495.

² Sharmin S et al. MSOutcomes: CORE Multiple Sclerosis Outcomes Toolkit. R package. doi:10.32614/CRAN.package.MSOutcomes.

Disclosures & funding

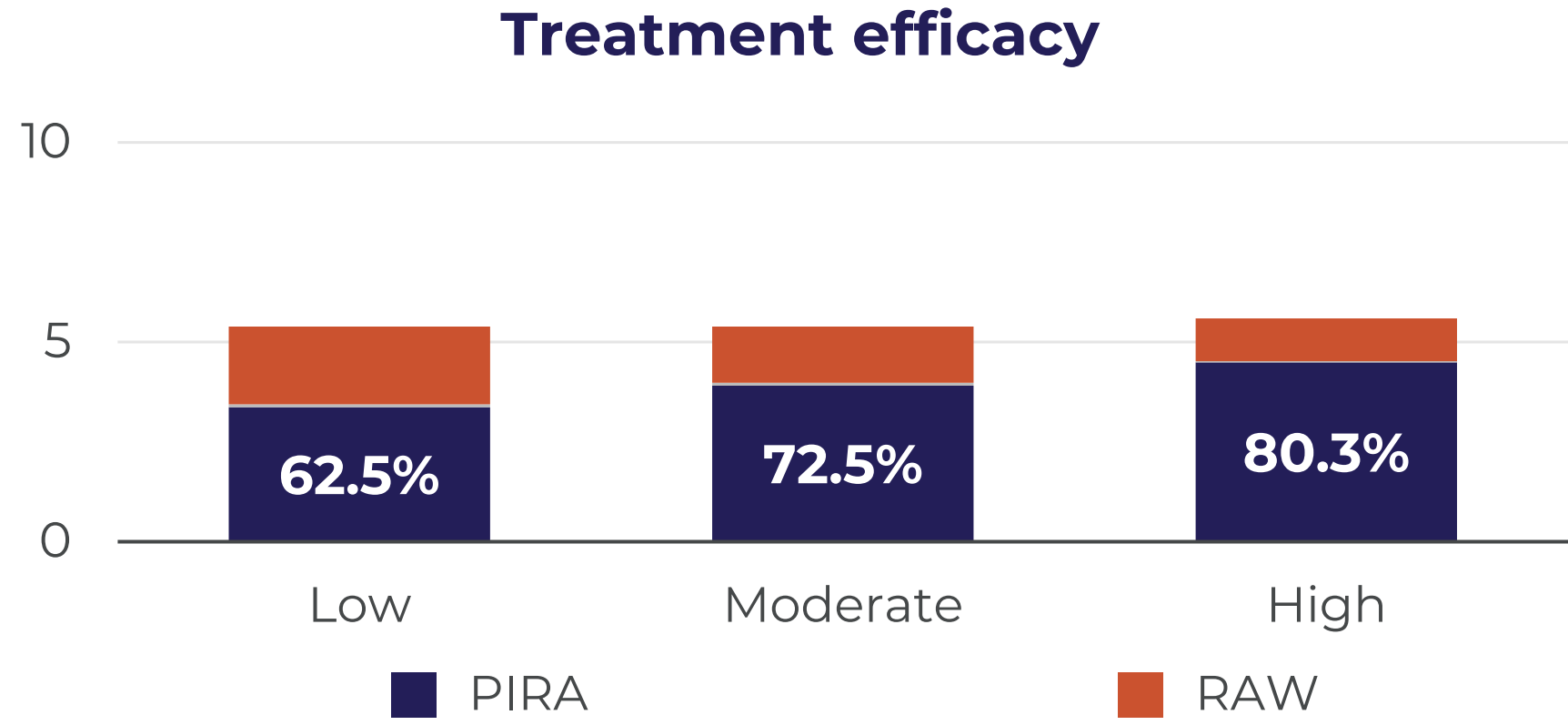
I. Roos reports advisory-board fees, travel support and/or speaker honoraria from Roche, Novartis, Merck, Neuraxpharm and Biogen. D. Horakova reports academic/public research grants and travel, speaking, consultancy and/or research support from Biogen, Novartis, Merck, Bayer, Sanofi Genzyme, Roche and Teva. S. Ozakbas reports research support from Merck, advisory/consultancy fees from Novartis and Roche, and speaker honoraria from ARIS and Sanovel. P. Hradilek reports travel support, speaker honoraria and/or consultancy fees from Biogen, Novartis, Merck, Sanofi, Roche, Janssen and Teva. F. Patti reports advisory fees and/or research grants from Almirall, Alexion, Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis and Roche, and research grants from FISM, Reload Association, the Italian Health Ministry and University of Catania. J. Libertínová reports speaker honoraria and travel support from Biogen, Merck and Teva. R. Alroughani reports speaker and advisory-board honoraria from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi Genzyme. G. Izquierdo Ayuso reports speaker honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva. C. Boz reports travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva, and trial participation with Sanofi, Roche and Novartis.

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CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening; CI, confidence interval; CrI, credible interval.

Proportion of disability worsening attributable to PIRA

Unadjusted worsening events per 100 person-years



Treatment efficacy and relapse–disability associations

Recurrent-event Cox proportional hazards models*

High- vs low-efficacy therapy

Outcome	HR (95% CI)
Relapse	0.41 (0.39–0.42)
CDW	0.85 (0.81–0.91)
RAW	0.43 (0.38–0.48)
PIRA	1.14 (1.06–1.22)

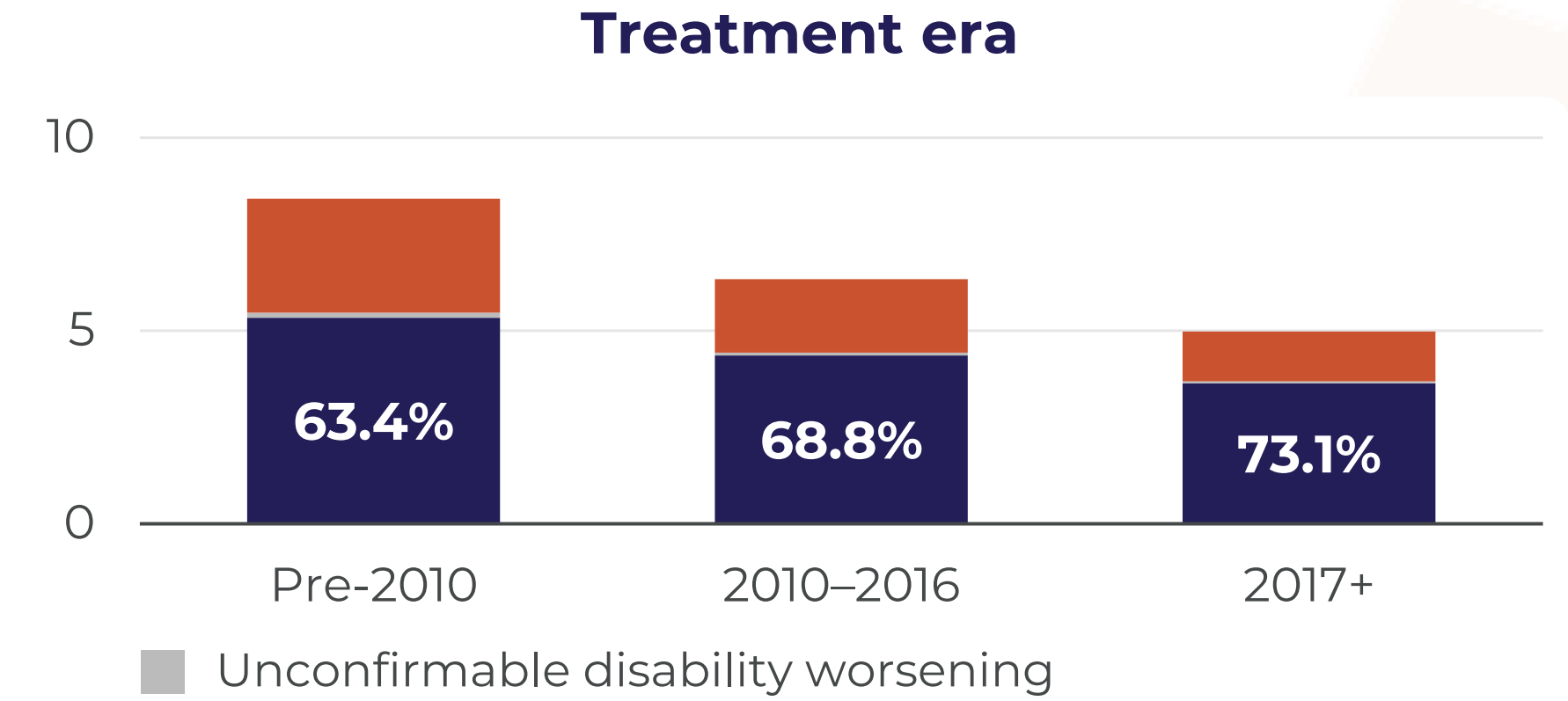
Relapse and RAW hazards were markedly lower with high-efficacy therapy than low-efficacy therapy. CDW was lower, while PIRA was not reduced.

Bayesian joint models

A twofold higher underlying relapse rate was associated with:
CDW HR 1.96 (95% CrI 1.92–2.01)
PIRA HR 1.44 (95% CrI 1.40–1.49)

Relapse trajectory was more strongly associated with CDW than PIRA. Both disability events remain linked to relapse propensity.

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Per additional prior relapse

Outcome	HR (95% CI)
CDW	1.13 (1.12–1.13)
PIRA	1.03 (1.02–1.04)

Cumulative relapse history was more strongly associated with CDW than PIRA.

Treatment × prior-relapse interaction

Outcome	Moderate vs low	High vs low
CDW	0.91 (0.90–0.93)	0.90 (0.88–0.91)
PIRA	0.96 (0.94–0.98)	0.96 (0.94–0.98)

Moderate/high-efficacy therapy attenuated the prior-relapse association, more for CDW than PIRA (interaction HRs, 95% CI).

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