

David Ellenberger^{1*}, Niklas Frahm^{1*}, Alexander Stahmann¹, Clemens Warnke², Kerstin Hellwig³, Christoph Kleinschnitz⁴, Peter Flachenecker⁵, Michaela Mai⁶, Matthias Grothe^{7†}, Uwe K. Zettl^{8†}

¹ German MS Register, MS Forschungs- und Projektentwicklungs- gGmbH (MS Research and Project Development gGmbH [MSFP]), Hannover, Germany
² University Hospital of Cologne, Medical Faculty, Department of Neurology, Cologne, Germany
³ St. Josef Hospital, Ruhr University, Department of Neurology, Bochum, Germany
⁴ University Hospital Essen, Department of Neurology and Center of Translational and Behavioral Neurosciences (C-TNBS), Essen, Germany
⁵ Neurological Rehabilitation Center Quellenhof, Bad Wildbad, Germany

⁶ Deutsche Multiple Sklerose Gesellschaft, Bundesverband e.V. (German Multiple Sclerosis Society [DMSG]), Hannover, Germany
⁷ University Medicine Greifswald, Department of Neurology, Greifswald, Germany
⁸ University Medical Center of Rostock, Department of Neurology, Neuroimmunological Section, Rostock, Germany
* Shared first authors
† Shared last authors

Background

- Disease-modifying therapies (DMTs) are essential in managing MS
- Decision to switch DMTs is influenced by various individual factors
- Age-related increased risk of comorbidities and side effects may be a relevant factor for ceasing/switching highly effective DMTs (HET)
 - ➔ systematic data on disease activity thereafter are rare
- At higher age (≥50 years vs. <50), any return of disease activity may become less likely when ceasing HET

Objectives

- Investigation of three switching scenarios: HET to HET (H-H), HET to moderately effective DMTs (H-M) and HET discontinuation for at ≥12 months (H-D)
- Focus on age-related differences and predictors of switching patterns

Methods

- Retrospective cohort study on patients from the German MS Register who had ended HET since 2018
- Relapse rates were assessed for each subgroup over a 12-months period before HET stop date (index), a 3-months period after index (washout) and up to subsequent 9 months under the new therapy
- Predictors for DMT switch pattern were investigated with boosted regression models and included reasons for discontinuing, recent disease activity, demographics and MS history

Results

- 1091 MS patients categorized into: H-H (n=786), H-M (n=86) and H-D (n=219) (Figure 1)
- Each subgroup stratified by age: <50 years (H-H [n=558], H-M [n=67], H-D [n=149]) and ≥50 (H-H [n=228], H-M [n=19], H-D [n=70]) (Table 1)
- Before HET stop date, higher annualized relapse rate (ARR) in H-H group (0.18) than in H-M (0.13) or H-D group (0.08)
- H-H ≤50: overall ARR increased temporarily during washout period (0.27) but subsequently decreased to 0.12 under the new HET
- H-M: ARR increased only in younger (0.36 during washout, 0.63 during new therapy) but not in older age group
- H-D: higher ARR in patients >50 vs. ≤50 years of age (0.14 vs. 0.05) before index, while an increase after 3 months after index was only observed in younger age group (0.11 vs. 0.13)

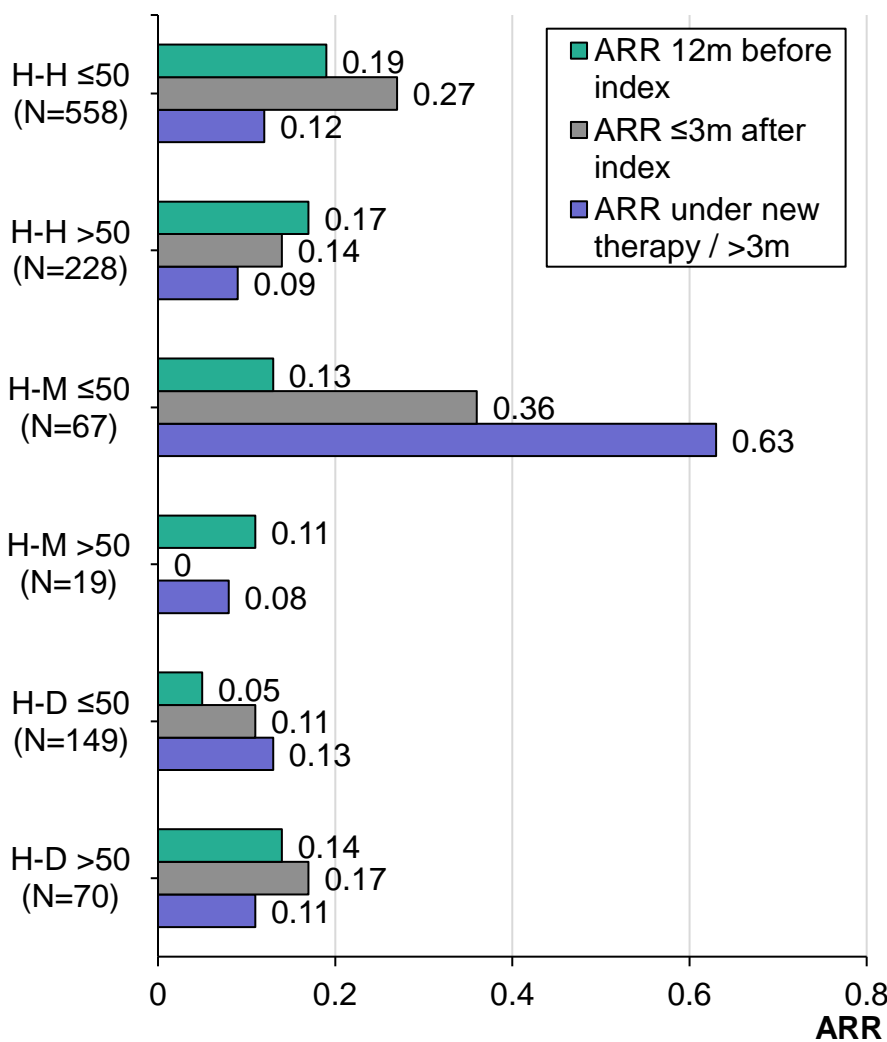
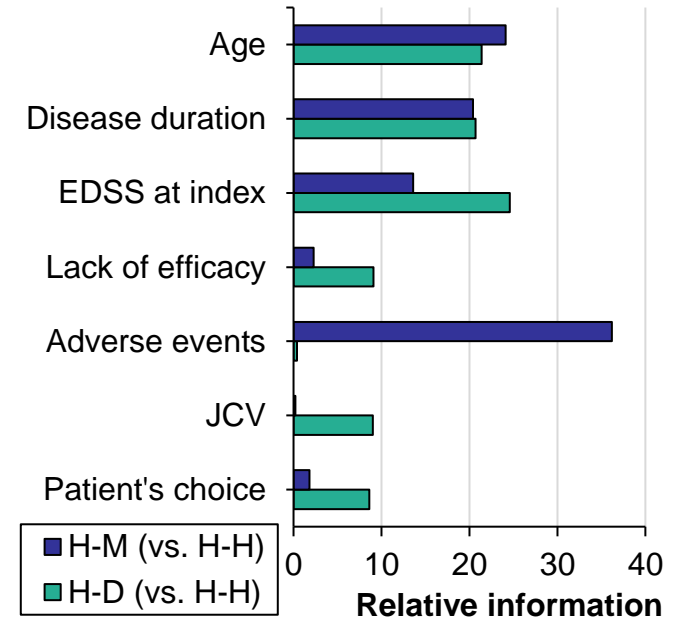


Figure 2. Estimated annualized relapse rates (ARR) in the last 12 months on discontinued HE-DMT (green), 3 months afterwards (grey), and from therapy start (restricted to >3 months) until 12 months after discontinuation / under new therapy (blue).

- Main factors associated with de-escalation (H-M vs. H-H): **adverse events, age, disease duration**, degree of disability (measured via Expanded Disability Status Scale [EDSS]) (Figure 3)
- **EDSS, age, and disease duration** were main factors for discontinuation (H-D vs. H-H)

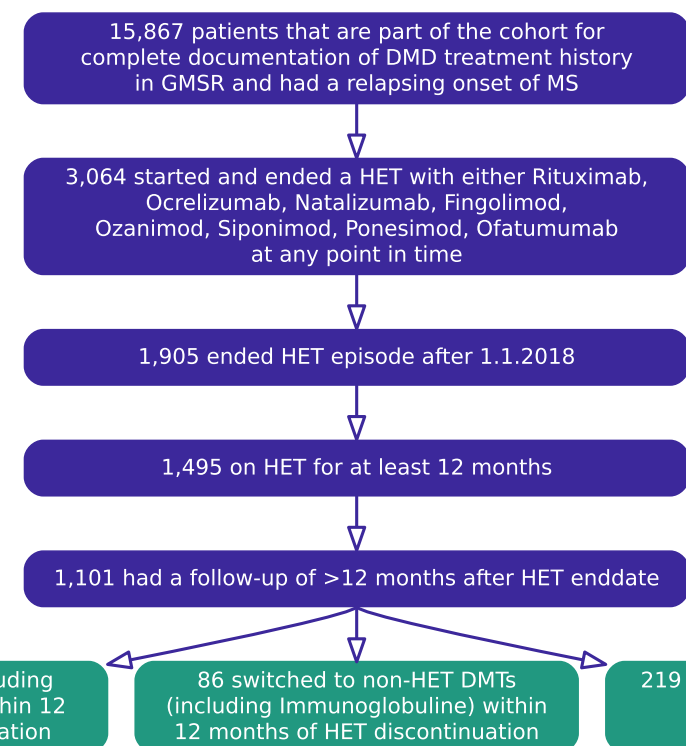


Figure 3. Factors distinguishing H-M (green) and H-D (blue) from H-H by relative information in the boosted regression models.
 Figure 1. Flowchart of applied inclusion criteria. N=10 DMT were unclassifiable, i.e., study medication, and excluded in the last step.

Table 1. Patient characteristics

	H-H			H-M			H-D		
	total	≤50y	>50y	total	≤50y	>50y	total	≤50y	>50y
	N=786	N=558	N=228	N=86	N=67	N=19	N=219	N=149	N=70
Females	72%	74%	68%	76%	76%	74%	74%	78%	67%
Age [years], mean (sd)	42.5 (11.3)	36.8 (7.6)	56.4 (4.7)	41.6 (10.4)	37.6 (7.5)	56.0 (4.8)	44.1 (11.7)	37.7 (7.4)	57.7 (6.1)
MS duration [years], mean (sd)	13.9 (8.4)	11.7 (6.7)	19.3 (9.7)	13.1 (7.3)	12.1 (7.0)	16.6 (7.4)	13.9 (8.1)	11.7 (6.9)	18.6 (8.4)
EDSS at index, mean (sd)	3.1 (1.9)	2.6 (1.7)	4.1 (1.7)	3.0 (1.8)	2.6 (1.6)	4.2 (2.0)	3.7 (2.2)	3.2 (2.2)	4.6 (1.8)
DMT discontinuation reasons:									
Lack of efficacy	30%	30%	30%	12%	12%	14%	18%	13%	26%
Adverse events	12%	10%	14%	38%	33%	57%	12%	10%	17%
Positive JCV status	17%	18%	14%	14%	17%	0%	5%	8%	0%
Patient's choice	11%	10%	13%	14%	15%	7%	23%	24%	21%

Conclusions

- Age does not strongly impact ARR following a switch between HET, but it does in the de-escalation groups
 - ▶ ARR increases after de-escalation (H-M and H-D) in patients <50 years, and remain unchanged in patients ≥50 years
- Beside age, the difference in relapse rates in older compared to younger patients might also be related to the different reasons for DMT discontinuation (i.e. adverse events and lack of efficacy) for H-M and H-D
- Effects stratified by DMT will be investigated in greater detail