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Age-dependent response to initial highly effective treatment in relapsing multiple sclerosis

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Portaccio, E., Betti, M., De Meo, E., Pastò, L., Razzolini, L., Patti, F., et al. (2025). Age-dependent response to initial highly effective treatment in relapsing multiple sclerosis. *MULTIPLE SCLEROSIS*, 31(8), 985-994 [10.1177/13524585251345317].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/1036230> since: 2026-01-11

*Published:*

DOI: <http://doi.org/10.1177/13524585251345317>

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## **Age-dependent response to initial highly effective treatment in relapsing multiple sclerosis**

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## **Key points**

**Question:** Does the superiority of immediate initiation of highly effective (HE) disease-modifying treatments (DMTs) in relapsing multiple sclerosis (MS) persist in elderly patients?

**Findings:** This multicenter cohort study of 3,396 patients with relapsing MS found that the benefit of immediate HE-DMT initiation diminishes in patients over 45 years of age. However, prolonged exposure to DMTs, regardless of their efficacy level, reduced disability accumulation, demonstrating the overall effectiveness of DMTs even in this older age group.

**Meaning:** While DMT exposure helps protect MS patients from disability accumulation across all age groups, the advantage of immediate HE-DMT initiation tends to wane with age. Our findings help optimize the risk-benefit balance in elderly subjects with MS and assist clinicians and patients in making more personalized therapeutic decisions.

## **ABSTRACT**

**IMPORTANCE:** Early initiation of highly effective (HE) treatment is increasingly favoured over the escalation approach in people with multiple sclerosis (MS), who are also experiencing increasing age with increasing life expectancy.

**OBJECTIVE:** To assess the impact of age on the superiority of HE disease-modifying treatments (DMTs) compared to platform DMTs in a real-world population of patients with relapsing MS.

**DESIGN, SETTING, AND PARTICIPANTS:** This cohort study utilized prospectively collected data from the Italian MS Register, including information from 82,197 patients across 77 Italian MS centres.

**MAIN OUTCOMES AND MEASURES:** The primary outcome was the occurrence of 24-week confirmed disability accumulation (CDA) events in patients treated with HE versus platform DMTs after 2 years from initiation and throughout the entire follow-up period.

**EXPOSURES:** Clinical and magnetic resonance imaging (MRI) characteristics, duration of exposure to DMT, either HE or platform.

**RESULTS:** After applying inclusion and exclusion criteria and conducting a 1:1 propensity score matching, the study evaluated 3,396 patients with MS (1,698 initiating HE DMTs, 1,698 initiating platform DMTs). After the first 2 years of follow-up, the proportion of CDA events was significantly lower in patients who started on HE DMTs (12.2%) compared to those on platform DMTs (15%), as confirmed by Cox regression analysis (HR=0.22, 95% CI 0.10-0.47;  $p<0.001$ ). A significant interaction between age and HE DMTs was observed, indicating reduced effectiveness

of HE DMTs with increasing age (HR=1.50, 95% CI 1.11-2.03; p=0.008). The protective effect of HE DMTs was evident in patients under 45 years of age (HR=0.49, 95% CI 0.39-0.63; p<0.001) but was not observed in patients over 45 (HR=0.77, 95% CI 0.54-1.08, p=0.125). Similar findings emerged when assessing the risk of CDA over the entire follow-up period. Notably, prolonged exposure to any DMT during follow-up reduced disability accumulation even in patients over 45 years of age (HR 0.13, 95% CI 0.02-0.99; p=0.050).

**CONCLUSIONS AND RELEVANCE:** This real-world study of relapsing MS patients demonstrates that the benefit of immediate initiation of HE treatment diminishes with age, particularly after 45 years. However, even in this older age group, DMT exposure appears to reduce disability accumulation, indicating the overall effectiveness of DMTs regardless of their efficacy level, even beyond 45 years of age. It is however possible that, on an individual level, early HE treatment could still be more effective in this age group. Our findings help assist clinicians and patients in making more personalized therapeutic decisions.

## **INTRODUCTION**

Recent epidemiological studies have shown an ever-growing prevalence of multiple sclerosis (MS) among the elderly, with peak-prevalence estimates occurring between the ages of 55 and 59 years;<sup>1-6</sup> moreover, a forward shift towards an older age at disease onset has been observed, possibly due at least in part to better case ascertainment and more sensitive diagnostic criteria and instruments.<sup>7,8</sup>

This evolution in MS epidemiology poses unique challenges in disease management, as therapeutic decisions for elderly patients must take into account additional risk factors associated with frequent

comorbidities,<sup>9</sup> polypharmacy,<sup>10</sup> and immunosenescence,<sup>11</sup> the physiological aging of the immune system. On the other hand, data on the efficacy and safety of disease-modifying treatments (DMTs) in this age group are extremely limited. Indeed, evidence-based medicine in MS primarily stems from trials that have mostly enrolled subjects between 18 and 55 years of age, while real-world, registry-based data indicate that a large proportion of patients older than 60 years are still being treated.<sup>12</sup>

While ample evidence supports the superiority of early introduction of highly effective (HE) DMTs in relapsing MS,<sup>13–16</sup> whether this benefit is unaffected by aging remains an unresolved issue. Post-hoc analyses and meta-analyses of randomized controlled trials, as well as preliminary real-world evidence suggest a decreasing efficacy of HE-DMTs with increasing age.<sup>17–20</sup> Regarding safety, immunosenescence makes older people more vulnerable to infections<sup>21–25</sup> and malignancies,<sup>26</sup> particularly when treated with HE-DMTs. This increases the complexity of balancing the benefits and risks of more aggressive treatment approaches in elderly MS patients.

Against this background, using data collected within the Italian MS Register, we compared the risk of disability accumulation between immediate initiation of HE-DMTs and platform DMTs in a real-world cohort of relapsing MS patients, taking into account the effect of age at treatment onset. We hypothesized that aging could affect DMT effectiveness by reducing the benefit of early HE-DMT initiation compared to an escalation paradigm.

## **METHODS**

### **Design**

This cohort study used prospectively acquired data extracted from the Italian MS Register<sup>27</sup> on 30 November 2022. The Italian MS Register was approved by the Policlinico of Bari Ethics Committee and by the local ethics committees in all participating centers. Written informed consent was obtained from all enrolled patients in accordance with the Declaration of Helsinki. The minimum dataset required for this study comprised the main demographic characteristics, the date of disease onset, clinical course, follow-up visit dates, Expanded Disability Status Scale (EDSS)<sup>28</sup> scores recorded at each visit, the date of relapses, start and end dates of DMTs and DMT type. Quality assurance through online certification of EDSS competency is required at each participating site. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

## **Patients**

Patients with a clinically isolated syndrome (CIS) or relapsing-remitting (RR) course at the first neurological evaluation, a minimum of four visits with EDSS evaluation, a minimum of two-year follow-up and starting any DMT, either platform (interferons, glatiramer acetate, azathioprine, dimethyl fumarate, teriflunomide) or HE DMTs (natalizumab, anti CD20s, S1P modulators, cladribine, alemtuzumab, mitoxantrone) were included. We excluded patients with a primary or secondary progressive course at the first neurological evaluation and those enrolled in randomized controlled trials. The baseline was defined as the nearest visit within 120 days before or after the first DMT starting date; if baseline visits occurred within 30 days from a relapse, baseline was defined as the following assessment with EDSS scoring performed outside of a relapse and within 1 year from the first evaluation. When re-baseline was not possible, patients were excluded. MS duration was calculated from the first demyelinating event. The follow-up time was defined as the time between baseline and last available EDSS evaluation. Confirmed disability accrual (CDA) was defined as  $\geq 24$ -week confirmed disability increase from study baseline, measured by EDSS (increase  $\geq 1.5$  points if baseline EDSS = 0; increase  $\geq 1.0$  point if baseline EDSS  $\geq 1.0$  and  $\leq 5.5$ ;

increase  $\geq 0.5$  point if baseline EDSS  $\geq 6.0$ ). The date of CDA was assigned at the first EDSS score at which an increase occurred. For DMT exposure, the proportion of time during which patients received DMT was defined by the recorded starting and ending dates. The total time a patient spent on treatment was calculated including any switches and gaps in treatment. We did not consider gaps  $< 3$  months as a therapy interruption. For DMT in which extended treatment effects are recognized, the estimated treatment effect duration was used to calculate the proportion of time that patients received therapy (6 months for mitoxantrone, rituximab, ocrelizumab; 5 years for alemtuzumab and autologous haematopoietic stem-cell transplantation; 2 months for natalizumab; 12 months for cladribine).<sup>29</sup>

### **Statistical Analysis**

Patients were matched on their Propensity Score (PS) of starting HE DMTs, with a 1:1 nearest neighbour matching ratio without replacement, within a caliper of 0.01 SD of the PS. Individual PS were calculated using a multivariable logistic model including the following covariates: sex, age, symptom at onset (multifocal versus monofocal), disease duration, disease course, EDSS score at baseline, number of relapses in the year before baseline.

The baseline and follow-up characteristics were expressed as mean and standard deviation (SD) or frequency and percentage for continuous and categorical covariates, respectively. Categorical and continuous variables were compared by using chi<sup>2</sup> statistic, Mann–Whitney and Kruskal–Wallis tests, as appropriate.

Predictors of CDA events in HE vs platform DMTs after 2 years and the entire follow up were assessed through Cox regression models. The proportional hazard assumption was assessed through graphical inspections of residuals and scaled Schoenfeld residual test. In case of assumption violation, a time-dependent interaction was added to the model.<sup>30</sup> Cox regression models were adjusted for visit density and percentage of time spent on DMT before the event. To verify the dependency of HE DMT effectiveness on patient age, age ( $\leq 20$ ; 20-40; 40-60;  $> 60$ ) and an

interaction term age ( $\leq 20$ ; 20-40; 40-60;  $> 60$ )\*HE DMT were added. In case of significant interaction, predictors of CDA events in HE vs platform DMTs after 2 years and the entire follow up were further assessed in patients with baseline age  $\leq 45$  and  $> 45$ . The cut-off of 45 years of age was selected on the base of available literature.<sup>20,26</sup>

Results of regression analyses were expressed as hazard ratio (HR) and 95% confidence interval (CI).

Two sensitivity analyses were performed: 1) including patients with baseline visit on or after the 1<sup>st</sup> January 2000; 2) including patients with brain/spinal MRI scan data available at baseline. In both cases, a new PS matching was applied with the same procedure as in the main analysis. In the sensitivity analysis with MRI data, baseline MRI activity (T1 gd enhancing lesions or new T2 lesions) was included among PS adjusting covariates.

All statistical analyses were performed with SPSS software, version 25.0 (SPSS inc.) and R, version 4.1.2 (R Foundation for Statistical Computing). A 2-sided P-value  $< 0.05$  was considered statistically significant.

Anonymized data, not published in the article, will be shared on reasonable request from a qualified investigator.

## **RESULTS**

Data extraction was completed on 30th of November 2022. We had access to 82197 register patients from 77 Italian MS centers. By applying inclusion and exclusion criteria, we identified 20984 patients. After PS matching, our sample consisted of 3396 patients, of whom 1698 starting platform DMTs, and 1698 starting HE DMTs (Figure 1). Characteristics of the study sample before and after propensity score matching are depicted in Table 1. The matching procedure reduced the difference in PS between the two groups from 0,05 to 0,001, corresponding to a 98% improvement in the overall balance. The close match on individual characteristics was demonstrated by

standardized differences <10% for all matched characteristics (Table1). After the first 2 year follow-up, in the whole matched cohort (n=3396), 462 (13,6%) CDA events occurred, of which 208 (12,2%) in patients starting on HE DMTs, 254 (15,0%) in those starting on platform therapies (p=0,021). In the multivariable Cox regression analysis, starting on HE DMTs (HR=0,22, 95%CI 0,10-0,47; p<0,001) and longer exposure to any DMT before the event (HR=0,39, 95%CI 0,25-0,61); p<0,001) were associated with lower risk of CDA. On the other hand, older age at baseline was associated with higher risk of CDA (HR=1,35, 95%CI 1,10-1,65; p=0,004) (Table 2). The interaction between age and HE DMTs was significant, indicating reduced effectiveness of HE DMT with increasing age (HR=1,50, 95%CI 1,11-2,03; p=0,008).

Focusing on the subgroup of patients aged  $\leq 45$  years (n=2697; 1358 starting platform and 1339 starting HE DMTs) in the first 2 year follow up the proportion of CDA was significantly lower in patients starting on HE DMTs (136, 10,2% vs 183, 13,5%; p=0,008). In the multivariable Cox regression analysis, immediate treatment with HE DMTs (HR= 0,49, 95%CI 0,39-0,63; p<0,001) and longer exposure to any DMT before the event (HR=0,31, 95%CI 0,19-0,54; p<0,001) were associated with lower risk of CDA (Table 3).

Conversely, in the subgroup of patients aged  $> 45$  years (n=699; 340 starting platform, 359 starting HE DMTs), the proportion of CDA in the first 2 years of follow up was not significantly different in the two groups (HE DMT 72, 20,1% vs platform 71, 20,9%; p=0,787), as confirmed in the Cox regression analysis (HR=0,77, 95%CI 0,54-1,08, p=0,125). A longer exposure to any DMT before the event was marginally associated with a lower risk of CDA in this age range, as well (HR 0,13, 95%CI 0,02-0,99; p=0,050) (Table 4).

The same Cox regression analyses were run over the entire follow up (8,6 $\pm$ 5,3 years) and confirmed the previous results. In particular, starting on HE DMTs was associated with lower risk of CDA in the total sample (HR=0,40, 95%CI 0,26-0,62 p<0.001, eTable 1 in the Supplement) and in patients aged  $\leq 45$  years (HR=0,65, 95%CI 0,57-0,74; p<0,001, eTable 2 in the Supplement), The

association was no longer significant in patients aged > 45 years (HR=1,01, 95%CI 0,83-1,23; p=0,908, eTable 3 in the Supplement).

The two sensitivity analyses confirmed the main study findings (eTables 4-15 in the Supplement).

## **DISCUSSION**

In this real-world, PS-matched cohort study, we found that the widely acknowledged superiority of immediate initiation of HE treatments compared to platform therapies in MS<sup>13-16</sup> tends to diminish with aging, particularly after the age of 45. This finding addresses a gap in RCTs, which primarily include patients aged 18-55 years, limiting the availability of data on treatment efficacy in “extreme” age ranges, such as children or adolescents and the elderly. Furthermore, our results align with preliminary evidence from post-hoc analyses of pivotal DMT trials<sup>31-34</sup> and a meta-analysis of RCTs<sup>17</sup>, which demonstrate a decline in the ability to prevent disability accrual in patients older than 40-53 years. Additionally, initial evidence from real-world studies indicates a decrease in DMT efficacy with age,<sup>19</sup> along with a tendency for the advantage of HE over platform DMTs to diminish.<sup>20</sup>

A recently published paper showed a significant reduction in the annualized relapse rate and longer time to first relapse when using ocrelizumab compared to two platform therapies, interferon and glatiramer acetate, in patients over 60 years of age, without differences in confirmed disability progression.<sup>35</sup> We believe that the choice of outcome measures plays a significant role, particularly in this age group. It is well known that relapse activity in MS declines with increasing age.<sup>36,37</sup> Therefore, using relapse rate as a measure of clinical effectiveness of a DMT in older subjects might represent a less meaningful outcome. We feel that the use of disability accrual risk as the primary outcome represents a significant strength of our study. In this context, immediate initiation

of HE-DMTs did not reduce disability accumulation in patients older than 45 years, compared to a treatment escalation approach.

It should be noted, however, that even in patients over 45 years of age, longer exposure to any DMT, regardless of its efficacy level, was associated with a reduction in disability accrual. This finding marginally emerged in a previous real-world study. Specifically, Amato et al.<sup>19</sup> observed a trend towards sustained DMT efficacy in patients with late-onset MS. In another recent study involving MS patients over 50, the use of DMTs, and switching DMTs in the case of relapses, was associated with stability over active (relapsing), but not over progressive disease.<sup>38</sup>

Overall, these findings show that while prompt initiation of DMT remains a cornerstone of MS treatment, with increasing age, starting with a platform DMT (i.e., the escalating approach) could achieve effectiveness comparable to that of immediate initiation of HE-DMTs (i.e., the early aggressive approach). The early aggressive approach seems particularly suited for younger patients. In elderly MS patients, the introduction of HE-DMTs might be more appropriate after disease activity or disability accrual persist despite the use of platform DMTs. Whether a specific threshold of age exists at which this shift occurs, and which individual characteristics contribute to determine the subject response to treatments, remain open issues. The cut-off used in our study is based on a real-world study and a meta-analysis of RCTs, which demonstrated reduced efficacy<sup>20</sup> and higher risk of neoplasms<sup>26</sup> of HE-DMTs in patients over 45 years of age. However, it is possible that, on an individual level, early HE treatments could still be more effective than early platform DMTs in selected cases, even in those older than 45 years.

In this regard, our study suggests that traditional clinical and MRI features, such as EDSS disability level, relapse rate, and the presence of gadolinium-enhancing lesions or new/enlarging T2 lesions on MRI, may not be entirely appropriate markers in this age group. This may be partly due to the overall low inflammatory activity in advanced age and longer disease duration,<sup>39-41</sup> where

“smoldering” prevails on acute inflammation.<sup>42</sup> Therefore, identifying reliable biomarkers to distinguish the subgroup of older patients who could benefit from immediate initiation of HE-DMTs is needed. Potential candidates include more granular clinical measures, such as quantitative motor assessments<sup>43</sup> and neuropsychological tests,<sup>44,45</sup> laboratory biomarkers related to neurodegeneration,<sup>46</sup> such as neurofilament light chain<sup>47</sup> and glial fibrillary acidic protein<sup>48</sup> serum levels, and more advanced MRI features, such as slowly expanding lesions (SELs),<sup>49,50</sup> paramagnetic rim lesions (PRLs),<sup>51</sup> as well as quantitative measures of global and regional atrophy,<sup>52,53</sup> including cervical cord atrophy.<sup>54</sup>

Among MRI parameters, also the "brain age gap"—the difference between a patient's chronological age and the biological age of their central nervous system—appears to be a promising marker.<sup>55</sup> Other multidimensional indexes of biological age, which combine routine laboratory or instrumental analyses, such as the National Health and Nutritional Survey (NAHNES) biological age index,<sup>56</sup> have been recently used also in MS patients. It is possible to speculate that subjects with a greater brain age gap might derive less benefit from early initiation of HE-DMTs.

The results from our study are particularly relevant in the context of the growing body of evidence that raises safety concerns about exposing elderly MS patients to DMTs, particularly the HE ones.<sup>57</sup> Older age is associated with immunosenescence,<sup>58</sup> and also with increased individual frailty<sup>59,60</sup> due to the frequent coexistence of comorbidities<sup>61</sup> and polypharmacy.<sup>62</sup> These factors can increase the risk of severe adverse events from drug-drug interactions<sup>63</sup> and serious infections.<sup>64</sup> For instance, the risk of progressive multifocal leukoencephalopathy (PML) with natalizumab and dimethyl fumarate,<sup>65</sup> herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections and reactivations,<sup>66</sup> and anti-CD20 related hypogammaglobulinemia appear to increase with age.<sup>67</sup> Moreover, a recent meta-analysis of RCTs involving depleting agents in MS patients revealed a higher risk of developing neoplasms after the age of 45.<sup>26</sup>

The indication that platform DMTs may offer sufficient effectiveness in older MS patients supports a more personalized approach, potentially reducing the safety risks associated with more aggressive DMTs while maintaining comparable disease activity control. Furthermore, our results underscore the need for more evidence on de-risking strategies for DMT use in elderly MS patients, including de-escalation<sup>68</sup> or cessation strategies.<sup>69</sup>

In interpreting our findings some limitations should be considered. The evaluation of patients at baseline and follow-up was based solely on clinical assessments, as MRI data were only partially available at baseline. Nevertheless, a sensitivity analysis that included baseline MRI data from 1,934 patients confirmed the main results of our study. Additionally, we could not assess the absolute efficacy of DMTs due to the lack of a placebo arm. However, shorter exposure to any DMTs during the follow-up period was associated with a higher risk of disability accumulation. Moreover, the sample size of MS patients older than 45 years was relatively small, limiting our ability to capture slight differences in efficacy between HE and platform DMTs. Finally, we did not evaluate the safety of DMTs due to incomplete safety data available in the registry.

## **CONCLUSION**

Our real-world study of relapsing MS patients indicates that the benefit of immediate initiation of HE treatments tends to diminish with age, particularly after 45 years. However, even in this age group, exposure to any DMTs, regardless of their efficacy level, is associated with a reduced risk of disability accumulation, confirming the overall effectiveness of DMTs in MS, even beyond 45 years of age. Nevertheless, on an individual basis it is possible that early HE treatment could be more effective also in this age group; further research focusing on imaging and fluid biomarkers is needed to identify those patients who may still benefit from a more aggressive treatment approach. Our findings help optimize the risk-benefit balance in elderly subjects with MS and assist clinicians and patients in making more personalized therapeutic decisions.

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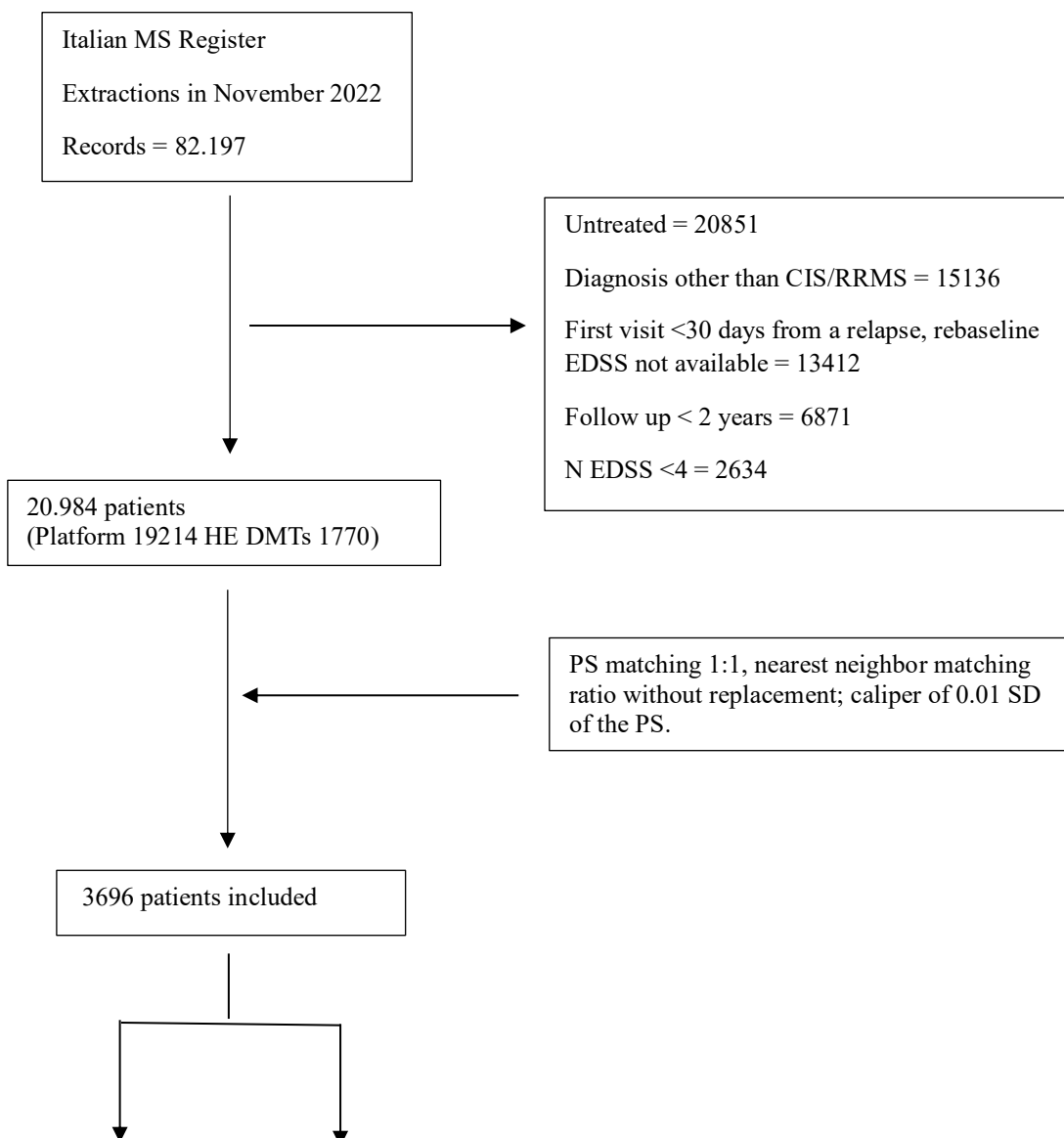
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**FIGURE 1. Flow Diagram of the Study Sample.**



1698 pts starting platform DMTs

1698 pts starting HE DMTs

**Table1. Demographic and Clinical Characteristics of the study sample before and after PS matching.**

	TOTAL	UNMATCHED			MATCHED		
	n=20984	PLATFOR M (n=19214)	HE (n=1770)	SDM	PLATFOR M (n=1698)	HE (n=1698)	SDM
<b>Sex, F, n (%)</b>	14108 (67.2)	12968 (67.5)	1140 (64.4)	0.064	1100 (64.8)	1088 (64.1)	0.015
<b>Age at baseline, mean (SD), years</b>	36.0 (10.8)	36.1 (10.8)	35.2 (11.4)	-0.077	35.3 (10.7)	35.1 (11.4)	-0.014
<b>Onset Topography, multifocal, n (%)</b>	2456 (11.7)	2204 (11.5)	252 (14.2)	0.079	234 (13.8)	233 (13.7)	-0.002
<b>Disease duration, mean (SD), years</b>	5.1 (6.5)	5.2 (6.6)	4.1 (6.0)	-0.183	4.3 (5.7)	4.2 (6.0)	-0.025
<b>EDSS at baseline, mean (SD)</b>	1.9 (1.3)	1.9 (1.2)	2.6 (1.6)	0.469	2.5 (1.4)	2.5 (1.5)	-0.004
<b>Disease course, n (%)</b> <b>CIS</b> <b>RRMS</b>	948 (4.5) 20036 (95.5)	874 (4.5) 18340 (95.5)	74 (4.2) 1696 (95.8)	0.018	63 (3.7) 1635 (96.3)	73 (4.3) 1625 (95.7)	-0.029
<b>Relapses in the year before baseline, mean (SD)</b>	1.0 (0.9)	1.0 (0.9)	1.2 (1.0)	0.207	1.2 (1.0)	1.2 (1.0)	-0.041

Abbreviations: HE, High Efficacy; SDM, standardized mean difference; F, female; SD, standard deviation; EDSS, expanded disability status scale; CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis

**Table 2. Multivariable Cox Regression Model in the total sample after first 2 year follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.22	0.10-0.47	<0.001
<b>Age at baseline</b>	1.35	1.10-1.65	0.004
<b>Age*HE DMT</b>	1.50	1.11-2.03	0.008
<b>Visit density <sup>a</sup></b>	1.66	1.59-1.74	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.39	0.25-0.61	<0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.

<sup>a</sup> Adjusted for an interaction term with time

**Table 3. Multivariable Cox Regression Model in patients  $\leq 45$  years of age after first 2 year follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.49	0.39-0.63	<0.001
<b>Visit density <sup>a</sup></b>	1.70	1.61-1.79	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.31	0.19-0.54	<0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.

<sup>a</sup> Adjusted for an interaction term with time

**Table 4. Multivariable Cox Regression Model in patients  $>45$  years of age after first 2 year follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.77	0.54-1.08	0.125
<b>Visit density <sup>a</sup></b>	1.68	1.52-1.86	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.13	0.02-0.99	0.050

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.

<sup>a</sup> Adjusted for an interaction term with time

**eTable1. Multivariable Cox Regression Model in the total sample over the entire follow up (CDA events = 1438 (42.3%); 607 (35.7%) in HE DMT, 831 (48.9%) in platform; p<0.001)**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.40	0.26-0.62	<0.001
<b>Age</b>	1.53	1.36-1.72	<0.001
<b>Age*HE DMT</b>	1.30	1.09-1.55	0.004
<b>Visit density<sup>a</sup></b>	1.49	1.45-1.53	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.68	0.53-0.86	0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
<sup>a</sup> Adjusted for an interaction term with time

**eTable2. Multivariable Cox Regression Model in patients ≤45 years of age over the entire follow up (CDA events = 1024 (38%); 404 (30.2%) in HE DMT, 620 (45.7%) in platform DMT; p<0.001)**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.65	0.57-0.74	<0.001
<b>Visit density<sup>a</sup></b>	1.51	1.47-1.56	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.51	0.38-0.69	<0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
<sup>a</sup> Adjusted for an interaction term with time

**eTable3. Multivariable Cox Regression Model in patients ≥45 years of age over the entire follow up (CDA events = 414 (59.2%); 203 (56.5%) in HE DMT, 211 (62.1) in platform; p=0.138)**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	1.01	0.83-1.23	0.908
<b>Visit density<sup>a</sup></b>	1.49	1.41-1.57	<0.001
<b>Percentage of time of follow up spent on DMT</b>	1.27	0.83-1.96	0.275

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
a Adjusted for an interaction term with time

## SENSITIVITY ANALYSES

**eTable4. Sensitivity analysis - MRI activity at baseline. Total sample (n=1934). 2year follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.71	0.55-0.92	0.009
<b>Visit density <sup>a</sup></b>	0.44	0.38-0.51	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.72	0.35-1.48	0.370

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
a Adjusted for an interaction term with time

**eTable5. Sensitivity analysis - MRI activity at baseline. Patients <45aa (n=1568). 2year follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.68	0.50-0.93	0.015
<b>Visit density <sup>a</sup></b>	0.46	0.39-0.54	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.75	0.31-1.80	0.513

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
a Adjusted for an interaction term with time

**eTable6. Sensitivity analysis - MRI activity at baseline. Patients >45aa (n=366). 2year follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.70	0.44-1.11	0.128
<b>Visit density <sup>a</sup></b>	0.36	0.26-0.51	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.78	0.22-2.83	0.705

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
a Adjusted for an interaction term with time

**eTable7. Sensitivity analysis - MRI activity at baseline. Total sample (n=1934). Entire follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.81	0.70-0.94	0.005
<b>Visit density <sup>a</sup></b>	1.00	0.99-1.01	0.504
<b>Percentage of time of follow up spent on DMT</b>	0.99	0.99-1.00	0.010
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable8. Sensitivity analysis - MRI activity at baseline <45aa (n=1568). Entire follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.75	0.63-0.90	0.002
<b>Visit density <sup>a</sup></b>	1.01	0.99-1.01	0.256
<b>Percentage of time of follow up spent on DMT</b>	1.27	0.81-1.99	0.302
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable9. Sensitivity analysis - MRI activity at baseline >45aa (n=366). Entire follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.97	0.73-1.29	0.832
<b>Visit density <sup>a</sup></b>	1.00	0.99-1.02	0.552
<b>Percentage of time of follow up spent on DMT</b>	1.30	0.62-2.69	0.488
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable10. Sensitivity analysis – Diagnosis after 1st January 2000. Total sample (n=3348). Follow up 2 years.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.81	0.68-0.98	0.027
<b>Visit density <sup>a</sup></b>	0.50	0.45-0.56	<0.001
<b>Percentage of time of follow up spent on DMT</b>	1.06	0.64-1.75	0.822
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable11. Sensitivity analysis – Diagnosis after 1st January 2000. Patients <45 years(n=2666). Follow up 2 years.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.76	0.61-0.95	0.017
<b>Visit density <sup>a</sup></b>	0.49	0.44-0.56	<0.001
<b>Percentage of time of follow up spent on DMT</b>	0.81	0.45-1.47	0.489
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable12. Sensitivity analysis – Diagnosis after 1st January 2000. Patients >45 years (n=682). Follow up 2 years.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.88	0.63-1.22	0.431
<b>Visit density <sup>a</sup></b>	0.55	0.44-0.67	<0.001
<b>Percentage of time of follow up spent on DMT</b>	2.01	0.81-5.34	0.126
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable13. Sensitivity analysis – Diagnosis after 1st January 2000. Total sample (n=3348). Entire follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.88	0.79-0.98	0.017
<b>Visit density <sup>a</sup></b>	1.00	1.00-1.01	0.216
<b>Percentage of time of follow up spent on DMT</b>	0.99	0.77-1.28	0.938
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable14. Sensitivity analysis – Diagnosis after 1st January 2000. Patients <45 years (n=2666). Entire follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	0.81	0.71-0.92	0.001
<b>Visit density <sup>a</sup></b>	1.01	0.99-1.01	0.105
<b>Percentage of time of follow up spent on DMT</b>	0.96	0.70-1.31	0.773
Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval. a Adjusted for an interaction term with time			

**eTable15. Sensitivity analysis – Diagnosis after 1st January 2000. Patients >45 years (n=682). Entire follow up.**

	<b>HR</b>	<b>95%CI</b>	<b>p value</b>
<b>HE vs platform DMTs</b>	1.05	0.86-1.28	0.632
<b>Visit density <sup>a</sup></b>	1.01	1.00-1.02	0.056
<b>Percentage of time of follow up spent on DMT</b>	1.37	0.88-2.11	0.160

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.  
<sup>a</sup> Adjusted for an interaction term with time