Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis

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Complete List of Authors:	Roos, Izanne; The University of Melbourne Department of Medicine and Radiology, CORe, Department of Medicine Sharmin, Sifat; University of Melbourne, CORe, Department of Medicine Malpas, Charles; University of Melbourne, Department of Medicine; Royal Melbourne Hospital, Department of Neurology Ozakbas, Serkan; Dokuz Eylul University, Department of Neurology Lechner-Scott, Jeanette; John Hunter Hospital Department of Neurology, Neurology Hodgkinson, Sue; University of New South Wales, Faculty of Medicine Alroughani, Raed; Amiri Hospital, Medicine - Neurology EICHAU, sara; Hospital Universitario Virgen Macarena, NEUROLOGY Boz, Cavit; Karadeniz Technical University, Neurology Van der Walt, Anneke; Monash University, Central Clinical School, Neuroscience; Alfred Health, Neurology Butzkueven, Helmut; Monash University, Van Cleef Centre for Nervous Diseases Buzzard, Katherine; Eastern Health, Department of Neurology; Monash University Eastern Health Clinical School, Eastern Health Clinical School Skibina, Olga; Box Hill Hospital, Neurology Foschi, Matteo ; Ospedale S.Maria delle Croci, AUSL Romagna, Neurology Unit Grand'Maison, Francois; Charles LeMoyne Hospital, Neurology John, Nevin; Monash Medical Centre Clayton, Neurology; Monash University, Department of Medicine Grammond, Pierre; Hotel Dieu De Levis, Neurology Terzi, Murat; Ondokuz Mayis University, Medical School, Neurology Prevost, Julie; CSSS Saint-Jerome, Neurology Barnett, Michael; Sydney Neuroimaging Analysis Centre, Sydney Neuroimaging Analysis Centre; University of Sydney, Brain and Mind

	Research Institute Laureys, Guy; UZ Brussels, Neurology Van Hijfte, Liesbeth; University Hospital Ghent, Department of Neurology Sanchez-Menoyo, Jose; Hospital de Galdakao-Usansolo, Department of Neurology Blanco, Yolanda; Hospital Clinic de Barcelona, Advanced imaging in neuroimmunological diseases (ImaginEM) Oh, Jiwon; University of Toronto, Neurology McCombe, Pamela; The University of Queensland, School of Medicine Ramo, Cristina; Hospital Universitario Germans Trias i Pujol, NEUROLOGY Soysal, Aysun; Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery , I. Neurology Department Prat, Alexandre; Université de Montréal, Neuroscience Duquette, Pierre; CHUM, Neurology; Université de Montréal, Neurosciences Yamout, Bassem ; American University of Beirut Medical Center, Department of Neurology Khoury , Samia J. ; AUB, Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon; Abu-Haidar Neuroscience Institute, American University of Beirut Medical Center Vanpesch, Vincent; Cliniques Universitaires, Neurology Macdonell, Richard; Austin Hospital, Neurology Sá, Maria José; Hospital S. João, Neurology; University Fernando Pessoa, Health Sciences Faculty Slee, Mark; Flinders Medical Centre, Department of Neurology Kuhle, Jens; University Hospital Basel, Neurology Maimone, Davide; Garibaldi Hospital, Division of Neurology Spitaleri, Daniele; Azienda Ospedaliera di Rilievo Nazionale e di Alta Specialita San Giuseppe Moscati, Neurology Willekens, Barbara; Universiteir Ziekenhuis Antwerpen, Neurology Al Asmi, Abdullah; Sultan Qaboos University Hospital, Department of Medicine Tallantyre, Emma; University Hospital of Wales, Neurology Robertson, Neil; Cardiff University, Neurology Coles, Alasdair; University of Cambridge School of Clinical Medicine, Department of Clinical Neurosciences Brown, James; University of Cambridge, Department of Clinical Neurosciences; University College London Institute of Neurology, NMR Research Unit Kalincik, Tomas; Royal Melbourne Hospital, CORe, Dement of Neurology; University of Melbourne, CORe, Department of Medicine
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Abstract:	Background: Comparisons between cladribine and other potent immunotherapies for multiple sclerosis are lacking. Objectives: To compare the effectiveness of cladribine against fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis. Methods: Patients with relapsing-remitting multiple sclerosis treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab were identified in the global MSBase cohort and two additional UK centres. Patients were followed for >=6/12 and had >=3 in-person disability assessments. Patients were matched using propensity score. Four

	pairwise analyses compared annualised relapse rates and disability outcomes. Results: The eligible cohorts consisted of 853(fingolimod), 464(natalizumab), 1131(ocrelizumab), 123 (alemtuzumab), or 493(cladribine) patients. Cladribine was associated with a lower ARR than fingolimod (0.07vs0.12, p=0.006), and a higher ARR than natalizumab (0.10vs0.06, p=0.03), ocrelizumab (0.09vs0.05, p=0.008), and alemtuzumab (0.17vs0.04, p<0.001). Compared to cladribine, the risk of disability worsening did not differ in patients treated with fingolimod (HR1.08, 95%CI 0.47-2.47) or alemtuzumab (0.73, 0.26-2.07), but was lower for patients treated with natalizumab (0.35, 0.13-0.94) and ocrelizumab (0.45, 0.26-0.78). There was no evidence for a difference in disability improvement. Conclusion: Cladribine is an effective therapy that can be viewed as a step-up in effectiveness from fingolimod, but is less effective than the most potent intravenous multiple sclerosis therapies.

Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis

Authors

Izanne Roos 1,2; Sifat Sharmin 1,2; Charles Malpas 1,2; Serkan Ozakbas 3; Jeannette Lechner-Scott 4,5; Suzanne Hodgkinson 6; Raed Alroughani 7; Sara Eichau Madueño 8; Cavit Boz 9; Anneke van der Walt 10,11; Helmut Butzkueven 10,11; Katherine Buzzard 2,12,13; Olga Skibina 10,12,13; Matteo Foschi 14,15; Francois Grand'Maison 16; Nevin John 17,18; Pierre Grammond 19; Murat Terzi 20; Julie Prévost 21; Michael Barnett 22; Guy Laureys 23; Liesbeth Van Hijfte 23; Jose Luis Sanchez-Menoyo 24; Yolanda Blanco 25; Jiwon Oh 26; Pamela McCombe 27,28; Cristina Ramo Tello 29; Aysun Soysal 30; Alexandre Prat 31; Pierre Duquette 31; Bassem I. Yamout 32; Samia Khoury 32; Vincent van Pesch 33; Richard Macdonell 34; Maria José Sá 35,36; Mark Slee 37; Jens Kuhle 38; Davide Maimone 39; Daniele L.A. Spitaleri 40; Barbara Willekens 41; Abdallah Al Asmi 42; Emma Tallantyre 43; Neil P Robertson 43; Alasdair Coles 44; J William L Brown 44; Tomas Kalincik 1,2
On behalf of the MSBase Study Group

Affiliations

1 CORe, Department of Medicine, University of Melbourne, Melbourne, Australia
2 Neuroimmunology Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia
3 Dokuz Eylul University, Konak/Izmir, Turkey
4 Hunter Medical Research Institute, University Newcastle, Newcastle, Newcastle, Australia
5 Hunter New England Health, John Hunter Hospital, Newcastle, Australia
6 Immune tolerance laboratory Ingham Institute and Dept of Medicine, UNSW, Sydney, Australia
7 Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait
8 Hospital Universitario Virgen Macarena, Sevilla, Spain
9 Karadeniz Technical University Medical Faculty, Trabzon, Turkey
10 Department of Neurology, The Alfred Hospital, Melbourne, Australia
11 Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Australia
12 Department of Neurology, Box Hill Hospital, Melbourne, Australia
13 Department of Neurosciences, Eastern Health Clinical School, Monash University, Melbourne, Australia
14 Department of Neuroscience, Multiple Sclerosis Center, S. Maria delle Croci Hospital of Ravenna, Ravenna, Italy
15 Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, Via Vetoio 1, L'Aquila, Italy
16 Neuro Rive-Sud, Quebec, Canada
17 Department of Neurology, Monash Health, Melbourne, Australia
18 Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Australia
19 CISSS Chaudière-Appalache, Levis, Canada
20 Medical Faculty, 19 Mayis University, Samsun, Turkey
21 CSSS Saint-Jérôme, Saint-Jerome, Canada
22 Brain and Mind Centre, Sydney, Australia
23 Department of Neurology, Ghent University Hospital, Ghent, Belgium

24 Department of Neurology, Hospital de Galdakao-Usansolo. Biocruces-Bizkaia Health Research Institute, Galdakao, Spain
25 Center of Neuroimmunology, Service of Neurology, Hospital Clinic de Barcelona, Barcelona, Spain
26 St. Michael's Hospital, Toronto, Canada
27 University of Queensland, Brisbane, Australia
28 Royal Brisbane and Women's Hospital, Brisbane, Australia
29 Hospital Germans Trias i Pujol, Badalona, Spain
30 Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey
31 CHUM MS Center and Universite de Montreal, Montreal, Canada
32 Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon
33 Cliniques Universitaires Saint-Luc, Brussels, Belgium
34 Austin Health, Melbourne, Australia
35 Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto, Portugal
36 Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal
37 College of Medicine and Public Health, Flinders University, Adelaide, Australia
38 Neurology, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Biomedicine and Clinical Research, University Hospital Basel, Basel, Switzerland
39 Centro Sclerosi Multipla, UOC Neurologia, ARNAS Garibaldi, Catania, Italy
40 Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy
41 Department of Neurology, Antwerp University Hospital, Edegem, Belgium; Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium
42 College of Medicine & Health Sciences and Sultan Qaboos University Hospital, Sultan Qaboos University, Al-Khodh, Oman
43 Department of Neurology, University Hospital of Wales, Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff, United Kingdom
44 Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom

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Corresponding author
Tomas Kalincik
eMail: tomas.kalincik@unimelb.edu.au
Mailing address: Neuroimmunology Centre, L7 635 Elizabeth Street, Melbourne, 3002, Victoria, Australia
Telephone number: +61 3 9342 4404

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ABSTRACT

Background:
Comparisons between cladribine and other potent immunotherapies for multiple sclerosis are lacking.

Objectives:
To compare the effectiveness of cladribine against fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis.

Methods:
Patients with relapsing-remitting multiple sclerosis treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab were identified in the global MSBase cohort and two additional UK centres. Patients were followed for >=6/12 and had >=3 in-person disability assessments. Patients were matched using propensity score. Four pairwise analyses compared annualised relapse rates and disability outcomes.

Results:
The eligible cohorts consisted of 853(fingolimod), 464(natalizumab), 1131(ocrelizumab), 123 (alemtuzumab), or 493(cladribine) patients. Cladribine was associated with a lower ARR than fingolimod (0.07vs0.12, p=0.006), and a higher ARR than natalizumab (0.10vs0.06, p=0.03), ocrelizumab (0.09vs0.05, p=0.008), and alemtuzumab (0.17vs0.04, p<0.001). Compared to cladribine, the risk of disability worsening did not differ in patients treated with fingolimod (HR1.08, 95%CI 0.47-2.47) or alemtuzumab (0.73, 0.26-2.07), but was lower for patients treated with natalizumab (0.35, 0.13-0.94) and ocrelizumab (0.45, 0.26-0.78). There was no evidence for a difference in disability improvement.

Conclusion:
Cladribine is an effective therapy that can be viewed as a step-up in effectiveness from fingolimod, but is less effective than the most potent intravenous multiple sclerosis therapies.

INTRODUCTION

Cladribine triggers lymphocyte apoptosis by inhibiting DNA synthesis and repair.[1] The superiority of cladribine over placebo in the treatment of relapsing-remitting multiple sclerosis (MS) was shown in the CLARITY randomised clinical trial, where 3.5mg/kg over two years reduced the frequency of relapses by 57%, and disability worsening by 33%.[2]

Since the CLARITY trial was placebo controlled, the comparative effectiveness of cladribine has not been studied in a randomised setting. In the absence of evidence from randomised trials, carefully designed observational studies can be used to compare the effectiveness of therapies, and subsequently guide treatment decisions.[3] A recent study from the MSBase registry concluded that cladribine was superior to other oral MS therapies (fingolimod, dimethyl fumarate and teriflunomide) in reducing relapses, and in treatment persistence.[4] A small number of head-to-head comparisons were of insufficient duration or power to evaluate disability outcomes, used merged data from registries and randomised trials, or did not compare cladribine to highly-effective therapies.[5-7] In particular, no generalisable information exists about the effectiveness of cladribine compared with ocrelizumab or alemtuzumab. In practice, cladribine is viewed as a highly-effective therapy suitable for patients with highly active MS who are at risk of accumulating disability.[8-10] Benchmarking cladribine against the most effective available therapies is therefore an unmet need essential for guiding evidence-based treatment selection.

In this study, we have emulated a trial comparing relapse activity, disability accumulation, and disability improvement among MS patients treated with cladribine and four other highly-

effective and widely used MS therapies: fingolimod, natalizumab, ocrelizumab and alemtuzumab.

METHODS

Database and population

Longitudinal patient data were extracted from MSBase[11], an international observational MS registry, and from two non-MSBase centres in the United Kingdom (Cambridge and Cardiff). The study was approved by the Melbourne Health Human Research Ethics Committee and local ethics committees in all centers. Written informed consent was obtained from all patients.

Patients with relapsing-remitting MS[12-14] who had been treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab between January 2018 and March 2023 were assessed for study inclusion. Inclusion criteria were: no prior treatment with haematopoietic stem cell transplantation, alemtuzumab or cladribine; no treatment with mitoxantrone in the preceding 3 years or anti-CD20 therapy in the preceding 12 months; minimum recorded follow-up (6-months before, and at least two disability scores ≥6 months apart after, treatment start); a minimum data set including sex, age, MS symptom onset, relapse dates, MS course and disability score at treatment start (within 6-months before and 1-month after starting therapy). Only in-person disability assessments were included.

For each pairwise treatment comparison, patients who received the comparator therapy before study inclusion were excluded.

Procedures

Treatment protocols for cladribine (1.75mg/kg in year 1; 3.5mg/kg over two years), fingolimod (0.5mg daily), natalizumab (300mg monthly), ocrelizumab (600mg 6-monthly) and alemtuzumab (12–24 mg intravenous once per day for 5 days [cycle 1] or for 3 days [subsequent cycles]), are described elsewhere.[2, 15-18] Baseline was the first commencement of a study therapy after January 2018. Patients were censored at the last recorded EDSS score, irrespective of change in treatment status (intention-to-treat contrast of interest).

Data were entered into the MSBase data entry system or local data entry systems as part of routine clinical practice and mostly at tertiary MS centres. The data entry procedures were consistent across both MSBase and non-MSBase centers. MRI data were included as reported by local radiologists based on local protocols. An MRI brain performed within 12 months before, and 1 month after, baseline was considered the baseline MRI. Missing baseline MRI data were addressed through multiple imputation.[19, 20]

A rigorous data quality assurance procedure was followed (eTable 1).[21]

Study endpoints

The primary study outcome was annualised relapse rate (ARR); secondary study outcomes were cumulative hazards of relapses, disability accumulation events, and disability improvement events.

Relapses were defined as new symptoms, or exacerbation of existing symptoms, for at least 24 hours in the absence of a concurrent illness or fever, and occurring ≥30 days after a previous relapse.[22]

Disability was quantified using the Expanded Disability Status Scale (EDSS). Disability accumulation was defined as an increase in EDSS by ≥1 step (1.5 step if EDSS 0, or 0.5 step if EDSS>5.5), confirmed over ≥6 months (in the absence of a relapse in the preceding 30 days), and sustained until the end of follow up. Disability improvement was defined as a decrease in EDSS by ≥1 step (1.5 steps if EDSS 1.5, or 0.5 step if EDSS>6) confirmed over at least 6 months.[23]

Statistical analysis

Four separate matched analyses of cladribine versus fingolimod, natalizumab, ocrelizumab or alemtuzumab were performed. Individual patients were matched, at baseline, on their propensity of being treated with cladribine conditional on clinicodemographic characteristics. Propensity scores were calculated using a multivariable logistic regression model containing the following baseline variables: age, sex, EDSS, MS duration from first symptom, number of relapses in the prior 12 months, disease activity in the prior year (relapses/ disability progression/both relapses and disability progression/no activity), number of prior MS immunotherapies, the most effective previously used treatment (categorised as high-efficacy [natalizumab, rituximab, ocrelizumab, ofatumumab, mitoxantrone], moderate-efficacy [fingolimod, dimethyl fumarate], low-efficacy [interferons β, glatiramer acetate, teriflunomide] or no therapy), presence/absence of new T2 or contrast-enhancing brain MRI lesions, MRI T2-lesion burden (1-2, 3-8, or ≥9 lesions), registry and country.[24]

In the absence of a baseline MRI brain, missing values were imputed using a multiple imputation with an expectation maximisation with bootstrapping algorithm based on treatment group, age, MS duration, EDSS, pre-baseline disease activity, pre-baseline therapy

and time since preceding therapy.[19, 25] A sensitivity analysis was conducted after loosening the assumption of missingness-at-random. Normalised weights were used to estimate inferences within the dataset assuming MRI missingness not at random.[26] The relationship between clinical and demographic variables and the absence of MRI data was assessed using multivariable logistic regression, with selection of δ guided by a published algorithm.[27]

Patients were matched, without replacement, in a variable (3:1 to 5:1) matching ratio by nearest neighbour matching within 0.1 standard deviations of the propensity score.[28] The matching ratio specifies the maximum allowed number of control units in each matched pair. Covariate balance was assessed using standardised mean differences. All subsequent analyses were performed using paired models, weighted to account for variable matching ratio. Within each matched patient pair, follow-up was censored at the shorter of the two follow-up periods (pairwise censoring) to mitigate differential treatment persistence and attrition bias. The last eligible timepoint for 6-month confirmed disability outcomes was 6-months before the censor date to ensure adequate follow-up for confirmation. ARRs were compared using a marginal negative binomial model with cluster term for matched patient set. Cumulative hazards of relapses, disability accumulation, and disability improvement events were analysed with weighted conditional proportional hazards models for recurrent events, adjusted for visit frequency for disability outcomes. Schoenfeld's global test was used to evaluate the proportionality assumption. The robustness of our findings to unidentified confounders was calculated using Rosenbaum sensitivity test for Hodges-Lehmann Γ.[29]

A sensitivity analysis required >= 18 months follow-up for all patients. In a further sensitivity analysis data were censored at treatment discontinuation, commencement of subsequent therapy, or the last recorded EDSS, whichever occurred first. For this analysis, the duration

of treatment effect was presumed based on pharmacokinetics, or previous evidence: cladribine 4years, alemtuzumab 5years, ocrelizumab 270days, natalizumab 60days and fingolimod 30days. Treatment discontinuation was assessed using weighted conditional proportional hazards models without pairwise censoring. The analysis was also repeated using inverse probability of treatment weighting.

Data were analysed using R, v4.2.1 (R CoreTeam).

RESULTS

Of 30142 patients with MS who were ever treated with a studied therapy, a total of 853 (fingolimod), 464 (natalizumab), 1131 (ocrelizumab), 123 (alemtuzumab) and up to 493 (cladribine) patients fulfilled inclusion criteria (Figure 1; eTable 2). The clinicodemographic details of the included population were similar to those of patients ever received studied therapy but were excluded from the analysis (eTable 3).

Prior to matching, the four treatment groups differed in their baseline characteristics (eTable 4). The probability of being treated with either therapy was calculated using a logistic regression model (eTable 5). Patients treated with cladribine were less likely to have received a high-efficacy therapy than patients treated with alemtuzumab, ocrelizumab or natalizumab, had lower EDSS scores than patients treated with alemtuzumab and ocrelizumab, and were older than patients treated with natalizumab.

Table 1 shows the characteristics of the matched cohorts for all four pairwise primary analyses. Characteristics of patients who were excluded by the matching procedure are in

eTable 6. Propensity score matching resulted in 86%-98% improvement in balance between the matched groups, with standardised mean differences of <10% (Table 1; eFigure 1; eFigure 2). Mean pairwise censored follow-up ranged from 1.8 to 2.1 years. Patient numbers allowed assessment of relapses for up to 3years for alemtuzumab, 3.5years for natalizumab, and 4years for fingolimod and ocrelizumab. Disability outcomes were evaluated for up to 2.5 years for fingolimod, natalizumab, and ocrelizumab, and 2years for alemtuzumab.

Effectiveness

Fingolimod vs cladribine

198 cladribine-treated patients were matched with 403 patients treated with fingolimod (Table 1). On average, patients received one prior MS therapy (low-efficacy in 48-52%), and a mean EDSS of 1.8. The mean ARR was higher in patients treated with fingolimod than cladribine (mean [SD], ARR 0.12[0.30] vs 0.07[0.23], Figure 2A). Similarly, the cumulative hazard of relapses was higher for fingolimod than cladribine (HR=1.71, 95%CI 1.12-2.63, Figure 2B). The difference was robust to unmeasured confounding to the magnitude of >100% of the cumulative effect of the measured confounding using Rosenbaum sensitivity test for Hodges-Lehmann Γ. There was no evidence for a difference in disability accumulation (HR=1.08, 0.47-2.47, Figure 2C) or disability improvement (HR=0.38, 0.13-1.1, Figure 2D) between groups.

Natalizumab vs cladribine

220 patients treated with cladribine were matched with 331 natalizumab patients. On average, patients received one prior MS therapy (moderate-efficacy in 45%), and had a mean EDSS of 2.1. The mean ARR was lower in patients treated with natalizumab than cladribine (ARR

0.06[0.22] vs 0.10[0.30], Figure 3A). Furthermore, both the cumulative hazard of relapses (HR=0.55, 0.33-0.93, Figure 3B) and disability accumulation (HR=0.35, 0.13-0.94, Figure 3C) were lower for natalizumab than cladribine. The difference in relapses was robust to the magnitude of 20% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability improvement (HR=0.65, 0.36-1.17).

Ocrelizumab vs cladribine

380 cladribine-treated patients were matched with 667 ocrelizumab patients. The mean age was 42 years, EDSS 2.4, and patients had received 2 previous MS therapies (43% moderate-efficacy, 18% high-efficacy). The mean ARR was lower in patients treated with ocrelizumab than cladribine (ARR 0.05[0.18] vs 0.09[0.27], Figure 4A). Furthermore, both the cumulative hazards of relapses (HR=0.61, 0.42-0.88, Figure 4B), and disability accumulation (HR=0.45, 0.26-0.78, Figure 4C) were lower for ocrelizumab than cladribine. The difference in relapses was robust to unmeasured confounders to the magnitude of 40% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability improvement (HR=0.8, 0.5-1.29, Figure 4D).

Alemtuzumab vs cladribine

173 cladribine-treated patients were matched with 68 alemtuzumab patients with a mean EDSS of 2.8, 2 previous MS therapies (48% moderate-efficacy, 27% high-efficacy), and recent disease activity in 60% of patients indicative of active MS. Both the mean ARR (ARR 0.04[0.19] vs 0.17[0.38], Figure 5A), and cumulative hazards of relapses (HR=0.25, 0.10-0.65, Figure 5B) were lower in patients treated with alemtuzumab than cladribine. The difference was robust to unmeasured confounders to the magnitude of 80% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability

accumulation (HR=0.73, 0.26-2.07, Figure 5C) or improvement (HR=1.3, 0.50-3.38, Figure 5D). The analysis was sufficiently powered to detect a minimum difference of 79% cumulative hazard of disability accumulation, and 73% disability improvement (based on 200 simulations at 1–β=0·8).

Sensitivity analyses

Sensitivity analyses (i) where patients were censored at the discontinuation of studied therapy, and (ii) where all patients were followed for >= 18 months after baseline, largely confirmed the results of the primary analysis (eTable 7). Inverse probability of treatment weighting was not superior to matching and provided consisted results. In keeping with the presumed duration of treatment effect, patients treated with cladribine were reported as more persistent on therapy than those treated with fingolimod, natalizumab or ocrelizumab, but not alemtuzumab (eFigure 3). All results were fully replicated with imputation of missing MRI data under the missing-not-at-random assumption.

DISCUSSION

In the expanding MS treatment landscape, understanding of the comparative effectiveness of available therapies is paramount to optimising patient outcomes. In this observational, propensity-score matched analysis of the global observational MSBase registry and two additional UK centres, we have studied the effectiveness of cladribine compared with four therapies commonly used in relapsing-remitting MS. Cladribine was superior to fingolimod, but inferior to natalizumab, ocrelizumab and alemtuzumab in reducing relapse activity. In addition, treatment with cladribine was associated with a greater probability of disability accumulation than natalizumab and ocrelizumab.

A previous inverse probability of treatment-weighted analysis from MSBase including 445 ocrelizumab-treated and 76 cladribine-treated patients suggested lower relapse rates for ocrelizumab than cladribine after cessation of fingolimod.[7] Our present study expands on this initial observation and generalises the conclusions to a broad range of clinical scenarios representative of the prevalent MS population. This study supports treatment with ocrelizumab as a step up in effectiveness compared to cladribine, with superior effect on both relapses and disability accumulation. Furthermore, this study is the first to compare the effectiveness of alemtuzumab and cladribine, describing superiority of alemtuzumab in suppressing relapses. The lack of an observed difference in disability outcomes between these two immune reconstitution therapies may be attributable to the characteristics of the matched cohort, who had moderate baseline EDSS scores (2.8-2.9), a high proportion of patients with a recent relapse/disability accumulation, and a modest follow-up period of 2 years.

The clinical scenarios within which treatments are used can influence the observed differences between compared therapies, and should therefore be carefully considered in study design.[30] For example, patients in the cladribine vs alemtuzumab pairwise comparison had the highest disease activity. The effectiveness of cladribine was compared to interferon-beta, fingolimod and natalizumab in a small, non-overlapping pilot study from MSBase.[5] Patients in this early study received cladribine as part of the Australian Product Familiarisation Program(2011), and outcomes were evaluated over a 1-year period. Cladribine was comparable to fingolimod and inferior to natalizumab in reducing relapses and disability accumulation and was more frequently associated with disability improvement than either fingolimod or natalizumab. Caution is advised in interpreting the pilot study results due to small cohort size, exposure to a single cladribine cycle for many patients, and a

follow-up duration too short to draw definitive conclusions about disability. A further study from MSBase, using a more contemporary cohort, also suggested that cladribine is superior to fingolimod in reducing relapse activity.[4] A study that combined data from the Italian MS registry and the CLARITY trial in treatment-naive patients with MS reported relapse outcomes that seemed comparable between fingolimod and cladribine.[6] However, whether treatment groups from registries can be compared to those from randomised trials is unclear.

Finally, our finding that natalizumab is superior to cladribine in reducing relapses concurs with previous reports.[5-7] Unlike the previous studies, however, our present study has found evidence for superiority of natalizumab over cladribine by showing a 65% reduction in the cumulative hazards of disability accumulation over 2.5-years.

Network meta-analyses combine direct and indirect evidence from multiple studies, assuming transitivity and consistency of observations.[31] This offers an alternative analytical approach for comparing treatments in the absence of randomised clinical trials. Our findings align with a network meta-analysis comparing cladribine to various therapies across 41 studies, ranking it fourth in effectiveness, behind alemtuzumab, ocrelizumab and natalizumab.[32] The use of different methodological approaches, each with their own limitations and assumptions, to arrive at similar conclusions provides additional confidence in the findings.

The most significant limitation of this study is its observational nature.[33] We have however performed a carefully designed propensity score matched analysis to minimise treatment indication and attrition bias, informative censoring and ensure that positivity assumption is satisfied. While this approach reduces measured confounding, it doesn't eliminate it, leaving observational studies vulnerable to potential unmeasured confounding. We have therefore

demonstrated that all analyses were robust to unmeasured confounders of a magnitude of >20% of the cumulative measured confounding. We improved homogeneity of disability assessments by excluding telehealth assessments, and ensuring Neurostatus certification at all centres.[34] Despite accessing data from the largest MS registry and two additional centres, the comparison of disability outcomes for alemtuzumab lacked statistical power. We report the effectiveness of cladribine in groups of patients with comparable baseline characteristics treated in common clinical contexts. Results may however not be generalisable to all patient populations, such as patients who are treatment naïve. The current analysis used an 'intention-to-treat' approach to evaluate the effectiveness of 3.5mg/kg cladribine over the available subsequent follow-up. Results were consistent using an 'as-treated' approach, using a presumed 4-year duration of treatment effect. Rigorous evaluation of the duration of treatment effect or the value of additional treatment doses would, be best pursued in a separate study. While treatment safety and patient comorbidities are important components of disease management, these data were not available for inclusion in the present study. Since information about pre-baseline MRI activity was only available for a subset of patients, we utilised multiple imputation. As previously described, this approach produces no difference in outcomes among patients with baseline MRI available.[20, 35] Limited information about MRI activity however precluded the evaluation of radiological outcomes.

Our findings support cladribine as an effective therapy for the treatment of relapsing-remitting MS. While we show a superior effectiveness of natalizumab and ocrelizumab on reducing relapses and disability accumulation compared to cladribine, the magnitude of this difference is small, and equates to a reduction by one relapse every 25 patient-years. Compared to cladribine, alemtuzumab reduced relapses by one relapse every eight patient-years. On the contrary, the effectiveness of cladribine was clearly superior to fingolimod in

preventing relapses (reduction by one relapse every 20 patient-years). Clinical application of these findings remains complex, and requires careful consideration of multiple factors, including cost, safety, and convenience. The results however help to place cladribine in the context of other MS therapies and suggest that cladribine can be viewed as a step-up in effectiveness from fingolimod, but less effective than the most potent intravenous therapies.

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DATA ACCESS, RESPONSIBILITY AND ANALYSIS
IR and TK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

DATA AVAILABILITY
The MSBase registry is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. External party access to data from either the MSBase centres or two non-MSBase UK centers is subject to reasonable requests and solely at the discretion of the principal investigators. Permission for data access must be sought individually from the respective principal investigators.

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TABLES

Table 1: Demographic, clinical and paraclinical characteristics of matched patients

	Clad-ribine	Fingo-limod	SMD	Clad-ribine	Natali-zumab	SMD	Clad-ribine	Ocreli-zumab	SMD	Clad-ribine	Alemtu-zumab	SMD
Number of patients	198	403		220	331		380	667		173	68	
Registry, n (%)[a]												
Cambridge	4.0 (2.0)	10.4 (2.6)		3.0 (1.4)	6.0 (1.8)		5.0 (1.3)	11.7 (1.8)		12.7 (7.4)	5.0 (7.4)	
Cardiff	3.0 (1.5)	6.8 (1.7)		3.0 (1.4)	4.3 (1.3)		2.0 (0.5)	1.8 (0.3)		7.6 (4.4)	1.0 (1.5)	
MSBase	191.0 (96.5)	385.8 (95.7)		214.0 (97.3)	320.7 (96.9)		373.0 (98.2)	653.5 (98.0)		152.6 (88.2)	62.0 (91.2)	
Female sex, n (%)	148 (75)	300 (74)	0.01	177 (79)	265 (80)	0.04	289 (76)	512 (77)	0.02	131 (75)	50 (74)	0.05
Age, y	39.4 (10.6)	39.3 (10.6)	0.01	38.3 (10.4)	39.1 (9.7)	0.08	42.3 (12.2)	42.3 (11.1)	<0.001	38.1 (9.9)	38.2 (10.9)	0.01
MS duration, y	9.8 (7.8)	10.0 (7.7)	0.03	8.9 (6.5)	9.0 (7.1)	0.02	10.6 (8.2)	10.2 (7.9)	0.05	9.9 (7.0)	10.5 (7.0)	0.08
Nr of relapses in prior 12 months	0.5 (0.7)	0.5 (0.7)	0.03	0.5 (0.7)	0.5 (0.7)	0.03	0.4 (0.6)	0.4 (0.6)	0.02	0.7 (0.8)	0.7 (0.8)	0.01
EDSS step	1.5 [1.0, 2.5]	1.5 [1.0, 2.5]	0.03	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.01	2.0 [1.0, 3.5]	2.0 [1.5, 4.0]	0.02	2.0 [1.5, 3.5]	2.5 [1.9, 4.1]	0.07
Disease activity over prior 12 months, n (%)												
none	98.0 (49.5)	210.8 (52.3)		107.0 (48.6)	159.5 (48.2)		218.0 (57.4)	391.4 (58.7)		67.1 (38.8)	31.0 (45.6)	
progression	22.0 (11.1)	37.0 (9.2)		22.0 (10.0)	26.6 (8.0)		30.0 (7.9)	50.3 (7.5)		18.1 (10.4)	6.0 (8.8)	
relapse	55.0 (27.8)	110.9 (27.5)		57.0 (25.9)	93.5 (28.3)		89.0 (23.4)	155.3 (23.3)		57.3 (33.1)	19.0 (27.9)	
relapse & progression	23.0 (11.6)	44.2 (11.0)		34.0 (15.5)	51.4 (15.5)		43.0 (11.3)	69.9 (10.5)		30.5 (17.6)	12.0 (17.6)	
MRI Brain: T2 lesion, n (%)												
Imaging available	65 (33)	123 (31)		65 (30)	71 (38)		90 (24)	153 (23)		50 (29)	27 (40)	
1-2	2.0 (1.0)	4.6 (1.2)		3.0 (1.4)	4.5 (1.4)		17.0 (4.4)	32.8 (4.9)		9.8 (5.7)	5.0 (7.4)	
3-8	5.0 (2.5)	12.5 (3.1)		23.0 (10.5)	37.9 (11.4)		25.0 (6.6)	49.1 (7.4)		12.2 (7.1)	4.0 (5.9)	
9+	191.0 (96.5)	385.8 (95.7)		194.0 (88.2)	288.6 (87.2)		338.0 (88.9)	585.1 (87.7)		151.0 (87.3)	59.0 (86.8)	
MRI Brain: new or contrast enhancing lesions, n (%)												
Imaging available	120 (60)	192 (48)		128 (58)	158 (48)		182 (49)	312 (47)		77 (45)	35 (51)	
Absent	88.0 (44.4)	184.9 (45.9)		90 (40.9)	139.7 (42.4)		201 (52.9)	353.7 (53.0)		57.8 (33.4)	25 (36.8)	
Present	110.0 (55.6)	218.1 (54.1)		130.0 (59.1)	191.3 (57.8)		179.0 (47.1)	313.3 (47.0)		115.2 (66.6)	43.0 (63.2)	
Nr of previous therapies	1 [1, 2]	1 [1, 2]	0.03	1 [1, 3]	1 [1, 2]	0.04	2 [1, 3]	2 [1, 3]	0.02	2 [1, 3]	2 [1, 3]	0.09
Top previous therapy category, n (%)												
None	20.0 (10.1)	39.8 (9.9)		30.0 (13.6)	50.2 (15.2)		42.0 (11.1)	73.7 (11.1)		27.4 (15.9)	6.0 (8.8)	

Low-efficacy	104.0 (52.5)	194.5 (48.3)		72.0 (32.7)	105.8 (32.0)		101.0 (26.6)	174.6 (26.2)		17.9 (10.4)	9.0 (13.2)	
Moderate-efficacy	60.0 (30.3)	120.4 (29.9)		98.0 (44.5)	152.0 (45.9)		166.0 (43.7)	287.0 (43.0)		85.4 (49.4)	31.0 (45.6)	
High-efficacy	14.0 (7.1)	48.3 (12.0)		20.0 (9.1)	23.1 (7.0)		71.0 (18.7)	131.6 (19.7)		42.2 (24.4)	22.0 (32.4)	
Pre-baseline follow up, y	5.0 [2.1, 8.7]	4.7 [2.3, 8.6]	0.06	4.5 [2.0, 8.0]	4.1 [1.7, 8.0]	0.06	4.7 [2.2, 8.3]	4.9 [2.0, 9.2]	0.03	5.0 [2.1, 8.4]	6.4 [2.7, 10.3]	0.17
Visit interval, m	6.9 [4.9, 9.0]	8.1 [6.0, 11.0]	0.28	6.3 [4.8, 8.9]	7.3 [5.7, 9.7]	0.22	7.2 [5.2, 10.0]	8.0 [6.1, 11.3]	0.22	6.3 [4.4, 8.7]	7.7 [6.1, 12.2]	0.5
Study follow-up, y	2.1 (0.9)	2.1 (0.9)	0.00	1.8 (0.8)	1.8 (0.8)	0.00	2.1 (0.8)	2.1 (0.8)	0.00	2.0 (0.8)	2.0 (0.8)	0.00

Mean (SD) or median [quartiles] as appropriate

[a] Weighted estimates yield decimals in the control group, reflecting the fractional weights assigned to individual units in 1-to-multiple propensity score matching

Top previous therapy category:

Low-efficacy: interferons, glatiramer acetate, teriflunomide; Moderate-efficacy: fingolimod, dimethyl fumarate, diroximel fumarate, daclizumab; High-efficacy: natalizumab, alemtuzumab, rituximab, ocrelizumab, mitoxantrone

Follow-up after pairwise censoring, as per the primary analysis

SMD – standardised mean difference

FIGURE LEGENDS

Figure 1: Patient disposition

MS, multiple sclerosis

Figure 2: Comparison of treatment outcomes for fingolimod vs cladribine
A. Annualised relapse rate
B. Cumulative hazard of relapses
C. Cumulative hazard of disability accumulation
D. Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

Figure 3: Comparison of treatment outcomes for natalizumab vs cladribine
A. Annualised relapse rate
B. Cumulative hazard of relapses
C. Cumulative hazard of disability accumulation
D. Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

Figure 4: Comparison of treatment outcomes for ocrelizumab vs cladribine
A. Annualised relapse rate
B. Cumulative hazard of relapses
C. Cumulative hazard of disability accumulation
D. Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

Figure 5: Comparison of treatment outcomes for alemtuzumab vs cladribine
A. Annualised relapse rate
B. Cumulative hazard of relapses
C. Cumulative hazard of disability accumulation
D. Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

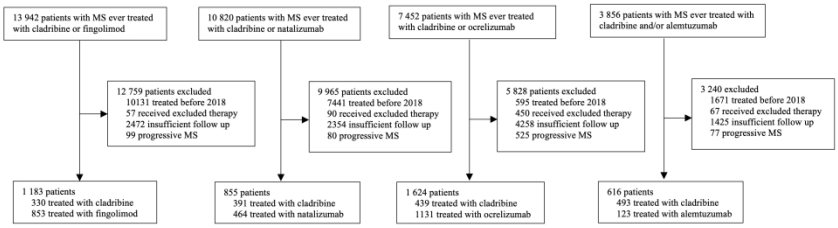


Figure 1: Patient disposition

1237x874mm (72 x 72 DPI)

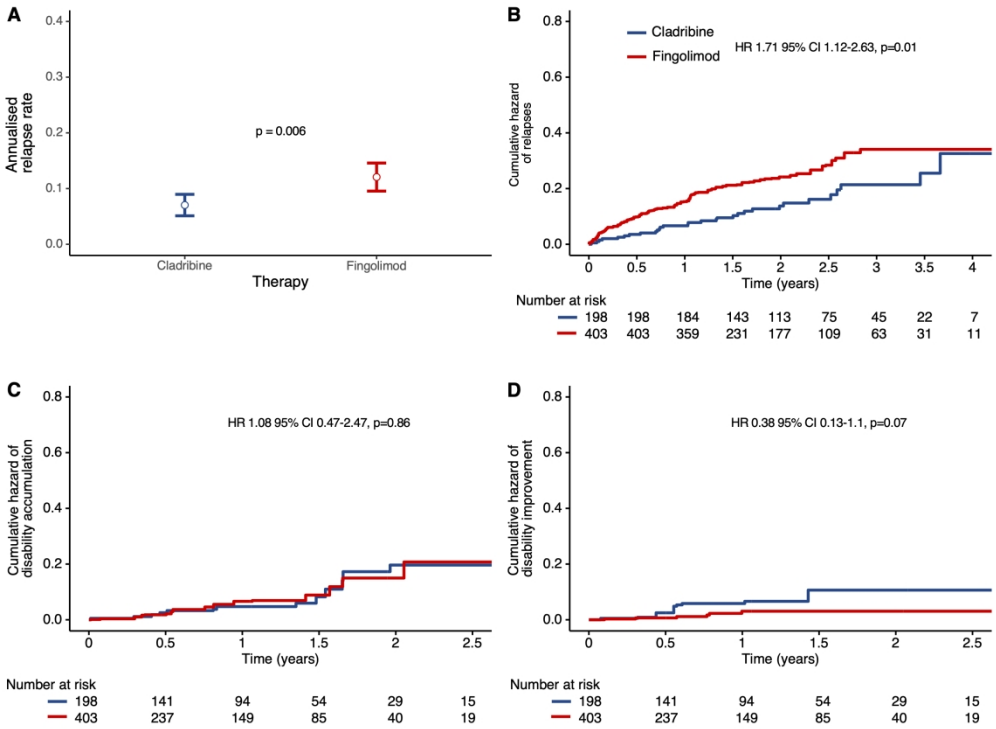


Figure 2: Comparison of treatment outcomes for fingolimod vs cladribine
A.Annualised relapse rate
B.Cumulative hazard of relapses
C.Cumulative hazard of disability accumulation
D.Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

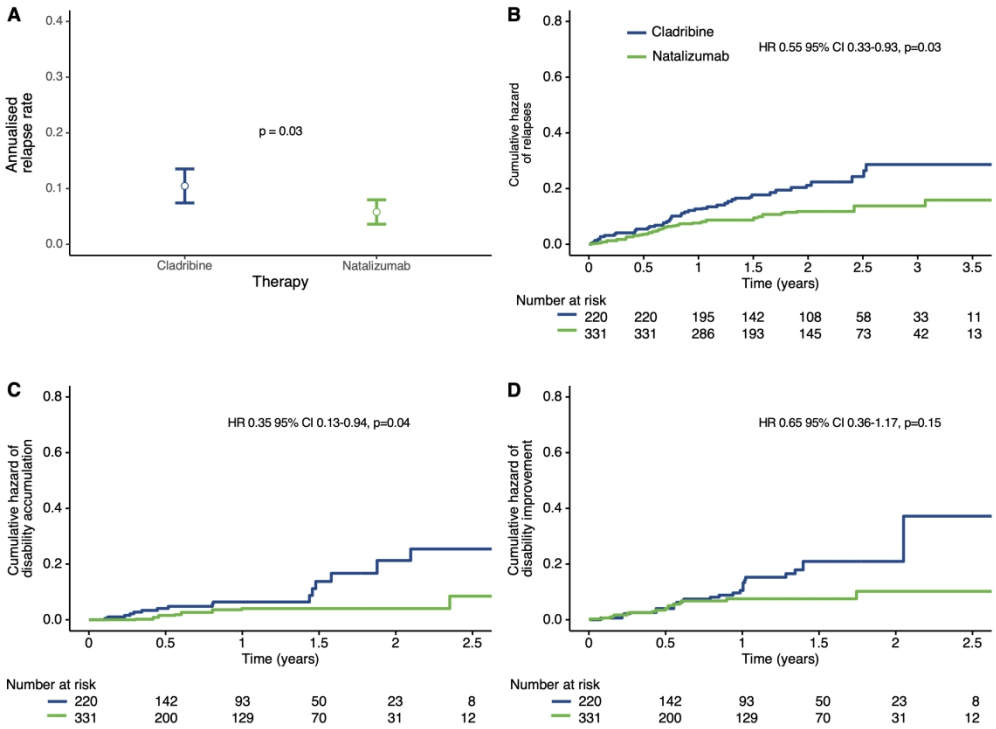


Figure 3: Comparison of treatment outcomes for natalizumab vs cladribine
A.Annualised relapse rate
B.Cumulative hazard of relapses
C.Cumulative hazard of disability accumulation
D.Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

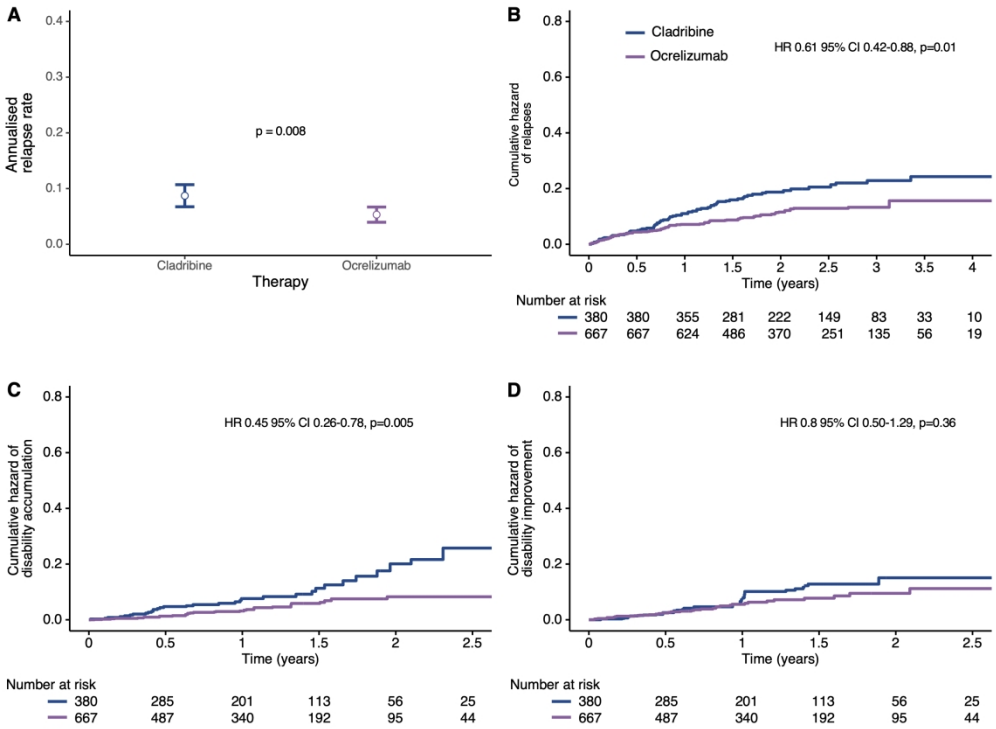


Figure 4: Comparison of treatment outcomes for ocrelizumab vs cladribine
A.Annualised relapse rate
B.Cumulative hazard of relapses
C.Cumulative hazard of disability accumulation
D.Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

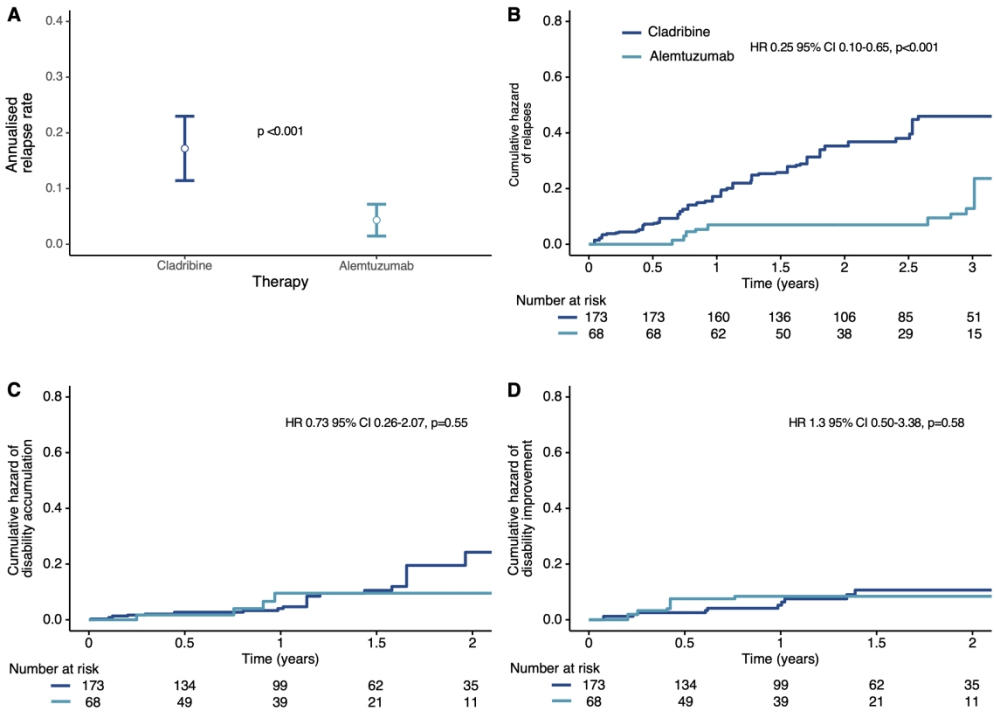


Figure 5: Comparison of treatment outcomes for alemtuzumab vs cladribine
A.Annualised relapse rate
B.Cumulative hazard of relapses
C.Cumulative hazard of disability accumulation
D.Cumulative hazard of disability improvement
HR, hazard ratio; CI, confidence interval

1058x793mm (72 x 72 DPI)

Supplementary Appendix

List of contributors

The following contributors participated in MSBase data acquisition:
From Hospital Universitario Virgen Macarena, Sevilla, Spain, Dr Guillermo Izquierdo
From CHUM MS Center and Universite de Montreal, Montreal, Canada, Dr Marc Girard
From University of Western Australia, Nedlands, Australia, Dr Allan Kermode, Dr Marzena Fabis-Pedrini
From Westmead Hospital, Sydney, Australia, Dr Justin Garber.
From Royal Hobart Hospital, Hobart, Australia, Dr Bruce Taylor.
From Concord Repatriation General Hospital, Sydney, Australia, Dr Todd Hardy, Dr Steve Vucic.
From St Vincent's Hospital Sydney, Sydney, Australia, Dr Jennifer Massey.
From AZ Alma Ziekenhuis, Sijsele - Damme, Belgium, Dr Danny Decoo.
From Pelt and Hasselt University, Hasselt, Belgium, Dr Bart Van Wijmeersch.
From Universidade Metropolitana de Santos, Santos, Brazil, Dr Yara Fragoso.
From Charles University in Prague and General University Hospital, Prague, Czech Republic, Dr Dana Horakova, Dr Eva Kubala Havrdova.
From Nemocnice Jihlava, Jihlava, Czech Republic, Dr Radek Ampapa.
From Kasr Al Ainy MS research Unit (KAMSU), Cairo, Dr Nevin Shalaby.
From Hospital Universitario Donostia, San Sebastián, Spain, Dr Tamara Castillo-Triviño, Dr Javier Olascoaga.
From University Hospital Reina Sofia, Cordoba, Spain, Dr Eduardo Aguera-Morales.
From Hospital Universitari MútuaTerrassa, Barcelona, Spain, Dr Sarah Besora.
From South Eastern HSC Trust, Belfast, United Kingdom, Dr Orla Gray.
From University Hospital Center Zagreb, Zagreb, Croatia, Dr Mario Habek.
From Isfahan University of Medical Sciences, Isfahan, Iran, Dr Vahid Shaygannejad.
From Booalisina Hospital, Iran, Dr Seyed Mohammad Baghbanian.
From Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy, Dr Elisabetta Cartechini, Dr Matteo Diamanti.
From GF Ingrassia, Catania, Italy, Dr Francesco Patti, Dr Clara Chisari, Dr Emanuele D'Amico, Dr Lo Fermo Salvatore.
From Hospital Angeles de las Lomas. Instituto Mexicano de Neurociencias., Huixquilucan Estado de Mexico, Mexico, Dr Eli Skromne.
From Zuyderland Medical Center, Sittard-Geleen, The Netherlands, Sittard-Geleen, Netherlands, Dr Oliver Gerlach, Dr Raymond Hupperts.
From Christchurch Hospital, Christchurch, New Zealand, Dr Deborah Mason.
From King Fahad Specialist Hospital-Dammam, Khobar, Saudi Arabia, Dr Talal Al-Harbi.
From Razi University Hospital, Tunis, Tunisia, Dr Riadh Gouider, Dr Saloua Mrabet.
From Hacettepe University, Ankara, Turkey, Dr Rana Karabudak.
From Koc University, Istanbul, Turkey, Dr Ayse Altintas.
From Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, Dr Recai Turkoglu.
From Royal Melbourne Hospital, Melbourne, Australia, Dr Mark Marriott, Dr Trevor Kilpatrick, Dr John King, Dr Katherine Buzzard, Dr Ai-Lan Nguyen, Dr Chris Dwyer, Dr Mastura Monif, Dr Izanne Roos, Ms Lisa Taylor, Ms Josephine Baker.
From CHUM MS Center and Universite de Montreal, Montreal, Canada, Dr Catherine Larochelle.

Administrative and technical support was provided by:
From the MSBase Administrations Ms Charlotte Sartori.

eTable 1: Data quality procedure

- Duplicate patient records were removed.
- Centres with <10 patient records were excluded.
- Patients with missing date of birth were excluded.
- MS onset dates after the data extract date were removed.
- Patients with missing date of the first clinical presentation of MS were excluded.
- The dates of MS onset and the first recorded MS course were aligned.
- Patients with the age at onset outside the 0-100 range were excluded.
- A logical sequence of the MS courses (e.g. clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS) was assured.
- Entries with the initiation of progressive MS prior to its clinical onset of MS were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of data extract were removed.
- EDSS scores outside the range of possible EDSS values were removed.
- Duplicate visits were merged.
- MS relapses with missing visit date or the recorded date after the date of MSBase data extract were removed.
- Duplicate MS relapses were merged.
- Relapses occurring within 30 days of each other were merged.
- Visits preceded by relapses were identified and time from the last relapse was calculated for each visit.
- Therapies were labelled as discontinued or continuing.
- Therapies with erroneous date entries were removed (e.g. commencement date > termination date, commencement after the MSBase data extract date, commencement of disease modifying therapy before the year 1980).
- MS disease modifying therapies were identified and labelled.
- Duplicate treatment entries were removed.
- Where multiple disease modifying therapies were recorded simultaneously, treatment end date of the previous therapy was imputed as the commencement date of the following therapy.

eTable 2: Patient disposition per country and treatment (only matched patients)

	Cladribine vs fingolimod		**Cladribine vs natalizumab**		**Cladribine vs ocrelizumab**		**Cladribine vs alemtuzumab**	
	Cladribine	*Fingolimod*	*Cladribine*	*Natalizumab*	*Cladribine*	*Ocrelizumab*	*Cladribine*	*Alemtuzumab*
Australia	35	96	90	139	191	360	22	9
Belgium	6	9	9	12	13	24	12	5
Canada	45	85	16	35	52	90	17	8
Switzerland	0	0	31	41	0	0	0	0
Spain	42	71	0	0	44	69	58	24
Great Britain	7	17	6	10	7	14	20	6
Italy	23	42	20	28	21	41	15	5
Kuwait	5	10	9	13	9	12	16	3
Lebanon	1	2	1	2	1	2	0	0
Netherlands	1	2	0	0	1	2	1	1
Oman	2	6	2	2	2	2	0	0
Portugal	2	6	2	4	4	4	2	1
Turkey	29	58	34	44	35	48	10	6

eTable 3: Disposition of patients treated with a study therapy, but who were excluded from the analysis

Nr of patients (% female)	**Clad-ribine** 1114 (75)	**Fingo-limod** 11645 (71)	**Clad-ribine** 1182 (74)	**Natali-zumab** 8783 (73)	**Clad-ribine** 1374 (75)	**Ocreli-zumab** 4452 (65)	**Clad-ribine** 1834 (72)	**Alemtu-zumab** 1406 (74)
Registry, n (%)								
Cambridge	14 (1.3)	92 (0.8)	13 (1.1)	89 (1.0)	16 (1.2)	85 (1.9)	381 (20.8)	16 (1.1)
Cardiff	22 (2.0)	125 (1.1)	22 (1.9)	154 (1.8)	23 (1.7)	132 (2.9)	193 (10.5)	23 (1.6)
MSBase	1078 (96.8)	11428 (98.1)	1147 (97.0)	8540 (97.2)	1335 (97.2)	4235 (95.2)	1260 (68.7)	1367 (97.2)
Age, y	42.8 (12.1)	38.4 (10.6)	42.9 (12.0)	37.3 (10.5)	43.5 (11.9)	43.1 (11.7)	36.0 (9.3)	43.7 (12.0)
MS duration, y	10.3 (9.3)	9.2 (7.5)	10.7 (9.3)	8.3 (7.3)	11.5 (9.5)	10.6 (8.6)	7.4 (6.7)	11.6 (9.5)
Nr of relapses in prior 12 months	0.4 (0.7)	0.6 (0.8)	0.4 (0.7)	0.9 (1.0)	0.4 (0.7)	0.3 (0.7)	1.0 (1.1)	0.4 (0.7)
EDSS step	2.5 (2.1)	2.7 (1.8)	2.3 (1.9)	3.3 (1.9)	2.6 (2.1)	3.8 (2.2)	3.1 (2.0)	2.7 (2.2)

Note: Patients in the excluded group are patients with multiple sclerosis who were treated with cladribine or the comparator therapy, but were excluded from the analysis based on insufficient treatment duration, inadequate follow-up, progressive MS or previous exposure to an excluded therapy. Baseline characteristics of the excluded patients are reported at the visit closest to the date of commencement of therapy.

eTable 4: Demographic, clinical and paraclinical characteristics of included patients before propensity score matching

Nr of patients	**Clad-ribine** 330	**Fingo-limod** 853	**SMD**	**Clad-ribine** 391	**Natali-zumab** 464	**SMD**	**Clad-ribine** 439	**Ocreli-zumab** 1131	**SMD**	**Clad-ribine** 493	**Alemtu-zumab** 123	**SMD**
Registry (%)												
Cambridge	20 (2.3)	4 (1.2)		4 (1.0)	4 (0.9)		5 (1.1)	13 (1.1)		5 (1.0)	12 (9.8)	
Cardiff	12 (1.4)	3 (0.9)		3 (0.8)	12 (2.6)		2 (0.5)	55 (4.9)		3 (0.6)	11 (8.9)	
MSBase	821 (96.2)	323 (97.9)		384 (98.2)	448 (96.6)		432 (98.4)	1063 (94.0)		485 (98.4)	100 (81.3)	
Female sex (%)	640 (75)	242 (73)		295 (75)	378 (81)		339 (77)	796 (70)		382 (77)	88 (72)	
Age, y	41.7 (11.9)	38.0 (10.5)	0.3	42.6 (12.0)	36.3 (9.6)	0.6	42.6 (12.1)	42.3 (11.2)	0.02	42.9 (11.9)	37.1 (8.9)	0.5
MS duration, y	9.9 (8.2)	9.3 (7.1)	0.1	10.7 (8.0)	8.6 (6.6)	0.2	10.8 (8.1)	11.2 (8.3)	0.05	11.1 (8.2)	9.8 (7.3)	0.2
Nr of relapses in prior 12 months	0.5 (0.7)	0.5 (0.7)	0.01	0.5 (0.7)	0.7 (0.8)	0.3	0.4 (0.7)	0.5 (0.7)	0.06	0.4 (0.7)	0.8 (0.9)	0.5
EDSS step	2.2 (1.7)	1.6 (1.5)	0.4	2.2 (1.7)	2.2 (1.7)	0.02	2.3 (1.7)	3.1 (1.9)	0.4	2.4 (1.8)	3.1 (1.9)	0.4
Disease activity over prior 12 months, n (%)												
none	179 (54.2)	446 (52.3)		215 (55)	179 (39)		256 (58.3)	559 (49.4)		293 (59.4)	46 (37.4)	
progression	22 (6.7)	56 (6.6)		31 (8)	44 (10)		31 (7.1)	146 (12.9)		36 (7.3)	11 (8.9)	
relapse	89 (27.0)	224 (26.3)		98 (25)	134 (29)		104 (23.7)	289 (25.6)		114 (23.1)	47 (38.2)	
relapse & progression	40 (12.1)	127 (14.9)		47 (12)	107 (23)		48 (10.9)	137 (12.1)		50 (10.1)	19 (15.4)	
MRI Brain: T2 lesion, n (%)												
Imaging available	79 (24)	517 (60)		91 (23)	231 (50)		100 (23)	400 (35)		106 (22)	45 (37)	
1-2	3 (1)	10 (2)		3 (3)	14 (6)		4 (4)	21 (5)		4 (4)	5 (11)	
3-8	10 (13)	22 (4)		10 (11)	21 (9)		12 (12)	29 (7)		14 (13)	1 (2)	
9+	66 (84)	447 (86)		78 (86)	196 (85)		84 (84)	351 (88)		88 (83)	39 (87)	
MRI Brain: new or contrast enhancing lesions, n (%)												
Imaging available	168 (51)	517 (60)		198	256		212 (48)	569 (50)		233 (47)	51 (41)	
Absent[a]	76 (45)	299 (57)		97 (49)	99 (39)		101 (48)	350 (62)		119 (51)	19 (37)	
Present[a]	92 (54)	218 (42)		101 (51)	157 (61)		111 (52)	219 (38)		114 (49)	32 (63)	
Nr of previous therapies	1 [1, 2]	1 [1, 2]	0.02	1 [1, 2]	2 [1, 3]	0.1	2 [1, 2]	2 [1, 3]	0.1	2 [1, 3]	2 [1, 3]	0.03
Top previous therapy category, n (%)												

None	48 (14.5)	44 (5.2)		48 (12.3)	59 (12.7)		48 (10.9)	140 (12.4)		49 (9.9)	25 (20.3)	
Low-efficacy	146 (44.2)	596 (69.9)		146 (37.3)	124 (26.7)		146 (33.3)	196 (17.3)		149 (30.2)	11 (8.9)	
Moderate-efficacy	72 (21.8)	163 (19.1)		174 (44.5)	207 (44.6)		174 (39.6)	404 (35.7)		181 (36.7)	48 (39.0)	
High-efficacy	64 (19.4)	50 (5.9)		23 (5.9)	74 (15.9)		71 (16.2)	391 (34.6)		114 (23.1)	39 (31.7)	
Prebaseline follow up, y	4.0 [1.8, 8.0]	4.7 [2.3, 8.1]	0.04	4.8 [2.3, 8.9]	4.2 [1.9, 7.6]	0.2	4.8 [2.2, 8.8]	5.2 [2.1, 9.3]	0.02	4.8 [2.4, 8.8]	4.8 [1.2, 8.9]	0.06
Visit density (per year)	1.7 [1.2, 2.4]	1.9 [1.4, 2.6]	0.2	1.7 [1.2, 2.3]	1.9 [1.3, 2.5]	0.3	1.6 [1.2, 2.3]	1.8 [1.2, 2.3]	0.08	1.7 [1.2, 2.4]	1.5 [1.0, 2.0]	0.2
Study follow-up, y	2.4 (1.0)	2.6 (1.1)	0.24	2.4 (1.0)	2.6 (1.1)	0.1	2.5 (1.0)	2.8 (1.1)	0.3	2.5 (0.9)	3.2 (1.0)	0.8

[a] *Proportion of patients with available MRI*

Top previous therapy category:
Low-efficacy: interferons, glatiramer acetate, teriflunomide; Moderate-efficacy: fingolimod, dimethyl fumarate, diroximel fumarate, daclizumab; High-efficacy: natalizumab, alemtuzumab, rituximab, ocrelizumab, mitoxantrone
SMD – standardised mean difference

eTable 5: Logistic regression model used to estimate propensity scores

Fingolimod vs cladribine (reference)

Independent variable	Coefficient	p-value
Male sex	0.13	0.52
Age	0.02	0.11
EDSS at baseline	-0.08	0.22
Nr relapses in 12 months before baseline	0.14	0.60
MS duration	-0.03	**0.03**
Nr of previous MS therapies	0.08	0.37
T2 lesion nr: 1-2	0.92	0.57
T2 lesion nr: 3-8	-0.27	0.82
T2 lesion nr: 9+	0.03	0.98
New T2 or Gd lesion at baseline	-0.23	0.24
Recent activity: progression	0.85	**0.01**
Recent activity: relapse	-0.08	0.84
Recent activity: relapse and progression	0.43	0.16
Country: CA	1.57	**<0.0001**
Country: ES	0.66	**0.03**
Country: GB	2.98	**<0.0001**
Country: IT	1.48	**<0.0001**
Country: KW	2.98	**<0.0001**
Country: LB	4.27	**<0.0001**
Country: OM	2.03	**0.02**
Country: PT	2.57	**<0.0001**
Top previous DMT category: low	0.29	0.37
Top previous DMT category: moderate	0.81	**0.01**
Top previous DMT category: none	0.66	0.15

Natalizumab vs cladribine (reference)

Independent variable	Coefficient	p-value
Male sex	-0.40	**0.05**
Age	-0.04	**<0.0001**
EDSS at baseline	0.04	0.49
Nr relapses in 12 months before baseline	0.24	0.31
MS duration	-0.01	0.71

Nr of previous MS therapies	0.01	0.89
T2 lesion nr: 1-2	-1.08	0.45
T2 lesion nr: 3-8	-1.53	0.06
T2 lesion nr: 9+	-1.82	**0.02**
New T2 or Gd lesion at baseline	0.95	**<0.0001**
Recent activity: progression	0.53	0.08
Recent activity: relapse	0.00	0.99
Recent activity: relapse and progression	0.55	0.15
Country: ES	-0.63	**0.03**
Country: IT	0.80	**0.01**
Country: KW	1.35	**<0.0001**
Country: LB	2.35	**0.03**
Country: TR	1.57	**<0.0001**
Top previous DMT category: low	-2.26	**<0.0001**
Top previous DMT category: moderate	-1.52	**<0.0001**
Top previous DMT category: none	-1.61	**<0.0001**

Ocrelizumab vs cladribine (reference)

Independent variable	Coefficient	p-value
Male sex	0.29	**0.05**
Age	-0.01	0.26
EDSS at baseline	0.16	**<0.0001**
Nr relapses in 12 months before baseline	0.14	0.54
MS duration	0.001	0.86
Nr of previous MS therapies	-0.01	0.85
T2 lesion nr: 1-2	1.30	0.13
T2 lesion nr: 3-8	0.44	0.26
T2 lesion nr: 9+	0.44	0.17
New T2 or Gd lesion at baseline	-0.13	0.32
Recent activity: progression	0.75	**<0.0001**
Recent activity: relapse	0.18	0.57
Recent activity: relapse and progression	0.25	0.45
Country: BE	1.29	**<0.0001**
Country: CA	0.39	**0.05**
Country: ES	-0.54	**0.02**
Country: IT	0.58	**0.05**
Country: KW	1.45	**<0.0001**
Country: PT	-2.11	**0.02**
Country: TR	1.93	**<0.0001**
Top previous DMT category: low	-2.03	**<0.0001**
Top previous DMT category: moderate	-1.13	**<0.0001**
Top previous DMT category: none	-1.02	**<0.0001**

Alemtuzumab vs cladribine (reference)

Independent variable	Coefficient	p-value
Male sex	0.36	0.31
Age	-0.05	**0.01**
EDSS at baseline	0.31	**0.002**
Nr relapses in 12 months before baseline	0.95	**0.02**
MS duration	0.03	0.26
Nr of previous MS therapies	0.03	0.83
T2 lesion nr: 1-2	-14.80	0.99

T2 lesion nr: 3-8	-1.96	**0.03**
T2 lesion nr: 9+	-0.80	0.27
New T2 or Gd lesion at baseline	0.51	0.13
Recent activity: progression	0.39	0.48
Recent activity: relapse	-0.82	0.22
Recent activity: relapse and progression	-1.35	0.07
Country: BE	2.44	**<0.0001**
Country: CA	1.70	**0.01**
Country: ES	3.04	**<0.0001**
Country: GB	4.17	**<0.0001**
Country: IT	2.87	**<0.0001**
Country: KW	4.47	**<0.0001**
Country: TR	2.08	**<0.0001**
Top previous DMT category: low	-2.38	**<0.0001**
Top previous DMT category: moderate	-0.87	**0.04**
Top previous DMT category: none	-0.31	0.66

Coefficients indicate change in log odds of being treated with the comparator vs CLD.
Only country variables with a significant contribution to the logistic model are shown.

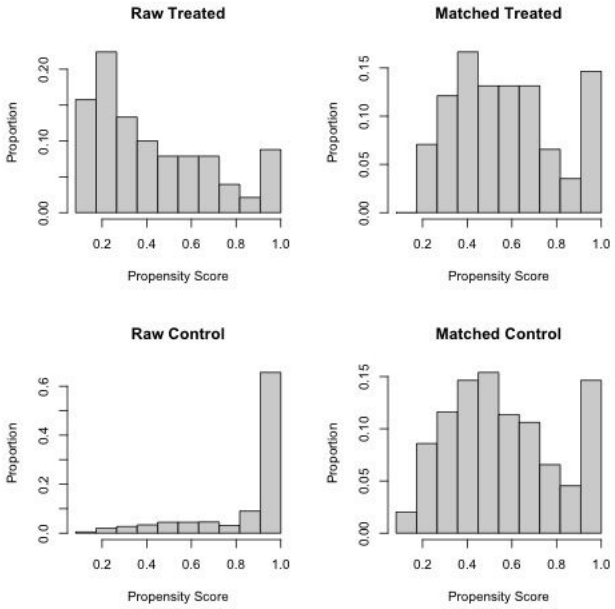
eTable 6: Demographic, clinical and paraclinical characteristics of patients who fulfilled inclusion criteria but were not propensity score matched

	Clad-ribine	**Fingo-limod**	**SMD**	**Clad-ribine**	**Natali-zumab**	**SMD**	**Clad-ribine**	**Ocreli-zumab**	**SMD**	**Clad-ribine**	**Alemtu-zumab**	**SMD**
Nr of patients	132	450		171	133		59	464		320	55	
Registry (%)												
Cambridge	0 (0.0)	4 (0.9)		1 (0.6)	0 (0.0)		0 (0.0)	2 (0.4)		0 (0.0)	7 (12.7)	
Cardiff	0 (0.0)	2 (0.4)		0 (0.0)	4 (3.0)		0 (0.0)	52 (11.2)		0 (0.0)	10 (18.2)	
MSBase	132 (100.0)	444 (98.7)		170 (99.4)	129 (97.0)		59 (100.0)	410 (88.4)		320 (100.0)	38 (69.1)	
Female sex (%)	94 (71)	344 (74)		122 (72)	107 (80)		50 (85)	421 (89)		242 (79)	43 (78)	
Age, y	45.2 (13.0)	37.6 (10.6)	0.64	48.2 (11.6)	32.5 (8.5)	1.53	44.8 (10.9)	42.6 (10.9)	0.21	44.5 (12.3)	36.6 (8.9)	0.73
MS duration, y	10.1 (8.9)	8.8 (6.7)	0.17	12.9 (9.2)	7.9 (5.9)	0.64	12.0 (7.9)	12.4 (8.4)	0.05	11.5 (8.5)	8.9 (7.7)	0.32
Nr of relapses in prior 12 months	0.5 (0.6)	0.5 (0.7)	0.06	0.4 (0.6)	0.9 (0.9)	0.74	0.5 (0.8)	0.5 (0.7)	0.1	0.4 (0.6)	1.0 (0.9)	0.82
EDSS step	2.7 (1.9)	1.5 (1.4)	0.74	2.4 (1.7)	2.3 (1.8)	0.03	1.5 (1.2)	3.8 (1.9)	1.37	2.3 (1.7)	3.3 (2.0)	0.54
Disease activity over prior 12 months, n (%)												
none	81 (61.4)	241 (53.6)		108 (63.2)	33 (24.8)		38 (64.4)	183 (39.4)		213 (66.6)	15 (27.3)	
progression	0 (0.0)	26 (5.8)		9 (5.3)	16 (12.0)		1 (1.7)	87 (18.8)		15 (4.7)	5 (9.1)	
relapse	34 (25.8)	108 (24.0)		41 (24.0)	41 (30.8)		15 (25.4)	126 (27.2)		66 (20.6)	28 (50.9)	
relapse & progression	17 (12.9)	75 (16.7)		13 (7.6)	43 (32.3)		5 (8.5)	68 (14.7)		26 (8.1)	7 (12.7)	
Nr of previous therapies	1.4 (1.2)	1.5 (0.8)	0.03	1.8 (1.3)	2.1 (1.2)	0.23	1.6 (1.1)	2.2 (1.6)	0.41	1.9 (1.5)	1.8 (1.7)	0.08
Top previous therapy category, n (%)												
None	28 (21.2)	12 (2.7)		18 (10.5)	11 (8.3)		6 (10.2)	66 (14.2)		31 (9.7)	19 (34.5)	
Low-efficacy	42 (31.8)	364 (80.9)		74 (43.3)	29 (21.8)		45 (76.3)	41 (8.8)		122 (38.1)	2 (3.6)	
Moderate-efficacy	12 (9.1)	63 (14.0)		76 (44.4)	56 (42.1)		8 (13.6)	159 (34.3)		97 (30.3)	17 (30.9)	
High-efficacy	50 (37.9)	11 (2.4)		3 (1.8)	37 (27.8)		0 (0.0)	198 (42.7)		70 (21.9)	17 (30.9)	

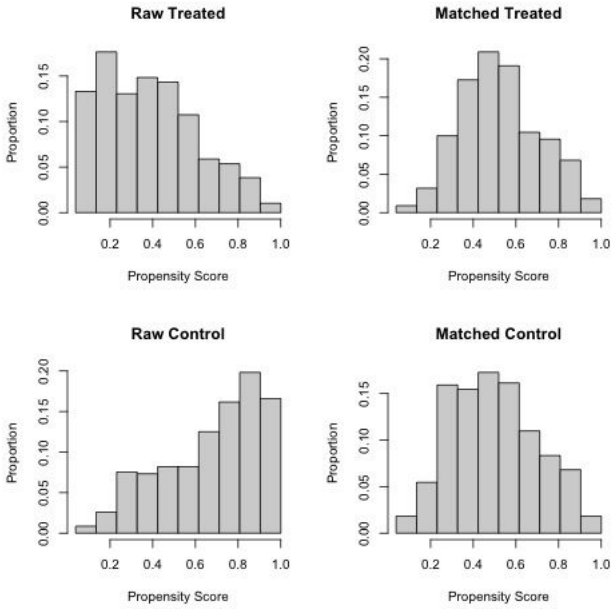
Top previous therapy category:
Low-efficacy: interferons, glatiramer acetate, teriflunomide; Moderate-efficacy: fingolimod, dimethyl fumarate, diroximel fumarate, daclizumab; High-efficacy: natalizumab, rituximab, ocrelizumab, mitoxantrone
SMD – standardised mean difference

eFigure 1: Propensity Scores

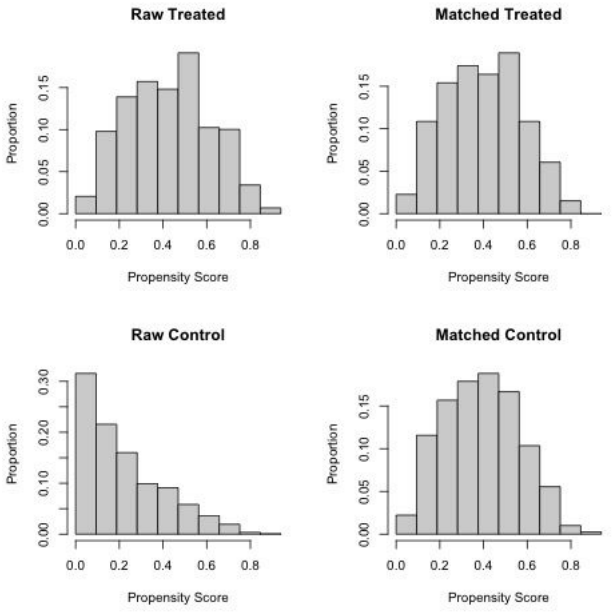
Propensity scores before and after matching among patients treated with fingolimod (treated) and cladribine (control)



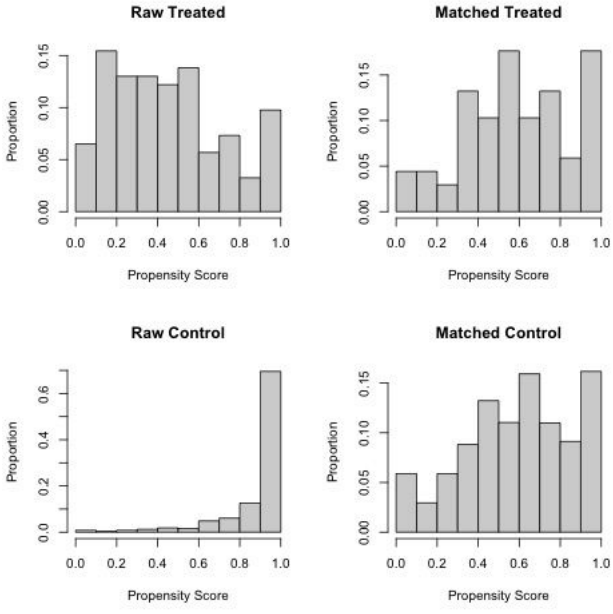
Propensity scores before and after matching among patients treated with natalizumab (treated) and cladribine (control)



Propensity scores before and after matching among patients treated with ocrelizumab (treated) and cladribine (control)

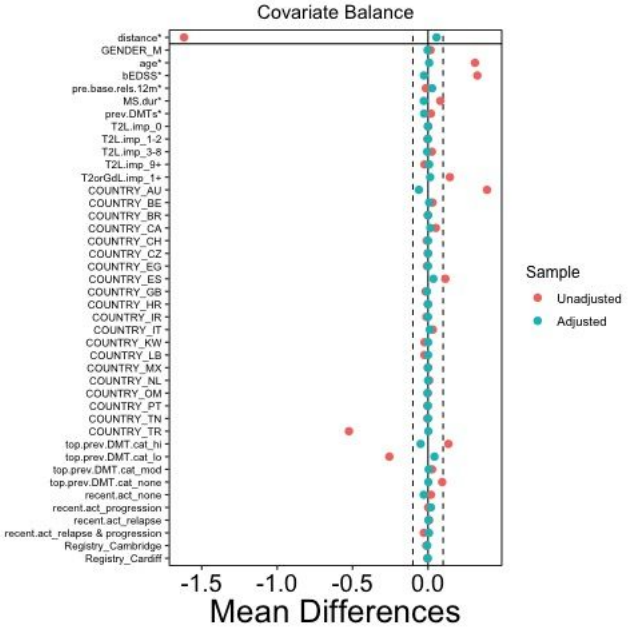


Propensity scores before and after matching among patients treated with alemtuzumab (treated) and cladribine (control)

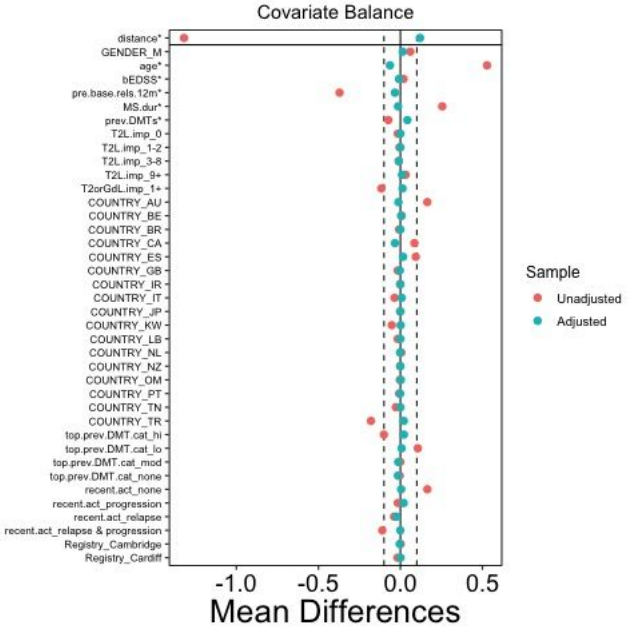


eFigure 2: Love plots

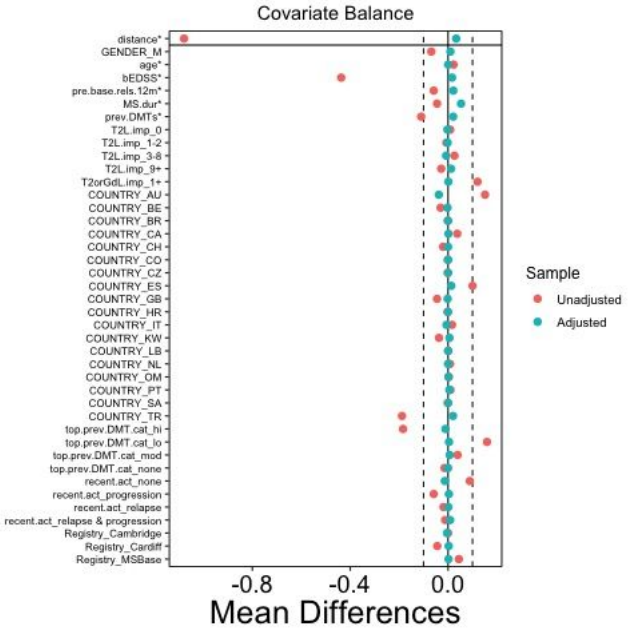
Standardised mean differences before and after matching among patients treated with fingolimod (treated) and cladribine (control)



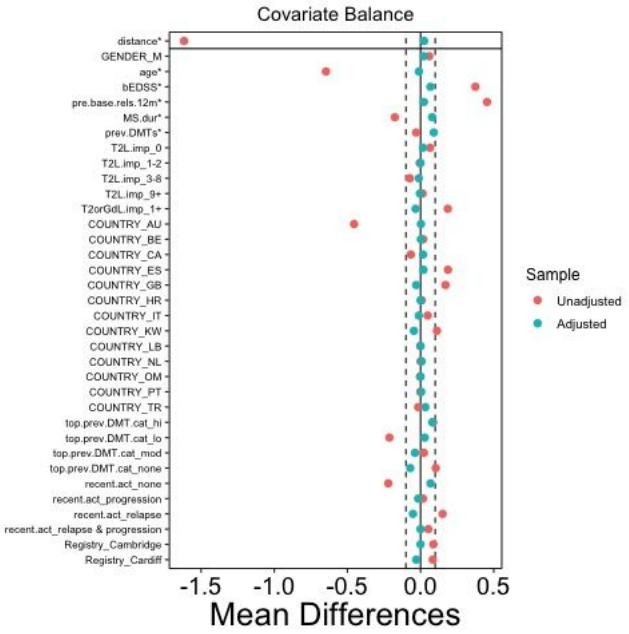
Standardised mean differences before and after matching among patients treated with natalizumab (treated) and cladribine (control)



Standardised mean differences before and after matching among patients treated with ocrelizumab (treated) and cladribine (control)



Standardised mean differences before and after matching among patients treated with alemtuzumab (treated) and cladribine (control)



eTable 7: Results of the sensitivity analyses

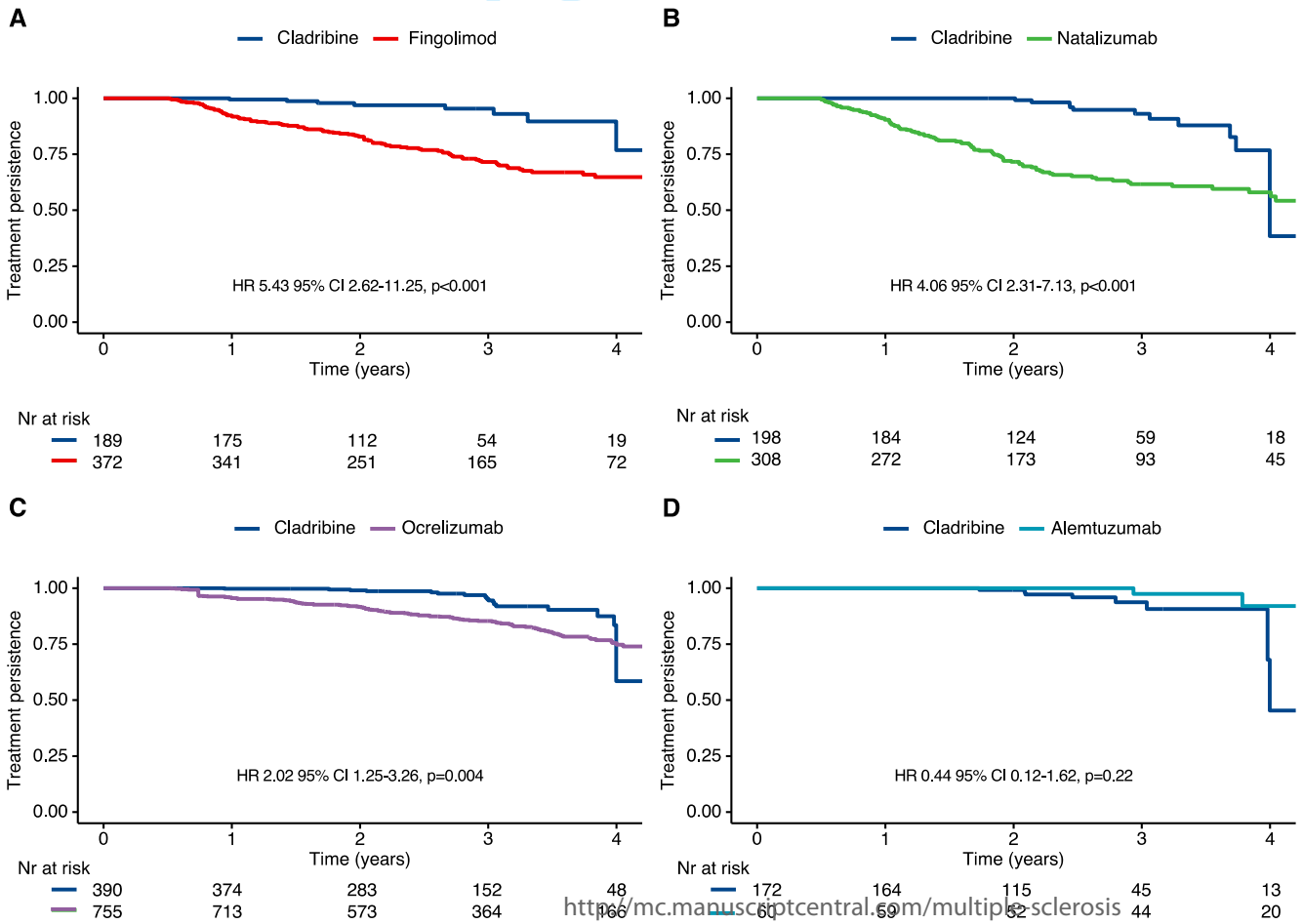
Cladribine vs fingolimod	**unmatched, n**		**matched, n**		**Annualised relapse rate**	**Cumulative hazard of relapses**	**Cumulative hazard of disability accumulation**	**Cumulative hazard of disability improvement**
Analysis	*Cladribine*	*Fingolimod*	*Cladribine*	*Fingolimod*	HR (95%CI)			
Primary analysis	**330**	**853**	**198**	**403**	**1.84 (1.36-2.50)**	**1.71 (1.12-2.63)**	**1.08 (0.47-2.47)**	**0.38 (0.13-1.10)**
'as treated' design	329	788	189	372	1.65 (1.18-2.34)	1.74 (1.04-2.93)	0.96 (0.36-2.53)	0.52 (0.21-1.29)
'Per protocol' design with 18 month follow-up	260	696	136	263	1.92 (1.25-3.00)	1.98 (1.17-3.36)	0.73 (0.43-1.55)	0.80 (0.33-1.93)

Cladribine vs natalizumab	**unmatched, n**		**matched, n**		**Annualised relapse rate**	**Cumulative hazard of relapses**	**Cumulative hazard of disability accumulation**	**Cumulative hazard of disability improvement**
Analysis	*Cladribine*	*Natalizumab*	*Cladribine*	*Natalizumab*	HR (95%CI)			
Primary analysis	**391**	**464**	**220**	**331**	**0.52 (0.32-0.83)**	**0.55 (0.33-0.93)**	**0.35 (0.13-0.94)**	**0.67 (0.36-1.17)**
'as treated' design	390	417	198	308	0.48 (0.28-0.80)	0.46 (0.26-0.83)	0.92 (0.31-2.70)	0.75 (0.39-1.44)
'Per protocol' design with 18 month follow-up	309	367	151	212	0.59 (0.35-0.98)	0.64 (0.38-1.07)	0.51 (0.21-1.30)	0.89 (0.48-1.67)

Cladribine vs ocrelizumab	**unmatched, n**		**matched, n**		**Annualised relapse rate**	**Cumulative hazard of relapses**	**Cumulative hazard of disability accumulation**	**Cumulative hazard of disability improvement**
Analysis	*Cladribine*	*Ocrelizumab*	*Cladribine*	*Ocrelizumab*	HR (95%CI)			
Primary analysis	**439**	**1131**	**380**	**667**	**0.67 (0.48-0.92)**	**0.61 (0.42-0.88)**	**0.45 (0.26-0.78)**	**0.80 (0.50-1.29)**
'as treated' design	438	1116	390	755	0.60 (0.43-0.84)	0.55 (0.38-0.82)	0.57 (0.35-0.93)	0.87 (0.53-1.44)
'Per protocol' design with 18 month follow-up	357	969	293	604	0.53 (0.39-0.75)	0.54 (0.36-0.81)	0.67 (0.41-1.12)	0.82 (0.50-1.33)

Cladribine vs alemtuzumab	unmatched, n		matched, n		Annualised relapse rate	Cumulative hazard of relapses	Cumulative hazard of disability accumulation	Cumulative hazard of disability improvement
Analysis	*Cladribine*	*Alemtuzumab*	*Cladribine*	*Alemtuzumab*	HR (95%CI)			
Primary analysis	**481**	**123**	**173**	**68**	**0.22 (0.11-0.42)**	**0.51 (0.10-0.65)**	**0.73 (0.26-2.07)**	**1.3 (0.50-3.38)**
'as treated' design	480	123	179	67	0.19 (0.08-0.41)	0.16 (0.06-0.41)	0.63 (0.21-1.91)	0.90 (0.81-2.06)
'Per protocol' design with 18 month follow-up	392	113	143	51	0.77 (0.42-1.43)	0.82 (0.41-1.65)	0.72 (0.31-1.69)	1.46 (0.78-2.71)

eFigure 3: Treatment persistence



Hazard ratio indicates risk of treatment discontinuation of study therapy vs cladribine

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.