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PEER-REVIEWED CONFERENCE REPORT

Focus on Earlier Stages of Alzheimer's Disease

Treatments are more likely to succeed in the prodromal phase than in the final, symptomatic stages of AD. The best entrance for understanding the cellular processes leading up to AD is genetics.

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Neuroinflammation in Epilepsy: Biomarkers and Treatment

Insights into the dynamics of neuroinflammation has generated several potential targets for developing new drugs, or for repurposing of available anti-inflammatory drugs. Moreover, there is value for inflammation-related biomarkers.

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Ischaemic Stroke Elicits Neuroinflammatory Response

Targeting stroke-related neuroinflammation may become an effective therapy to improve outcome after ischaemic stroke in the future, but requires caution with regard to timing and adverse effects.

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Letter from the Editor

Prof. Hans-Peter Hartung

Dear Reader,

Inflammatory processes are involved in the etiopathology of most neurological diseases, even for conditions previously considered as 'non-inflammatory' such as Alzheimer's disease, ALS, epilepsy, movement disorders, stroke, and migraine.

With neuroinflammation as the overarching theme, the European Academy of Neurology held its 5th annual meeting in Oslo. It provided a forum for researchers, clinician scientists, and practising neurologists. Cutting-edge research related to elucidating the etiopathogenesis were presented, as well as results of new treatment trials for neurological conditions across the board.

This peer-reviewed conference report summarises the highlights from the programme. We hope you will find these mini-reviews useful.

Yours sincerely,

Hans-Peter Hartung

Biography

Prof. Hartung has been Chair of the Department of Neurology at Hein-rich-Heine-University in Düsseldorf since 2001. He is also Director of the Center of Neuropsychiatry and the Department of Conservative Medicine at University Hospital Düsseldorf. He studied medicine at the Universities of Düsseldorf, Glasgow, Oxford, and London. After graduation he served an immunology fellowship at the University of Mainz.

Prof. Hartung's clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies. He has been involved as steering committee member in multiple clinical trials of new drugs for the treatment of multiple sclerosis, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy.

Prof. Hartung is a former President of ECTRIMS.

Disclosures:
Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme, CSL Behring, Octapharma, and Teva, with approval by the Rector of Heinrich-Heine-University.

Alzheimer's Disease and other Dementias

A necessary shift of focus to the earlier stages of Alzheimer's

Prof. Bart de Strooper (Katholieke Universiteit Leuven, Belgium) delivered an inspiring plenary lecture on the prodromal, cellular phase of Alzheimer's disease (AD) [1]. He noted that the success rate of AD trials is not exceptionally low, but that we must continue to invest heavily in innovative research. Attention should be shifted towards the prodromal phase of AD, in which the window of opportunity for treatments to succeed will be much larger than in the final, symptomatic stages of AD.

"Most interventions are deployed in the advanced, clinical phase, when it is very hard to alter the course of the disease. "It is like treating cancer only in the late stages, when it has already metastasised", Prof. De Strooper said. "We have to further increase our understanding of the cellular processes leading up to AD, which have generally started some 30 years earlier, before the formation of plaques."

According to Prof. De Strooper, the best entrance for understanding AD is genetics. There are 3 causal genes: amyloid precursor protein (APP) and presenilin 1 and 2 (PSEN1 and PSEN2). "Destabilisation of PSEN and release of longer amyloid-beta peptides is at the core of the pathological mechanism." He pointed out the main reasons why trials targeting these pathways have failed so far: flaws in the trials' design; intervening at a late stage of the disease; and the brain being too diffuse a target. An example is the failed trial of the small-molecule gamma-secretase inhibitor semagacestat [2]. "The idea was not wrong", Prof. De Strooper said, "but in an attempt to minimise side-effects, the dose may well have been sub-therapeutic".

He also argued that understanding how risk genes drive dementia is of paramount importance in developing new drug targets. Twins studies have shown that two thirds of the risk for sporadic disease is genetic. So far, over 1,000 loci have been identified that may predict an elevated risk of developing AD. Prof. De Strooper foresees a future in which individual polygenic risk score analysis may identify persons at high risk [3], thus enabling early and effective interventions.

1. De Strooper B, et al. EAN 2019, PLEN02_1.
2. Doody RS, et al. N Engl J Med 2013;369:341-50.
3. Escott-Price V, et al. Neurobiol Aging. 2017;49:214.e7-214.e11.

Biomarkers and how to use them

Biomarkers are diagnostic tools that can detect disease-specific alterations in the brain. Depending on what moment in the disease process these alterations occur, biomarkers are more suitable for early or differential dementia diagnosis. Ideal biomarkers also allow monitoring of disease progression. Optimisation of existing biomarkers as well as the development of novel biomarkers is required to improve early and differential dementia diagnosis.

- Synaptic dysfunction is the best correlate of cognitive impairment that precedes neuronal cell death in patients along the Alzheimer's disease (AD) continuum. EEG topographical markers were found to correlate with surrogate synaptic markers and therefore contribute to early detection of synaptic dysfunction in patients along the AD continuum [1]. In both patients diagnosed with mild cognitive impairment (MCI, n=40) and AD (n=20), the pattern of regional brain glucose hypometabolism correlated with localisation of brain electrical sources and decreased Global Field Synchronization (GFS). Being a widely available and non-invasive diagnostic method, the authors think EEG might have broad implications in AD drug trials and clinical practice.
- Neurofilament light (NfL) protein is a known marker of neuroaxonal damage, but its levels in cerebrospinal fluid and serum might be associated with age and sub-clinical morphologic brain changes in the normal population as well. A study reported rising and more variable serum NfL levels in healthy individuals >60 years, indicating accelerated neurodegeneration which may be confounded by subclinical pathologic brain changes [2]. Serum NfL was measured by a single molecule array in 335 healthy individuals who were followed for a mean of 6 years. Mean serum NfL levels were more stable below the age of 60 years, but then increased in a non-linear manner (see Figure). An increase of group variances in serum NfL levels above 60 years was also observed. Baseline serum NfL (β=0.549, P<0.0001) and its change over time (β=0.486, P<0.0001) were the strongest

independent predictors for future brain atrophy in the age group above 60 years. In younger individuals, baseline normalised brain volume (β=0.530, P<0.01) was the strongest predictor.

- Insulin-like growth factor binding protein-2 (IGFBP2) was identified as a novel biomarker for incident dementia [3]. IGFBP2-related pathways may play an important role in the development of dementia. Plasma IGFBP2 was measured in 1,596 dementia-free Framingham Heart Study Offspring cohort participants (1998-2001), with a mean age of 69 years. During a median follow-up of 12 years, 131 participants developed dementia (of which 98 AD). The highest quintile of IGFBP2, when compared with the lowest quintile, was associated with an increased risk of incident dementia (HR 2.82) as well as AD (HR 3.28). Higher circulating IGFBP2 levels were also associated with poorer performance on tests of global cognition and abstract reasoning.

Diagnostic algorithm

A consensual diagnostic algorithm to guide the combined use of biomarkers has been developed for the first time [4]. Dementia experts joined a Delphi procedure on behalf of 5 Italian scientific societies (SINdem, AIP, AIMN, AINR, and SIBioC). Their recommendations attempt to maximise biomarkers' informative value over costs.

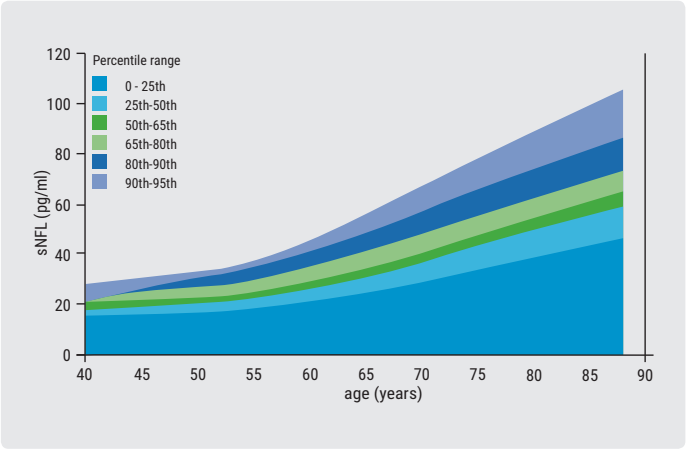
The panel identified a diagnostic algorithm including clinical and cognitive assessment, blood examination, and MRI with both exclusionary and inclusionary value at baseline. Different examinations are then prescribed, based on the diagnostic hypothesis: cerebrospinal fluid biomarkers -or amyloid PET as second choice- for suspected AD; FDG-PET for suspected frontotemporal lobar degeneration (FTLD) and low confidence of AD; and I-123 MIBG cardiac scintigraphy for suspected Lewy body dementia (DLB). Biomarker investigation for AD in older patients with consistent clinical and MRI findings should be considered based on its plausible clinical impact.

1. Smailovic U, et al. EAN 2019, O1105.
2. Khalil M, et al. EAN 2019, O1103.
3. McGrath E, et al. EAN 2019, O3111.
4. Boccardi K, et al. EAN 2019, O1101

Antipsychotics increase mortality regardless of comorbidity

Results of a Danish nationwide study confirm that antipsychotic treatment strongly increases risk of mortality in patients with dementia [1]. Adjusted risk of death was increased by about one third. The mortality risk was not influenced by diabetes, cardiovascular, and cerebrovascular comorbidity.

Figure: Percentile range areas of serum NfL in normal elderly during the course of ageing [2]



Dr Ane Nørgaard (Rigshospitalet, Denmark) said that there is limited evidence for an effect of antipsychotic treatment on behavioural symptoms and psychosis in dementia. Numbers needed to harm (death of a patient) after 12 weeks of treatment is 100. A matched cohort study was conducted, including all Danish residents aged 65-95 years diagnosed with dementia between 2009 and 2014. Every patient exposed to antipsychotics (n=8,244) was matched with up to three unexposed patients (n=24,730). Total mortality was 5,938 after 180 days of follow-up (3,945 in the unexposed group vs 1,993 in the exposed group). The crude mortality rate per 100 person-years was 36.3 and 58.3, respectively (HR 1.49). Adjusted HR was 1.35. "Patients with pre-existing cardiovascular disease and diabetes are at increased risk of death when treated with antipsychotics", Dr Nørgaard said. She stated that clinical guidelines should include a risk stratification to identify patients who can benefit from antipsychotic treatment with the lowest risks. This is a very common and disturbing problem for the family and the patients but the study does not provide information on alternatives in handling psychotic behaviour in dementia patients.

1. Nørgaard A, et al. EAN 2019, O1104.

PDD and DLB represent two different disorders

Lewy body dementias include two conditions, Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB).

In an analysis of 64 brain donors (52 PDD, 12 DLB), multiple clinical and neuropathological differences between PDD and DLB were observed [1]. This result supports the hypothesis that PDD and DLB represent two different disorders. Compared to PDD patients, DLB patients had:

- shorter disease duration (P<0.001);
- older age at motor symptoms onset (P=0.022);
- less frequent tremor (P=0.017);
- no dyskinesia (P<0.001);
- less severe parkinsonism at the time of dementia (P<0.001);
- lower MMSE scores (P=0.006).

DLB patients took less levodopa, dopamine agonists, monoamine oxidase inhibitors, amantadine, and anticholinergics compared to PDD patients. Alzheimer's disease neuropathology scores were significantly higher in DLB vs PDD (B-score P=0.018; C-score P=0.016).

1. Holton J, et al. EAN 2019, O4119.

Epilepsy

Neuroinflammatory pathways as biomarkers and treatment targets

The important role of neuroinflammation in epilepsy featured in a plenary presentation by Prof. Annamaria Vezzani (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy) [1]. About 30% of epilepsy patients are not seizure-free, despite the introduction of 20-30 new anti-epileptic drugs over the past 30 years. Prof. Vezzani argued that the identification of the pathogenic mechanisms of epileptogenesis will allow the design of novel treatments which are apt to prevent or reduce the generation of epileptic seizures.

Neuroinflammation is a maladaptive brain response commonly ignited in human epileptogenic brain regions and is clearly involved in animal models of epilepsy, Prof. Vezzani explained. Experimental studies in animal models showed that -if not adequately controlled- neuroinflammation is involved in the pathogenesis of seizures, neuronal cell loss, and neurological comorbidities. Neuroinflammation has now been related to several types of human epilepsy:

- temporal lobe epilepsy with or without hippocampal sclerosis;
- malformations of cortical development, i.e. hemimegaloencephaly (HME), focal cortical dysplasia (FCD) type II, tuberous sclerosis;
- Rasmussen's encephalitis;
- febrile infection-related epilepsy syndrome (FIRES);
- acute symptomatic seizures and status epilepticus;
- neonatal febrile seizures;
- acquired epilepsies;
- absence seizures and progressive myoclonus epilepsy of Unverricht-Lundborg type (EPM1).

Insights into the dynamics of neuroinflammation in epilepsy has generated several potential cellular and molecular targets for developing new drugs, or for repurposing of available anti-inflammatory drugs, acting on key pathogenic mechanisms. Inflammatory mediators such as interleukin (IL)-1β, tumour necrosis factor (TNF), high mobility group box 1, transforming growth factor-β, and prostaglandins can alter neuronal, glial, and blood–brain barrier functions by activating transcriptional and post-translational mechanisms in brain cells. Proof-of-concept target-specific anti-inflammatory interventions in animal models of epilepsy have reported anti-ictogenic, anti-epileptogenic, and disease-modifying therapeutic effects. Prof. Vezzani specifically mentioned the IL-1 receptor antagonist anakinra, which has been administered to several patients [2].
Moreover, blood inflammatory mediators and molecular imaging of neuroinflammation are providing potential diagnos-tic, prognostic, and predictive biomarkers for epilepsy which are instrumental for patient stratification in future clinical studies.

1. Vezzani A. EAN 2019, PLEN03_1.
2. Jyonouchi H, et al. J Clin Cell Immunol 2016;7:5.

Panel of inflammation-associated microRNAs as epilepsy biomarker

The identification of epilepsy biomarkers has represented one of the most significantly growing fields of study in recent years. A panel of 3 circulating microRNAs (miRs) with promising value as biomarker for genetic generalised epilepsy (GGE) was reported [1].

Several genome-wide studies in both animals and patients have demonstrated a dysregulation on the expression profile of miRs in epilepsy, with a focus on miRs associated with inflammation. In the reported study, researchers characterised circulating inflammation-associated miR-146a, miR-155, and miR-132 expression in 79 GGE patients and 67 healthy individuals. Serum levels of miR-146a and miR-155 were significantly upregulated compared with controls (3.13-fold and 6.05-fold, respectively). Combining miR-146a, miR-155, and miR-132 circulating levels increased biomarker performance to discriminate GGE patients from controls with an area under the curve (AUC) of 0.85, with 80% specificity and 73% sensitivity. The authors stated that their results reinforce the relevance of inflammation-associated molecules in epilepsy, opening new avenues in drug development.

1. Ferreira R, et al. EAN 2019, O3221.

Clinical and cost effectiveness of levetiracetam vs valproate

The longer-term clinical and cost effectiveness of levetiracetam and valproate in newly diagnosed generalised and unclassified epilepsy have been compared in a randomised trial [1]. Levetiracetam was not non-inferior to valproate for time to 12-month remission, and was inferior for time to treatment failure for inadequate seizure control and for time to 24-month remission.

The so-called Standard And New Antiepileptic Drugs II (SANAD II) study was a randomised unblinded controlled trial comparing starting treatment with levetiracetam or valproate in patients with generalised (n=396) and unclassified (n=124) epilepsy. The trial was designed to assess the non-inferiority of levetiracetam for time to 12-month remission. Levetiracetam was not found to be non-inferior to valproate for this endpoint: HR 1.19 (non-inferiority margin: 1.314). The HR was not constant over time. After 3 years, there was little to no difference between the 12-month remission rates for each group. In the levetiracetam group, 24% had an immediate 12-month remission, compared to 33% in the valproate group.

Valproate was superior to levetiracetam for time to treatment failure (HR 0.65). It was also superior for time to first seizure (HR 0.82), and time to 24-month remission (HR 1.43). No difference was found in treatment failure due to adverse events (HR 0.93), but valproate was superior for treatment failure due to inadequate seizure control (HR 0.43). In the original SANAD study, which assessed valproate compared to other therapies in 716 patients, valproate was shown to be better tolerated than topiramate and more efficacious than lamotrigine [2].

1. Marson T, et al. EAN 2019, O4125.
2. Marson AG, et al. Lancet. 2007;369(9566):1016-26.

Long-term effect of recurrent febrile seizures

Febrile seizures are relatively common in childhood, affecting 3-4% of children, and are generally considered benign. Recurrent febrile seizures in children, however, were associated with a high risk of epilepsy and mental illness later in life in a Danish study [1].

Results were presented by Dr Julie Werenberg Dreier (Aarhus University, Denmark). She said previous studies were not large enough to investigate the long-term consequences of recurrent febrile seizures. In a cohort of 2.1 million children born between 1977 and 2011, a total of 75,593 children (3.6%) were diagnosed with a first febrile seizure between 1977 and 2016. The risk of recurrent febrile seizures was 22.7% after the first febrile seizure, 35.6% after the second febrile seizure, and 43.5% after the third febrile seizure. At 3 years of age, about 90% of all the children with febrile seizures will have presented, according to Dr Werenberg Dreier. She added that the risk of epilepsy increased progressively with the number of admissions with febrile seizures. The 30-year cumulative risk of epilepsy and psychiatric disorders in children who had three or more febrile seizures was 15.8% and 29.1%, respectively. At birth, the 30-year cumulative risk is 2.2% and 17.2%, respectively. Mortality was increased among children with recurrent febrile seizures, but only in those who later developed epilepsy.

1. Werenberg Dreier J, et al. EAN 2019, O3219.

Migraine

The role of neurogenic inflammation in migraine

In his plenary lecture, Prof Lars Edvinsson (Lund University, Sweden) discussed the evidence for a role of neuroinflammation in initiation of a migraine attack; the possibility of neurogenic inflammation caused by subsequent antidromic neuropeptide release during an attack (predominantly calcitonin gene-related peptide (CGRP); and the novel concept of neurogenic neuroinflammation in migraine chronification [1].

"It has taken me 35 years to convince the world of the important role CGRP plays in migraine", Prof. Edvinsson said. He has always believed migraine to be a brain disease, a disorder in which CNS dysfunction plays a pivotal role: "Migraine symptoms all come from the brain." The trigeminal ganglion (TG) plays a key role in primary headache pathophysiology, being central to the trigeminovascular reflex, which is triggered to protect against vasoconstriction. The triggering of this system leads to the perception of pain in patients with migraine. CGRP and its receptors are expressed in trigeminal neurons. In acute migraine, CGRP is released into the cranial venous outflow. Supporting the importance of CGRP is the observation that intravenous CGRP induces migraine-like symptoms in migraine patients.

Prof. Edvinsson added that recent clinical evidence does not support the notion that neuroinflammation in the dura is the cause of trigeminal activation in migraine. So, is there still a role for inflammation and/or inflammatory mediators in migraine? Yes, inflammation may play a role in chronic migraines, most notably by a mechanism termed 'neurogenic neuroinflammation'. This mechanism possibly entails increased expression of cytokines via activation of protein kinases in neurons and glial cells of the trigeminovascular system. Neurogenic inflammation is characterised by the release of neuropeptides, such as CGRP, from the trigeminal innervation.

CRGP has been shown to induce release of inflammatory mediators from trigeminal satellite glial cells. Blockade of this effect by anti-CGRP medication –the so-called gepants and monoclonal antibodies (mAbs)– may contribute to their anti-migraine effects. Inflammatory mediators in the TG may also contribute to sensitisation and chronification of migraine mechanisms.

"Apparently, migraine drugs act outside of the blood-brain barrier (BBB)", Prof. Edvinsson stated. He added that CGRP targets are found both in the CNS and peripherally. "The TG and dura are not protected by the BBB, which may help explain the therapeutic effect of the antibodies." About the ability of different migraine drugs to cross the BBB, he noted the following:

- sumatriptan does not readily cross the BBB (<3%);
- CGRP-receptor blockers (gepants) hardly cross the BB (only 2-3%);
- antibodies are large molecules and do not cross the BBB (<0.1%).

Prof. Edvinsson summarised CGRP-treatments as follows:

- mAbs binding to CGRP: eptinezumab, fremanezumab, galcanezumab.
- mAb binding to the CGRP-receptor: erenumab.
- Small-molecule CGRP-receptor antagonists, all currently undergoing clinical trials: ubrogepant (formerly MK-1602) for acute migraine; atogepant (MK-8031) for the prevention of migraine, and rimegepant (via nasal spray) for acute attacks as well as prevention of migraine.

Key properties of mAbs as treatment options for migraine:

- exquisite specificity (high avidity from two binding sites);
- no liver toxicity;
- long half-life (weeks/over one month);
- large size (150 kDa): they must be injected and not cross the BBB.

1. Edvinsson L. EAN 2019, PLEN03_4

Atogepant efficacious, safe, and well-tolerated for migraine prevention

In a phase 2b/3 trial the efficacy, safety, and tolerability of atogepant vs placebo for prevention of episodic migraine was evaluated. The results of this novel, oral CGRP receptor antagonist indicate that atogepant can be an effective and safe migraine treatment for patients who experience <15 headache days per month.

In this multicentre, double-blind, placebo-controlled, parallel-group trial, 834 adult migraine patients, with or without aura, and with 4-14 migraine days in the 28-day baseline period, were randomised 2:1:2:1:2:1 to 12 weeks of treatment with placebo, atogepant 10 mg once-daily, 30 mg once-daily, 30 mg twice-daily, 60 mg once-daily, or 60 mg twice-daily, respectively [1].

Mean baseline monthly migraine days (MMDs) were 7.67. Reductions from baseline in the mean MMD for all 5 atogepant treatment groups were statistically significant compared with reductions in the placebo group after 12 weeks. Mean change in MMDs was for placebo: -2.85, atogepant 10 mg once-daily: -4.00 (P=0.0236), 30 mg once-daily: -3.76 (P=0.0390), 30 mg twice-daily: -4.23 (P=0.0034), 60 mg once-daily; -3.55 (P=0.0390), 60 mg twice-daily: -4.14 (P=0.0031). The proportion of subjects with a 25%, 50%, 75%, and 100% reduction from baseline in MMDs favoured atogepant.

Atogepant was also well-tolerated. Treatment-emergent adverse events were reported by 480 subjects (58.2%); 22% of atogepant and 16% of placebo patients reported adverse events that were considered treatment-related. A total of 7 subjects (0.8%) reported serious adverse events, none considered treatment-related. There were 10 cases of treatment-emergent ALT/AST elevations >3 times the upper limit of normal, balanced across groups. Only 1 out of 10 cases (atogepant) was considered probably related.

1. Goadsby P, et al. EAN 2019, EPO3117.

Short- and long-term efficacy of erenumab in hard-to-treat patients

In a hard-to-treat patient population with multiple prior preventive treatment failures, efficacy of erenumab 140 mg was sustained throughout a 24-week period in an open-label extension phase (OLE) of the LIBERTY study [1]. Erenumab also showed sustained efficacy through week 52 in patients with ≥1 prior preventive treatment failures in the STRIVE study [2].

The placebo-controlled LIBERTY study demonstrated efficacy of erenumab 140 mg after 12 weeks in episodic migraine patients with prior preventive treatment failures. The 240 patients completing the double-blind phase were then enrolled into the OLE to receive monthly erenumab 140 mg.

Overall, efficacy data over 24 weeks (assessed over weeks 13–16, 17–20, and 21–24) was generally in line with prior erenumab trials. Patients with continuous use of erenumab showed sustained efficacy in all outcomes assessed. Patients who switched from placebo to erenumab in the OLE showed improvement from the first measurement at week 16 on all outcomes assessed [1].

Of 228 patients (95.0%) who completed the 24-week visit, 39.2% had achieved at least a 50% reduction in monthly migraine days (MMDs), 15.9% at least a 75% reduction, and 7.0% a 100% reduction. The mean change from the double-blind treatment phase baseline was -2.7 in MMDs, -1.4 in monthly acute migraine-specific medication days (MSMD), -7.6 in Headache Impact Test-6 (HIT-6) score, -2.5 in Migraine Physical Function Impact Diary (MPFID) physical impairment score, and -4.0 in MPFID everyday activities score.

In the double-blind 24-week treatment phase of the STRIVE study, 955 patients were randomised (1:1:1) to placebo, erenumab 70 mg or erenumab 140 mg monthly. For the subsequent 28-week active treatment phase, 845 patients were re-randomised (1:1) to erenumab 70 mg or 140 mg. Of these, 343 (41%) had failed ≥1 prior preventive therapy.

At week 52, a consistent decrease in both MMD and MSMD was observed with erenumab 70 and 140 mg [2]. Mean change in MMD was -3.4 and -4.2, respectively; mean change in MSMD was -1.9 and -2.5. The proportion of patients achieving ≥50% MMD reduction in the last month of the active treatment phase was 52% and 55%, respectively; 29% and 33% achieved ≥75% MMD reduction, and 12% and 16% a 100% reduction. Erenumab was generally well-tolerated over the duration of the extended dose-blinded active treatment phase in this subgroup.

1. Reuter U, et al. EAN 2019, EPO2147.
2. Schwedt J, et al. EAN 2019, EPO2148.

Fremanezumab results of the FOCUS study

The overall positive efficacy and safety/tolerability results of fremanezumab in the placebo-controlled FOCUS study were reported in different posters.

Participants had episodic or chronic migraine and inadequate response to 2-4 classes of migraine preventive medications. A total of 838 patients were randomised to monthly fremanezumab (month 1: chronic migraine, 675 mg &

Table: Least-squares mean change in monthly migraine days over 12 weeks [1]

	placebo (n=278)	fremanezumab monthly (n=283)	fremanezumab quarterly (n=276)
Change from baseline	-0.6 (0.34)	-4.1 (0.34)	-3.7 (0.34)
Difference vs placebo	/	-3.5 (0.36); P<0.001	-3.1 (0.36); P<0.001

episodic migraine, 225 mg; months 2 and 3: 225 mg), quarterly fremanezumab (month 1: 675 mg; months 2 and 3: placebo), or matched monthly placebo. Reductions in monthly average migraine days, clinically meaningful response rates within 4 weeks, and sustained ≥50% response rates over 3 months were significantly greater with fremanezumab vs placebo (both P<0.0001; see Table) [1]. Higher proportions of patients achieved ≥50% and ≥75% reductions in migraine days within 4 weeks and sustained ≥50% reductions through the 12-week treatment period with fremanezumab versus placebo.

Fremanezumab was generally safe and well-tolerated, with similar incidences of adverse events (AEs) compared with placebo [2]. The most common AEs (incidence ≥5%) were injection-site erythema, injection-site induration, and nasopharyngitis. Individual cardiovascular or hepatobiliary AEs were reported by <1% of patients in each treatment group. AEs leading to discontinuation and serious AEs were infrequent (≤1%) across treatment groups. No serious AEs were considered to be treatment-related by investigators, and no safety signals were identified.

A third analysis showed that fremanezumab treatment significantly reduced any as well as migraine-specific acute headache medication use compared with placebo in the FOCUS study [3].

1. Spierings EL, et al. EAN 2019, EPO3113.
2. Ferrari M, et al. EAN 2019, EPO2127.
3. Diener HC, et al. EAN 2019, EPO1136.

Galcanezumab reduces healthcare resource utilisation

Findings from the phase 3 REGAIN study revealed that galcanezumab treatment significantly reduced migraine-specific healthcare resource utilisation as well as migraine headache days (MHD) that require acute medication use in patients with chronic migraine [1].

Table: Change in mean migraine headache days per month across different stages of REGAIN [1]

	placebo	galcanezumab 120 mg	galcanezumab 240 mg
Baseline	15.5	15.1	14.5
Double-blind phase	-2.59	-4.88	-4.21
Month 6 OLE	-6.34	-6.38	-5.63
Month 12 OLE	-7.04	-7.62	-6.77

In the phase 3 study REGAIN, patients with chronic migraine were randomised to placebo (n=558), galcanezumab 120 mg (n=278), or galcanezumab 240 mg (n=277). A 3-month double-blind period was followed by a 9-month open-label extension (OLE) phase with flexible dosing. Changes in mean migraine-specific healthcare resource utilisation across baseline, double-blind, and OLE phases (per 100 patient-years) were calculated for healthcare professional visits, emergency room visits, admissions to hospital, and overnight hospital stays. Mean reductions from baseline across time in number of MHD/month with acute medication use were significant in each of the 3 groups (see Table).

The majority of patients in the REGAIN study shifted from chronic to episodic migraine status [2]. After 3 months, a greater proportion of galcanezumab-treated patients shifted from chronic to episodic status (30.9%) versus placebo-treated patients (19.7%). Across the 12-month period, 65.1% of galcanezumab-treated patients shifted to episodic status for ≥3 consecutive months. The authors concluded that long-term treatment with galcanezumab may lead to substantial reductions in disability and economic burden.

1.Joshi S, et al. EAN 2019, EPO2137.
2. Detke H, et al. EAN 2019, EPO1134.

Lasmiditan in migraine patients with CV risk factors

Oral lasmiditan could provide an effective acute migraine treatment for patients with cardiovascular risk factors. This was concluded from the safety and efficacy results of lasmiditan in the phase 3 SAMURAI and SPARTAN trials in patients with cardiovascular risk factors [1]. Lasmiditan did not affect the risk of cardiovascular treatment-emergent adverse events.

Migraine is an independent risk factor for cardiovascular disease and is associated with an increased risk of

cardiovascular events. Lasmiditan is a centrally-penetrant, serotonin 5-hydroxytryptamine receptor 1F (5-HT1F) receptor agonist which differs structurally and mechanistically from other treatments of acute migraine and lacks vasoconstrictive effects. To analyse safety and efficacy of lasmiditan in patients with cardiovascular risk factors, data were used from SAMURAI and SPARTAN, two similarly designed randomised, double-blind, placebo-controlled trials treating a single migraine attack in adults with lasmiditan 50 mg, 100 mg, or 200 mg. Both studies included patients with cardiovascular risk factors; SPARTAN did not exclude patients with coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension.

At baseline, nearly 80% of patients had at least 1 cardiovascular risk factor; more than 40% had 2 or more cardiovascular risk factors. In SAMURAI as well as SPARTAN, significantly more patients in the lasmiditan groups were free of headache and the most bothersome associated symptoms vs placebo. The presence of cardiovascular risk factors did not impact on the efficacy results: there was no statistical difference in lasmiditan efficacy or the frequency of likely cardiovascular treatment-emergent adverse events. The only likely cardiovascular treatment-emergent adverse event seen across patients who had at least 1 cardiovascular risk factor, was palpitations.

1. Hochstetler H, et al. EAN 2019, O2205.

Factors influencing choice of prophylactic migraine therapy

Results of the PANORAMA study provided insights into the current treatment paradigm for migraine in Germany, revealing a disproportionately long patient-journey. The choice of prophylactic migraine therapy was determined by a large number of factors, with the guidelines seemingly playing only a marginal role [1].

A total of 119 specialised German centres contributed to PANORAMA with over 10 months of data collection. Individual centre profiles were obtained, followed by a thorough database research to characterise the patients' treatments. Additionally, in an expert interview, the significance of migraine therapy in each centre was defined.

Of all treated patients per calendar quarter, 13.8% had migraine; about 88% of these patients were referred from other centres. The majority of patients (60%) had at least 4 migraine days per month; 13% had a chronic condition. An average of 43% received prophylactic treatment, while 68% were using triptans. Choice of prophylactic therapy was determined by a wide range of factors: comorbidities (49.6%); demography/patient situation (47.1%); adverse reactions/tolerability (33.6%); concomitant medication (22.7%); patient's wish (18.5%); previous therapy (14.3%); effectiveness (10.1%); guidelines (10.1%); easy to use (6.7%).

1. Koch M, et al. EAN 2019, EPR2041.

Multiple Sclerosis

Treating MS from disease onset

Recent EAN/ECTRIMS guidelines highlight the need for early introduction of disease-modifying treatment (DMT). However, a study presented at the EAN 2019 illustrated that this is still far from reality in clinical practice. The results showed that time to first DMT varies strongly across countries [1]. Another study illustrated the importance of timely management by showing that MS patients have an increased risk of death, with pneumonia being the most common cause [2].

The two studies were pointed out in a highlights session by Dr Kjell-Morten Myhr (Haukeland University Hospital, Norway). Stahmann et al. investigated the time to first DMT after diagnosis in 3 large MS registry populations: NARCOMS, United Kingdom (UKMSR), and Germany (GMSR) [1]. Inclusion criteria were a relapsing disease course, diagnosis in 2014 or later, and provided data on DMT and disability status. Criteria were met by 2,506 participants (325 in NARCOMS, 453 in UKMSR, and 1,728 in GMSR). Of those patients, 2,065 (82.4%) had started a DMT. The overall mean time to first DMT was shortest in Germany, followed by the UK, and NARCOMS (P<0.001). Only 6.5% of NARCOMS participants had not received a DMT 4.5 years after diagnosis, which was significantly less than in Germany (16.4%), and the UK (>29%). Time to first DMT was shortest

for mild disability levels in Germany, moderate levels in the UK, and severe levels in NARCOMS.

A UK study matched 4,029 MS patients diagnosed from 2001-2015 with 39,874 non-MS patients. Incidence rates (IRs) and incidence rate ratios (IRRs) were calculated, and cumulative incidence curves for all cause and cause-specific mortality after cohort entry generated [2]. During a median follow-up of 12.7 years, 369 MS patients and 1,653 non-MS patients died, at a mean age of 63 and 68 years, respectively. IRs of all-cause death were twice as high in MS patients (P<0.0001). While IRs were higher among older patients, IRRs were higher among younger patients. Pneumonia was the most common cause of death for MS patients and was nearly 5 times more common than non-MS patients. Cardiovascular death was slightly elevated among MS patients; death of cancer was not elevated.

1. Stahmann A, et al. EAN 2019, EPR3078.
2. Persson R, et al. EAN 2019, O1206.

Prognostic blood and MRI biomarkers

In a Norwegian study, serum vitamin D levels were found to predict the long-term disease course of MS. Higher 25-hydroxy-vitamin D (25-OH-D) levels were associated with lower long-term disability in MS [1]. Neurofilament light chain (NfL) was found to correlate with cognitive impairment [2], while patients at higher risk of secondary progressive MS had more severe early brain atrophy [3].

Over a period of 2 years, serum levels of 25-OH-D were measured 9 times in 88 relapsing-remitting MS patients included in a randomised trial of omega 3 fatty acids (the OFAMS study). In 92% of participants, the expanded disability status scale (EDSS) could be assessed 10 years later [1]. The overall mean 25-OH-D levels in the baseline period was 74.0. The median EDSS score increased from 2.0 at baseline to 2.5 at follow-up. Higher 25-OH-D were associated with significantly lower disability progression 10 years later. Change in EDSS score per 20-unit increase in 25-OH-D was -0.5 (P=0.01).

CSF as well as blood NfL holds promise as a biomarker of disease course and treatment response in relapsing-remitting MS. The predictive value of NfL levels for cognitive impairment in patients with secondary progressive MS has now also been explored [2]. In consented participants of the EXPAND trial of siponimod, high baseline NfL levels were associated with an elevated risk for cognitive worsening, regardless of focal lesion activity. Patients with Gd+ T1 lesions at baseline had a more pronounced risk of cognitive worsening. A previous finding in the EXPAND study was that high NfL levels at baseline correlated with low baseline Symbol Digit Modalities Test (SDMT) scores. In 1,397 patients, high baseline NfL levels were associated with a 41.4% higher risk of reaching a 6-month confirmed worsening on SDMT (6mCWSDMT) by 4-points from baseline, compared to patients with low NfL levels. This higher risk was especially pronounced in patients with Gd+ T1 lesions at baseline (n=296/1,397; see Table).

Table: Risk of reaching 6-month confirmed worsening on Symbol Digit Modalities Test [2]

	High NfL (≥30 pg/mL) versus low NfL (<30 pg/mL)	
	Hazard ratio (95% CI)	P-value
All patients	1.41 (1.09; 1.84)	0.0103
Patients with Gd+ T1 lesions	2.35 (1.09; 5.06)	0.0289
Patients without Gd+ T1 lesions	1.34 (0.99; 1.83)	0.061

CI confidence interval; Gd+, gadolinium-enhancing; NfL, neurofilament light chain

A study assessing long-term predictors of global cortical thinning found that patients with more severe early cortical pathology and demonstrating a faster rate of cortical thinning are at higher risk of converting to secondary progressive MS [3]. A total of 219 relapsing-remitting MS patients were followed for 7.9 mean years; 59 (27%) patients converted to secondary progressive MS. In a multivariate model, more severe global cortical thinning loss over time was independently predicted by:

- larger accumulation of cortical lesions (OR=3.47; P=0.01);
- faster cortical thinning during the first 2 years (OR=1.43; P=0.001);
- ≥3 early relapses (OR=8.41; P<0.001).

The authors concluded that early focal cortical damage and early relapses affect the severity of grey matter loss in the long term, and can be used to identify groups potentially benefiting from early aggressive treatment.

1. Wesnes K, et al. EAN 2019, EPO3216.
2. Kuhle J, et al. EAN 2019, EPO2201.
3. Scalfari A, et al. EAN 2019, EPR2085.

Long-term effects of established treatments

Within the large armamentarium of MS treatments, it remains important to investigate long-term safety and efficacy of established options.

Alemtuzumab

In the 2-year CARE-MS I trial, alemtuzumab improved clinical and MRI outcomes vs IFN-beta-1a in treatment-naïve relapsing-remitting MS patients. Safety remained consistent and manageable through year 8 in 2 consecutive extensions (TOPAZ). Efficacy was also maintained through year 8, with over half of patients (56%) receiving no additional treatment in the extension [1].

Six-year alemtuzumab efficacy and safety was reported in patients who were treated with IFN-beta-1a in CARE-MS I and switched to open-label alemtuzumab after two years [2]. This group showed improved efficacy outcomes, with a consistent safety profile. These improvements were maintained through year 6, with 67% receiving no additional treatment.

Cladribine

A post-hoc analysis was presented of efficacy and sustainability in patients with high disease activity who received cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) in the CLARITY study and placebo in the CLARITY extension study [3]. Clinical effect of cladribine was sustained in this subgroup of 98 patients. The annualised relapse rate (ARR) for qualifying relapses was 0.15. This was equal to or similar to the ARRs for all patients, independent of high disease activity status. Confirmed EDSS progression in the high disease activity subgroups was lower in the CLARITY extension study than in CLARITY.

Another poster analysed the rate and severity of relapse in CLARITY, with hospitalisation and steroid use as proxy indicators [4]. Relapse frequencies at week 96 in the CLARITY extension study were similar to those in CLARITY, and were notably lower than for the subgroup who switched to placebo in the extension study. Therefore, the efficacy of cladribine tablets demonstrated in CLARITY was sustained for each relapse type vs placebo in the CLARITY extension study without further treatment.

Teriflunomide

Teriflunomide's effect on percentage of diffuse grey matter volume change (%GMVC) was found to be independent of its previously established effects on focal lesions and relapses among patients with a first clinical episode of MS shown in the phase 3 TOPIC study [5]. In the adjusted model, mean %GMVC after 2 years was −1.91% in the placebo (n=66) versus −1.10% in the 14 mg teriflunomide (n=87) groups (estimated treatment effect 0.80%; P=0.06). The estimated treatment effect of teriflunomide on %GMVC, independent of effects on lesions and relapses, was 100%.

Natalizumab

The effect of long-term natalizumab treatment on metabolite biomarkers of neuronal and membrane integrity in lesional white matter (LWM) was assessed in relapsing-remitting MS patients [6]. At T0, myo-inositol ratios were significantly increased in LWM of natalizumab (n=8; P=0.019) and IFN/glatiramer acetate (n=10; P=0.022) patients compared with normal-appearing white matter of healthy controls (n=7). Over 48 months, myo-inositol ratios decreased significantly in the LWM in natalizumab vs IFN/glatiramer acetate patients (median change: -32%, P=0.033 vs -9%, P=0.084). The reduction in myo-inositol ratios in LWM of natalizumab-treated patients could reflect a decrease in gliotic activity, which may be related to natalizumab's association with preservation of brain tissue integrity.

1. Comi G, et al. EAN 2019, O1202.
2. Montalban X, et al. EAN 2019, EPO2221.
3. Vermersch P, et al. EAN 2019, EPO3211.
4. Schippling S, et al. EAN 2019, EPO3196.
5. Sprenger T, et al. EAN 2019, EPO3205.
6. Schoonheim M, et al. EAN 2019, EPO3197.

Randomised and observational studies comparing treatments

In two randomised phase 3 studies, SUNBEAM and RADIANCE, ozanimod reduced whole brain volume loss (BVL), cortical grey matter volume, and thalamic volume in relapsing MS patients compared with IFN-beta-1a [1]. In two other studies comparing MS treatments, there was no difference in long term efficacy of IFN and azathioprine [2], while in another study resting state functional connectivity was significantly increased in both fingolimod- and natalizumab-treated relapsing-remitting MS patients [3].

In the SUNBEAM and RADIANCE studies, participants received oral ozanimod hydrochloride 1 or 0.5 mg/day or intramuscular IFN beta-1a 30 µg a week for ≥12 months (SUNBEAM; n=1,346) or 24 months (RADIANCE; n=1,313).

The effects on whole BVL were presented by Prof. Giancarlo Comi (Vita-Salute San Raffaele University, Italy) [1]. After 12 months in SUNBEAM, whole BVL was -0.61, -0.49, and -0.41 in the IFN-beta-1a, ozanimod 0.5 mg, and ozanimod 1 mg group, respectively (nominal P-values for ozanimod 0.5 mg and 1 mg: P=0.0092 and P<0.0001, respectively). After 24 months in RADIANCE, whole BVL was -0.94, -0.71, and -0.71 in the 3 respective groups (nominal P-values for ozanimod 0.5 mg and 1 mg: P=0.0002 and P<0.0001, respectively). Both ozanimod doses also reduced two prespecified exploratory endpoints vs IFN: cortical grey matter volume loss and thalamic volume loss.

In a single-centre study, long-term efficacy of IFN (n=562) and azathioprine (n=373) in relapsing-remitting MS was retrospectively compared [2]. At 10 year follow up, 50% of patients were free of any disability worsening and 25% were relapse-free, with no differences between IFN and azathioprine. Safety was also similar, but higher adherence in the azathioprine group suggests better tolerability of azathioprine.

In another study, longitudinal changes of resting state functional connectivity were evaluated in 50 relapsing-remitting MS patients treated with fingolimod (n=23) or natalizumab (n=27) over a period of 2 years [3]. Significant reduction of disease activity, stability of the EDSS score, and improvement of cognitive performance were found in both groups. Resting state functional connectivity significantly increased in the main large-scale functional networks in fingolimod- and natalizumab-treated groups, possibly reflecting a recovery from disease activity before treatment start and subsequent disease stability.

Two anti-CD20 monoclonal antibodies, one chimeric (rituximab; n=53) and one humanised (ocrelizumab; n=38) were compared [4]. B cell levels in the peripheral blood were equally decreased. However, CD4+ and CD8+ lymphocyte reduction was more pronounced in the ocrelizumab group. Patients treated with ocrelizumab presented with 10.6% more reduced overall lymphocyte count (P=0.030) and 8% more increased of CD4/CD8 ratio (P=0.042) after 1 month. After 3 months, patients treated with ocrelizumab presented with 15.2% more reduction of CD4+ lymphocytes (p=0.034).

1. Arnold D, et al. EAN 2019, O1201.
2. Mecchi C, et al. EAN 2019, O4110.
3. Rocca MA, et al. EAN 2019, O4112.
4. Nozzolillo A, et al. EAN 2019, EPO2227

Experimental MS treatments

Research continues on possible treatments to add to the existing spectrum. Safety and efficacy are still being established.

Biotin

Long-term safety data of MD1003 (high dose pharmaceutical grade biotin) in the MS-SPI trial were presented [1]. Results from the open-label extension phase (OLE; month 12-48) indicated that biotin was well-tolerated, with no new safety signals. Among the 133 patients who entered the extension phase, 49% were still receiving treatment after 48 months. The main reasons for treatment withdrawal in the extension phase were lack of efficacy and withdrawal of consent. Adverse events (AEs) were experienced by 78% vs. 88% of patients in the treatment and placebo groups, respectively. Serious AEs were experienced by 35% vs 36% of patients. Progressive MS relapse rate did not appear to be influenced by MD1003.

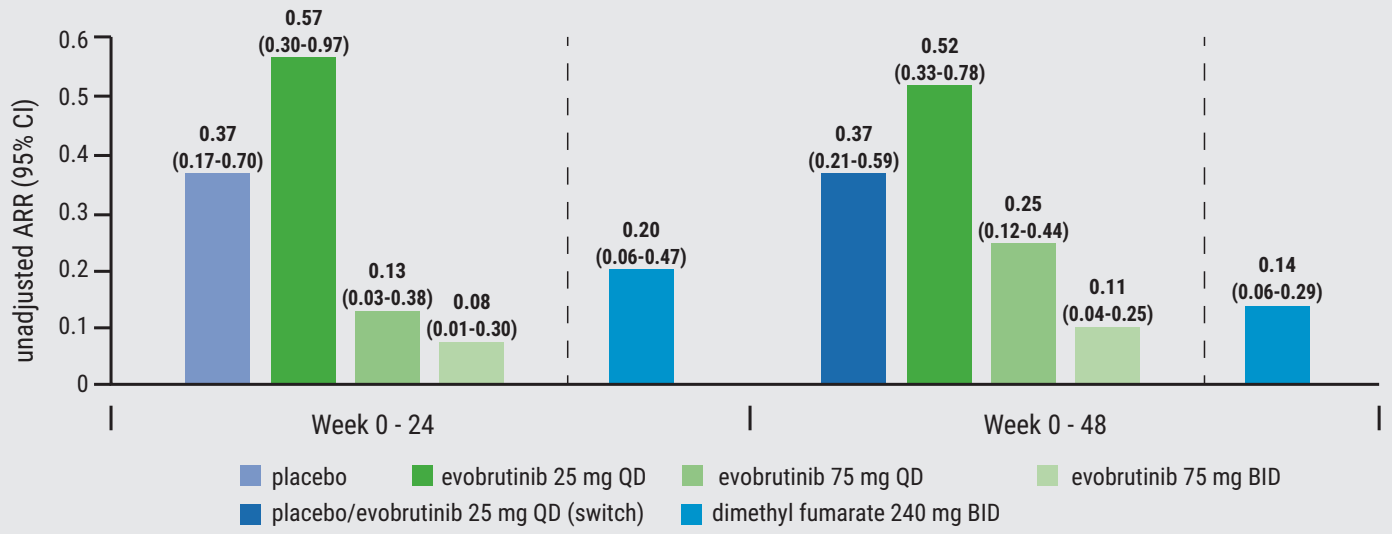
Evobrutinib

Evobrutinib (M2951) is the first inhibitor of Bruton's tyrosine kinase (BTK) that demonstrated reduction of disease activity in relapsing MS [2]. In the presented trial, participants were randomised to evobrutinib 25 mg once-daily (QD), 75 mg QD, 75 mg twice-daily (BID), open-label dimethyl fumarate (240 mg BID; reference arm), or placebo for 48 weeks. Placebo-treated patients transitioned to evobrutinib 25 mg QD after 24 weeks. Among 261 patients, the number of Gd+ T1-lesions were significantly reduced with evobrutinib 75 mg QD (P=0.002) and 75 mg BID (P=0.03) vs placebo in weeks 12–24. Annualised relapse rate (ARR) decreased over 24 weeks at both evobrutinib doses. ARR over 48 weeks was 0.25 and 0.11 for evobrutinib 75 mg QD and 75 mg BID, respectively (see Figure, page 14). The sum of new or enlarging T2 lesions in weeks 12–24 was reduced in the evobrutinib 75 mg BID group vs placebo (P=0.02). Evobrutinib was well-tolerated; the most common treatment-emergent AEs were nasopharyngitis and reversible, asymptomatic liver enzyme elevations.

Ublituximab

The novel monoclonal antibody ublituximab targets a unique epitope on the CD20 antigen and is glyco-engineered for enhanced B cell depletion through antibody-dependent cellular cytotoxicity (ADCC). In the OLE of the phase 2 trial TG1101-RMS201, 1-hour infusions of ublituximab continued to be safe and well-tolerated in relapsing MS patients [3]. The

Figure: Annualised relapse rate at weeks 24 and 48 (modified intention-to-treat population) [2]



ARR, annualised relapse rate; BID, twice daily; CI, confidence interval; QD, once daily; SD, standard deviation

45 OLE participants received 450 mg ublituximab infusions every 24 weeks for 96 weeks. B cells were efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab. A median B cell depletion of >99% was observed at week 4, and maintained at week 24 and 48. At week 48, ARR was 0.07, with 93% of subjects being relapse-free and 74% fulfilling NEDA criteria. Not a single Gd-enhancing T1 lesion was detected at week 24 or 48 (P=0.003). AEs possibly related to ublituximab were infrequent during the extension phase. Infusion related reactions (all grade 1 or 2) occurred in 4 patients (9%).

1. De Seze J, et al. EAN 2019, EPO3200.
2. Montalban X, et al. EAN 2019, O1205.
3. Fox E, et al. EAN 2019, O4107

Generalised EBV vaccine for progressive MS well-tolerated

ATA188 is a pre-manufactured, unrelated donor Epstein-Barr virus (EBV)-targeted T cell immuno-therapy for progressive MS. In a phase 1 study, ATA188 was well-tolerated by adults with progressive MS [1].

Previously, the same group had shown that treatment with an autologous EBV-targeted T cell immunotherapy may prevent progression in MS patients; 6 of 10 treated patients experienced both symptomatic and objective neurological improvement [2]. The study presented at the EAN evaluated safety and feasibility of monotherapy with ATA188 in EBV-seropositive adults with primary and secondary progressive MS. In this multicentre, open-label, single-arm, two-population, dose-escalation study, 4 dose cohorts, received $5.0x10^6$, $1.0x10^7$, $2.0x10^7$, and $4.0x10^7$ cells, respectively, on days 1, 8, and 15 in two cycles.

Preliminary results of 6 participants in cohort 1 and 6 participants in cohort 2 who had received ≥1 dose were presented. Both doses were well-tolerated, with no dose-limiting toxicities. In 7 of 12 (58%) participants treatment-emergent adverse events were seen: 4 of 6 in cohort 1 and 3 of 6 in cohort 2; all were grade 1 (17%) or grade 2 (42%). Rhinorrhoea, falls, contusion, and headache (n=2) were most common. In cohort 1, there were 3 participants who had upper respiratory infection symptoms, with 2 developing symptoms 2-5 months after treatment. Plasma inflammatory biomarkers (IL-2, IL-1β, TNF-α, IL-6) remained at or near baseline throughout treatment.

1. Pender M, et al. EAN 2019, EPO2229.
2. Pender M, et al. JCI Insight. 2018;3(22).

Autologous hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation (aHSCT) is a promising treatment for aggressive refractory relapsing-remitting MS, as was illustrated

in a workshop; it may however be effective in the progressive phase as well. Stabilisation of disability progression was observed in 75% of the patients and normalisation of brain atrophy in 35%, respectively [1].

A focused workshop was dedicated to aHSCT in relapsing-remitting MS. A meta-analysis of HSCT-studies from 1995 to 2016 showed that transplant-related mortality had dropped substantially over 20 years [2]. Patients with aggressive RRMS who have not yet accumulated a high level of disability, had the most favourable benefit-risk profile for this treatment. The pooled proportion of patients with NEDA was 67% after 5 years and almost 50% after 10 years.
At the same workshop results from the phase 3 MIST trial were presented. In this randomised trial, nonmyeloablative HSCT treatment was compared to standard disease-modifying therapy (DMT) [3]. Patients had had at least 2 relapses while receiving DMT in the prior year, and an EDSS score of 2.0 to 6.0. HSCT resulted in prolonged time to disease progression compared to DMT; 78.5% of patients in the HSCT group were without signs of disease activity at 5 years of follow-up.

A study presented by Dr Alice Mariottini (Careggi University Hospital, Italy), included 20 patients with a median age at aHSCT of 37 years, median disease duration of 11.5 years, and median EDSS of 6.0; 15 were females. EDSS worsened in 14 patients (70%) at year 5 of follow-up. Also, persistent interruption of disability progression following a single-step EDSS deterioration was seen in 9/14 patients. The progressive course of disability was not altered in the remaining 5/14 patients. The only baseline feature correlating with clinical outcome was annualised brain volume change. In patients who progressed, annualised brain volume change was non-significantly higher (with a median of -0.45) compared to those who showed EDSS stabilisation (median -0.14).
The authors speculate that the absence of a correlation between brain volume change and disability suggests a possible major role of spinal cord involvement in disability progression. They also conclude that interruption of disability progression could be a good outcome measure of treatment efficacy in progressive MS.

1. Mariottini A, et al. EAN 2019, O4109.
2. Sormani RP, et al. Neurology. 2017;88(22):2115-22.
3. Burt RK, et al. JAMA. 2019;321(2):165-74.

Promising results of novel NMOSD treatments

There are as yet no registered treatments for neuromyelitis optica spectrum disorders (NMOSD), but that will change soon. Three monoclonal antibodies -inebilizumab, satralizumab, and eculizumab- submitted promising safety and efficacy results in terms of relapse prevention in the past year. At the EAN 2019, efficacy and safety results of inebilizumab and satralizumab were presented [1,2].

Inebilizumab, an anti-CD19 monoclonal antibody, reduced attacks, disability progression, hospitalisations, and new lesions in NMOSD compared with placebo in the randomised controlled period of the N-MOmentum pivotal study [1]. The drug was well-tolerated, with adverse event (AE) rates similar to placebo. A total of 230 patients were randomised to inebilizumab (n=174) or placebo (n=56) monotherapy for 6.5 months. Of those, 91% were aquaporin 4-IgG seropositive (AQP4-IgG+). Study recruitment was stopped early because of clear evidence of efficacy. Inebilizumab reduced the risk of attacks by 72.8% (P<0.001). This percentage was even higher in the AQP4-IgG+ population: 77.3% (P<0.001). During the randomised controlled period, 87.9% of participants did not have a single attack. The most common AEs included urinary tract infections and infusion-related reactions, without any difference between groups.

Additional analyses of the SAkuraSky study revealed that satralizumab, an IL-6R inhibitor, significantly reduced relapse risk, especially in AQP4-IgG+ patients [2]. The 83 participating NMOSD patients had been randomly assigned to receive satralizumab 120 mg or placebo at week 0, 2, and 4 and every 4 weeks thereafter, added to stable immunosuppressant treatment. Satralizumab significantly reduced risk of protocol-defined relapse by 62% vs placebo (P=0.0184). Relapse risk was reduced by 79% with satralizumab in AQP4-IgG+patients (n=55). The proportion of relapse-free patients at weeks 48 and 96 were 91.5% and 91.5% with satralizumab, and 59.9% and 53.3% with placebo, respectively. In AQP4-IgG- patients, relapse risk was reduced by 34% vs placebo. In the overall study population, annualised relapse risk was 0.11 in the satralizumab group and 0.32 in the placebo group.

1. Cree B, et al. EAN 2019, O4122.
2. Yamamura T, et al. EAN 2019, O4113.

Neuromuscular Disorders

AVXS-101 and nusinersen for spinal muscular atrophy type 1

For spinal muscular atrophy (SMA), nusinersen is currently the only registered therapy. Another very promising therapy in late-stage development is onasemnogene abeparvovec (AVXS-101) gene-replacement therapy.

AVXS-101 for non-ambulatory patients with SMA was feasible, well tolerated, and might improve motor functions, as concluded from interim data analysis of the phase 1/2a STRONG study [1]. In this open-label study, SMA patients of ≥6 to <60 months of age who could not stand or walk, received one of 3 doses intrathecal AVXS-101 (dose A: $6.0x10^{13}$; B: $1.2x10^{14}$; C: $2.4x10^{14}$ vector genomes [vg]). As of 24 March 2019, 31 patients from 11 sites were enrolled. All participants experienced treatment-emergent adverse events (AEs) but none were fatal. In 4 patients, 7 serious treatment-emergent AEs occurred, which were all resolved. Patients aged ≥24 to <60 months showed rapid improvement on the Hammersmith Functional Motor Scale Expanded (HFMSE). Half of the patients had at least a 3-point increase from baseline 1 month after treatment. Patients aged ≥6 to <24 and ≥24 to <60 months averaged a 4.2-point increase from baseline HFMSE score at last follow-up. Ten patients achieved 22 additional motor milestones.

In a post-hoc analysis of two trials, AVXS-101 was compared to nusinersen in the treatment of SMA type 1. The results showed that AVXS-101 led to improved survival and motor function, lower use of pulmonary support, as well as decreased hospitalisation and associated direct medical costs. The analysed trials were CL-101 (cohort 2, n=12) and ENDEAR (n=80). In CL-101, patients were treated with AVXS-101 at a dose of 2.0 X 10^{14} vg/kg; in ENDEAR, patients were treated with nusinersen [2]. In nusinersen-treated patients, 66% were alive without permanent ventilation, in AVXS-101-treated patients this occurred in 100%. In the nusinersen cohort, 19% required permanent assisted ventilation, in the AVXS-101 cohort 0%. In nusinersen-treated patients, 8% sat independently and 1% stood; in AVXS-101-treated patients 92% sat unassisted, 17% stood with assistance, and 17% walked independently. The mean unadjusted annualised rate of hospitalisations was 4.5 and 2.1 for nusinersen- and AVXS-101-treated patients, respectively.

In a case series (CS2/CS12), 5 teenagers who were treated with nusinersen demonstrated stable or improved outcomes in terms of motor function and health-related quality of life measures [3]. The participants (SMA type 2, n=1; type 3, n=4) were 14 or 15 years at treatment initiation in CS2 (phase 1b/2a). They received intrathecal nusinersen 12 mg in the open-label extension CS12. At the last visit (day 715) they were 17 or 19 years old and had transitioned to the long-term extension SHINE study. At CS2 baseline, 3 participants were ambulatory. The participants with SMA type 2 achieved improvement on the HFMSE to CS12 day 715. In the other 4 participants, HFMSE scores remained stable or improved slightly. 6-minute walking test distance increased from CS2 baseline to day 715 in 2 participants; another walked independently for short distances without support in CS2, and walked unaided during CS12 visits (23–74 m).

1. https://clinicaltrials.gov/ct2/show/NCT03381729
2. Arjunji R, et al. EAN 2019, EPR1049.
3. Deconinck N, et al. EAN 2019, EPR1055.

Ataluren in nonsense mutation Duchenne

Adding ataluren to standard of care slowed disease progression in Duchenne muscular dystrophy patients with nonsense mutation (nmDMD) [1].

This comparison could be made by using data from Strategic Targeting of Registries and International Database of Excellence (STRIDE; n=187) and from the Cooperative International Neuromuscular Research Group (CINRG; n=187) Natural History Study. STRIDE is an observational registry providing data on use of ataluren in nmDMD patients in routine clinical practice. Patients from CINRG, receiving only standard of care, served as controls.

Mean age at first symptom onset in the STRIDE and CINRG cohort was 2.7 and 2.9 years, respectively. In both cohorts, the majority of patients received corticosteroids for ≥12 months (56.7% vs 55.1%). In STRIDE, 36 patients (19.3%) lost ambulation compared to 109 (59.2%) in CINRG. This occurred at a later median age in STRIDE: 14.5 versus

11.0 years. Ataluren plus standard of care was found to delay age of ambulation loss compared to standard of care alone (P<0.0001).

1. Muntoni F, et al. EAN 2019, O4120.

Motor nerve biopsy for early diagnosis of lower motor neuron syndromes

In a retrospective evaluation of 90 indicated patients, the diagnostic performance of motor nerve biopsy in lower motor neuron syndromes (LMNS) was informative [1]. Motor nerve biopsy was conclusive in 76.4% of cases and correctly classified 95.4% of pathologic biopsies as ALS or MN.

Of 90 patients, 49 were classified as MND (57%), 17 as MN (19.8%), 20 as non-diagnostic (23.2%), and 4 as technically non-evaluable (4.4%). At follow-up, the pathological diagnosis showed a sensitivity and specificity of 78% and 88.9% for ALS, and 85% and 100% for MN, respectively. The outcomes were also used to retrospectively validate the new-revised El Escorial Criteria (NR-EEC) in ALS and ALS-mimics. Compared to the older version of these criteria, NR-EEC showed a significant increase in sensitivity: 45,9% versus 11%. The degree of axonal degeneration was associated with shortened survival in ALS. TAR DNA-binding protein-43 (TDP-43)-immunoreactivity in motor nerves correlated with the risk of developing ALS and could be a potential new biomarker for ALS.

1. Riva N, et al. EAN 2019, O4121.

Parkinson's Disease and other Movement Disorders

Inflammation may change the course of Parkinson's disease

Inflammation may start early in Parkinson's disease (PD), long before motor symptoms occur, according to Prof. Vidar Gundersen (University of Oslo, Norway) in a plenary talk about the central theme of EAN 2019: "Neuroinflammation" [1].

In PD, microglia are activated and are present in dopamine neurons long before the accumulation of α-synuclein pathology. This implies that microglial activation probably contributes to the development of α-synuclein pathology [2]. Early activation of microglia has also been demonstrated in translocator protein (TSPO) PET imaging [3]. Both pro- and anti-inflammatory cytokines are activated, such as TNF and IL-1-beta. The pro-inflammatory cytokine IFN-gamma is also involved in inflammatory-induced neurodegeneration in PD [4].

Prof. Gundersen went on to explain how inflammation may contribute to dopamine neurodegeneration. He suggested that the adaptive immune system is involved in PD pathology and that PD might even be an auto-immune disease. When in the disease process naïve T cells prime is unclear. "If microglia are activated and present α-synuclein to T cells prior to neuronal death", he postulated, "then MS drugs might be effective against PD".

Prof. Gundersen also touched upon the gut hypothesis. In this 'gut to brain' scenario, PD pathology may start in the gastrointestinal tract and then spread through the vagus nerve to the brain. α-synuclein has been found to be located in gut neurons before the start of motor symptoms in PD, not in controls [5]. However, other observations contradict this concept. "The only way to find out is a proper interventional study", said Prof. Gundersen. An attempt was recently made in a placebo-controlled trial of the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide [6]. This intervention had positive effects on off-medication motor scores in PD, which were sustained beyond the exposure period. However, whether exenatide affects the underlying disease pathophysiology or only induces long-lasting symptomatic effects, is uncertain. Prof. Gundersen said larger, longer-duration studies are needed which include patients with prodromal PD. His overall conclusion was: "Inflammation matters: it may change the course of PD".

1. Gundersen V. EAN 2019, PLEN03_2.
2. Olanow CW, et al. Brain. 2019;142(6):1690-1700.
3. Iannacone S, et al. Parkinsonism Relat Disord. 2013;19(1):47-52.
4. Mangano EN, et al. Neurobiol Aging. 2012;33(7):1411-26.
5. Shannon KM, et al. Mov Disord. 2012;27(6):709-15.
6. Athauda D, et al. Lancet. 2017;390(10103):1664-75.

No disease-modifying effect of levodopa/carbidopa in Parkinson's

Determining disease-modifying qualities of levodopa could result in a rationale for initiating treatment earlier in the course of PD. In a double-blind, placebo-controlled, delayed-start trial, treatment with levodopa/carbidopa had no disease-modifying effect over the course of 80 weeks in patients with early PD [1,2]. In patients without overt disability in daily activities, early start with levodopa improved disease-related quality of life.

These were the results of a Dutch multicentre study designed to see if levodopa/carbidopa can slow disease progression in the early phase of the disease. A total of 445 patients with early PD were randomised to levodopa/carbidopa 100/25 mg three times a day for 80 weeks (early-start group), or placebo for 40 weeks followed by levodopa/carbidopa for 40 weeks (delayed-start group). The primary outcome was the mean change in the total score on the Unified Parkinson's Disease Rating Scale (UPDRS) at week 80. This change was −1.0 and −2.0 points in the early- and delayed-start group, respectively (P=0.44). This non-significant difference led the authors to conclude that levodopa has no disease-modifying effect, either beneficial or detrimental. In the early-start group, the disease-related quality of life (PDQ-39) score showed a clinically relevant improvement in the first 40 weeks. There was no significant difference in rates of dyskinesia and levodopa-related fluctuations in motor response.

Whether higher doses of the drug, longer periods of administration, or initiation of the drug at later stages of the disease could alter the disease course, warrants evaluation in future trials, the authors said.

1. De Bie R, et al. EAN 2019, O3224.
2. Verschuur CVM, et al. N Engl J Med. 2019;380(4):315-24.

Novel solution of levodopa/carbidopa prodrugs via CSCI

ABBV-951 is a novel solution of levodopa and carbidopa prodrugs delivered via minimally invasive continuous subcutaneous infusion (CSCI). It was safe, generally well-tolerated, and did not cause notable skin reactions at low -yet clinically relevant- doses administered in a confined area of the abdomen continuously for 10 consecutive days [1].

A dose of ABBV-951 equivalent to ~600 mg of levodopa and an equal volume of saline were administered in two demarcated areas, 5 cm in diameter, on opposite sides of the abdomen of 34 healthy volunteers. Infusion sets were changed and reapplied daily on the same skin surface. There were no notable skin reactions in the ABBV-951 site, and only one in the placebo site. There was no significant difference between ABBV-951 and placebo in outcomes of dermatological assessment via the Infusion Site Evaluation scales (P=0.820; P=0.363). The most frequently reported adverse events were infusion site erythema (92%); infusion site reaction (44%); and infusion site pain (32%). All events were mild or moderate, and resolved quickly.

The authors proposed that ABBV-951 has the potential to provide the broad range of levodopa exposure required to adequately control motor symptoms and to be an alternative therapeutic option for PD patients. The results supported their phase 1b study of ABBV-951 delivered via CSCI in PD patients in an outpatient setting over 28 days. The primary objective will be to assess the local and systemic safety and tolerability of ABBV-951 [2]. Efficacy will also be explored.

1. Facheris M, et al. EAN 2019, EPO1200.
2. Facheris M, et al. EAN 2019, EPO1199.

Opicapone: follow-up on the BIPARK I and II trials

The peripheral catechol-O-methyltransferase (COMT) inhibitor opicapone proved effective in the treatment of motor fluctuations in PD patients in BIPARK-I and II [1,2].

In a post-hoc analysis of these two large, pivotal, multinational trials, opicapone was effective regardless of baseline presence of dyskinesia and of concurrent rasagiline use [3,4]. In another post-hoc analysis, opicapone was effective in reducing motor fluctuations in 'early fluctuators', resulting in a significant proportion of responders (achieving at least 1 hour of OFF-time reduction or 1 hour of ON-time increase), similar to the total study population [5].

In the 1-year extension of the BIPARK-I study, the placebo and entacapone groups switched to open-label opicapone. During this period there was no worsening of non-motor symptoms for subjects in these groups [6]. Patients who had switched from placebo presented significantly less disability. At the end of the double-blind period, total scores on the Non-Motor Symptoms Scale (NMSS) in the 199 'switchers' had decreased in all treatment groups. Mean changes from baseline were -5.7, -4.7, and -2.0 for placebo, entacapone, and opicapone 50 mg, respectively. During the 1-year extension the scores further decreased: -3.8 (P=0.041), -0.2 (P=0.899), and -0.4 (P=0.849), respectively.

1. Ferreira J, et al. Lancet Neurology 2016;15(2):154-65.
2. Lees A, et al. JAMA Neurol. 2017;74(2):197-206.
3. Fabregues O, et al. EAN 2019, EPO1198.
4. Lees A, et al. EAN 2019, EPO2174.
5. Ferreira J, et al. EAN 2019, EPR1075.
6. Lees A, et al. EAN 2019, EPO2176.

Epigallocatechin gallate does not modify MSA progression

In the placebo controlled PROMESA trial, epigallocatechin gallate (EGCG) did not modify disease progression in patients with multiple system atrophy (MSA). EGCG, found in low levels in green tea, was well-tolerated. The hepatotoxic effects observed in some patients limit dosing, however [1].

These results where shared as a late-breaking abstract at the EAN 2019 and simultaneously published [2]. First author Dr Johannes Levin (Ludwig-Maximilians-University of Munich, Germany) explained that the polyphenol EGCG inhibits α-synuclein aggregation in higher doses. A dozen specialist centres in Germany participated in the trial. In total, 92 participants were randomly assigned to oral EGCG 400 mg or matching placebo once daily for 4 weeks, then twice daily for 4 weeks, followed by three times daily for 40 weeks; 63 patients completed the study per protocol.
After 52 weeks, there was no difference in change from baseline in motor examination scores on the Unified Multiple System Atrophy Rating Scale (UMSARS), which was the primary endpoint. The UMSARS score was 5.66 and 6.60 in the EGCG and placebo group, respectively (P=0.51). An MRI analysis in 19 patients treated per protocol revealed a significant reduction of over 50% in brain atrophy rate. Two patients in the EGCG group had to stop treatment because of severe hepatotoxicity. This is why, according to Dr Levin, doses of more than 1,200 mg should be avoided.

1. Höglinger G, et al. EAN 2019, PLEN 04_6.
2. Levin J, et al. Lancet Neurol. 2019;18(8):724-35.

Stroke

Thrombo-inflammation during ischemia/reperfusion

Prof. Guido Stoll (University of Würzburg, Germany) reviewed T cell and platelet signalling pathways involved in thrombo-inflammation during ischemia/reperfusion (I/R), and also discussed clinical trials targeting acute stroke-related inflammation [1].

Ischaemic stroke elicits a strong neuroinflammatory response in the acute and chronic stage, according to Prof. Stoll. However, the functional relevance and therapeutic potential of neuroinflammation has only recently become apparent. T cells contribute to ischaemia–reperfusion injury after recanalization in an antigen-independent manner. "Surprisingly, the detrimental T cell effects are platelet-dependent. Glycoprotein (GP)Ib-mediated and GPVI-mediated platelet activation, but not GPIIb–IIIa-mediated platelet aggregation, is an important checkpoint that orchestrates thrombotic and pro-inflammatory pathways. Downstream activation of coagulation factor XII is a driving force of ischaemia–reperfusion injury in acute stroke."
The evidence therefore suggests that during ischaemia–reperfusion injury, T cells interact with platelets and facilitate further infarct development through a complex process known as thrombo-inflammation.

However, in the majority of patients with ischaemic stroke, recanalization cannot be achieved. The contribution of neuroinflammation to permanent ischaemia and subacute stroke is less clear and more complex. Immune cells

contribute to secondary infarct growth, but also to tissue remodelling. In certain settings, T cells aggravate neuronal damage late after the ischaemic insult, but stroke likewise induces a systemic immuno-depression syndrome which probably prevents stroke-induced autoimmunity to CNS antigens. Monocytes/macrophages, the main scavenger cells, in addition contribute to sealing of the damaged blood brain barrier and thereby help to maintain haemostasis in the ischaemic brain.

Targeting stroke-related neuroinflammation may become an effective adjunct therapy to improve outcome after ischaemic stroke in the future, but requires caution with regard to timing and adverse effects. A number of studies have already investigated anti-inflammatory therapies, such as the MS drugs natalizumab and fingolimod, in acute stroke. In the placebo-controlled ACTION trial, natalizumab failed to reduce infarct volume growth, but was associated with improved clinical outcomes over 90 days [2]. Much more promising, according to Prof. Stoll, is fingolimod. The open-label FAMTAIS trial assesses effectiveness and safety of fingolimod combined with bridging therapy in large vessel occlusion acute ischemic stroke patients, and will control for recanalization [3,4].

1. Stoll G. EAN 2019, PLEN03_3.
2. Elkins J, et al. Lancet Neurol. 2017;16(3):217-26.
3. Zhu Z, et al. Circulation. 2015;132(12):1104-12.
4. Zhang S, et al. Int J Stroke. 2017;12(8):906-9.

Haematoma expansion and mortality in intracerebral haemorrhage after OAC

Results of a meta-analysis show that in patients with intracerebral haemorrhage (ICH), use of vitamin K antagonists (VKA) leads to larger haematoma volume, increased rate of secondary haematoma expansion (HE), and higher mortality compared with non-vitamin K antagonist oral anticoagulants (NOACs) or not using oral anticoagulants (non-OACs) [1].

In this systematic review and meta-analysis, a total of 19 studies with data on 16,546 ICH patients using VKA and 128,561 ICH patients using non-OACs were included; moreover, 2 studies reported data on 4,943 ICH patients using NOACs.

Results showed that haematoma volume was significantly larger in VKA-users (mean difference vs non-OACs-users of +9.66 mL; P<0.001) and HE occurred significantly more often in VKA-users than in non-OACs-users (OR 2.96; 95% CI 1.74-4.97; P<0.001). The risk of in-hospital mortality (OR 1.83, 95% CI 1.61-2.07; P<0.001) and 3-months mortality (OR 2.24; 95% CI 1.52-3.31; P<0.001) was also elevated in VKA-users. There was insufficient data available for the comparison between NOACs-users and non-OACs-users, to determine if NOACs have similar effects.

1. Goeldlin M, et al. EAN 2019, O2201.