Meilensteine in der Therapie von Migräne und Kopfschmerz: 35 Jahre Kopfschmerzforschung

Prof. Dr. med. Hans-Christoph Diener
Medizinische Fakultät der Universität Duisburg-Essen
Conflict of Interest Statement

- German Research Council
- German Ministry of Education and Research
- EU
  - Böhringer-Ingelheim
  - Astra-Zeneca
  - Sanofi-Aventis
  - Pfizer
  - Bayer
  - Janssen-Cilag
  - Teva
- Novartis
- Schering
- J&J
- BMS
- Novo Nordisk
- MSD
- Lilly
- Wyeth
- Solvay
- CoLucid
- Allergan
- Addex
- MAP
- Coherex
- Menarini
- Endo Pharmac.
- GSK
- Medtronic
- Almirall
- Eisai
- Neuroscore
- St. Jude Medical
- Amgen
- Chordate
- Labrys
- Electrocore
- Weber & Weber
- Alder
- Chordate
Central Effects of Drugs Used in Migraine Prophylaxis Evaluated by Visual Evoked Potentials

First study to show central action of migraine preventive therapy

Fig 3. Arithmetic means of visual evoked potential (VEP) amplitudes after transient checkerboard stimulation at baseline (BL), high dosage (HD), and follow-up (FU) in patients that responded to beta blocking therapy (RESP), in patients that did not respond to beta blockers (NON), and in patients receiving nifedipine (NIF).

Hans-Christoph Diener, MD, Erich Scholz, MD, Johannes Dichgans, MD, Wolf-Dieter Gerber, PhD, Agnes Jäck, Artur Bille, and Uwe Niederberger

Central Effects of Drugs Used in Migraine Prophylaxis Evaluated by Visual Evoked Potentials

- Migraine is a disorder of the brain
- Beta-blockers have a central mode of action
POSSIBLE BENEFIT OF GR43175, A NOVEL 5-HT$_1$-LIKE RECEPTOR AGONIST, FOR THE ACUTE TREATMENT OF SEVERE MIGRAINE

ALFRED DOENICKE$^1$  
JOCHEN BRAND$^2$  
VAL. L. PERRIN$^3$

Department of Anaesthesics, Ludwig-Maximilians University, Munich,$^1$ Migraine clinic, Koenigstein, West Germany,$^2$ and Medical Division, Glaxo Group Research Ltd, Greenford$^3$
First into Humans
Subcutaneous Sumatriptan in the Treatment of Headache During Withdrawal From Drug-Induced Headache

- Pilot study to investigate the efficacy of sumatriptan in the worst possible migraine attack
- Investigated cerebral blood flow and ECG

This experiment was almost the end of sumatriptan

H.C. Diener, J. Haab, C. Peters, S. Ried, J. Dichgans and A. Pilgrim  
(Headache 31:205-209, 1991)
Subcutaneous Sumatriptan in the Treatment of Headache During Withdrawal From Drug-Induced Headache

- One patient showed ST-elevation on ECG 5 minutes after the injection of sumatriptan
- Patient had not disclosed that she had a severe overuse of ergots

Can you imagine the consequences if the patient had died?

H.C. Diener, J. Haab, C. Peters, S. Ried, J. Dichgans and A. Pilgrim
My Major Failures

War of the Triptans

- Sumatriptan
- Zolmitriptan
- Naratriptan
- Rizatriptan
- Eletriptan
- Almotriptan
- Frovatriptan

Avitriptan (Hepatonecrotiuptan) and Alniditan
Expectations promoted by industry

- The triptans are the solution for migraine as a disease
- No more need for ASS
- No more need for migraine prevention
- Triptans are safe
- Triptans have only minor adverse events
The Triptan Era

- Industry helped to make the disease „migraine“ aware for patients, physicians and health care providers
- Industry supported the education of young physicians in headache
- Industry supported major headache meetings
• 7 migraine patients overused sumatriptan and developed medication overuse headache

• All patients had a prior history of MOH

• Time to MOH was about 9 months

BMJ 1994; 308 doi: http://dx.doi.org/10.1136/bmj.308.6943.1573d (Published 11 June 1994) Cite this as: BMJ 1994;308:1573

H Kaube, A May, H C Diener, V Pfafferath
Headache after frequent use of serotonin agonists Zolmitriptan and Naratriptan

<table>
<thead>
<tr>
<th>Patient, age, sex</th>
<th>Primary headache since</th>
<th>Prior treatment with ergot-derivatives</th>
<th>Prior treatment with triptans</th>
<th>Triptan since (month), last dosage in previous 3 month</th>
<th>Chronic daily headache, type</th>
<th>Increase in attack frequency (initial/final)</th>
<th>Comments</th>
<th>Effects of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD, 51, f</td>
<td>M, 20 y</td>
<td>No</td>
<td>No</td>
<td>10 m, 12×2.5 mg monthly</td>
<td>No</td>
<td>2 to 6 monthly</td>
<td>Increase in frequency under monotherapy with zolmitriptan</td>
<td>Significant reduction in frequency</td>
</tr>
<tr>
<td>KR, 44, f</td>
<td>M, 24 y</td>
<td>Yes</td>
<td>No</td>
<td>12 m, 24×2.5 mg monthly</td>
<td>Yes, daily migraine-like</td>
<td>Initially yes</td>
<td>Complete relief of daily headache</td>
<td></td>
</tr>
<tr>
<td>BM, 46, f</td>
<td>M, 20 y</td>
<td>Yes</td>
<td>sumatriptan</td>
<td>12 m, 12×2.5 mg monthly</td>
<td>Yes, daily TTH-like</td>
<td>2 to 8 monthly</td>
<td>Complete relief of daily headache</td>
<td></td>
</tr>
<tr>
<td>MoM, 44, f</td>
<td>M, 6 y TTH 20 y</td>
<td>No</td>
<td>Yes, sumatriptan</td>
<td>12 m, 10×2.5 mg monthly</td>
<td>Daily TTH-like</td>
<td></td>
<td>Complete relief of daily headache</td>
<td></td>
</tr>
<tr>
<td>WA, 63, f</td>
<td>M, 40 y</td>
<td>Yes</td>
<td>No</td>
<td>12 m, 30×2.5 mg monthly</td>
<td>Yes, daily migraine-like</td>
<td></td>
<td>Complete relief of daily headache</td>
<td></td>
</tr>
<tr>
<td>YG, 20, f</td>
<td>M, Ma, 17 y</td>
<td>No</td>
<td>No</td>
<td>12 m, 20×2.5 mg monthly</td>
<td>Yes, daily TTH-like</td>
<td></td>
<td>Complete relief of daily headache</td>
<td></td>
</tr>
<tr>
<td>BA, 50, f</td>
<td>M, 10 y</td>
<td>Yes</td>
<td>sumatriptan</td>
<td>8 m, 12×2.5 mg monthly</td>
<td>No</td>
<td>2 to 8 monthly</td>
<td>Increase in frequency under monotherapy with zolmitriptan</td>
<td>Significant reduction in frequency</td>
</tr>
<tr>
<td>MM, 43, f</td>
<td>M, 23 y</td>
<td>No</td>
<td>No</td>
<td>18 m, 18×2.5 mg monthly</td>
<td>Yes, daily migraine-like</td>
<td>Initially yes</td>
<td>Complete relief of daily headache</td>
<td></td>
</tr>
<tr>
<td>DP, 25, f</td>
<td>M, 10 y</td>
<td>No</td>
<td>No</td>
<td>12 m, 12×2.5 mg monthly</td>
<td>No</td>
<td>3 to 10 monthly</td>
<td>Increase in frequency under monotherapy with zolmitriptan</td>
<td>Significant reduction in frequency</td>
</tr>
<tr>
<td>SA, 42, f</td>
<td>M, 22 y</td>
<td>No</td>
<td>No</td>
<td>6 m, 15×2.5 mg monthly</td>
<td>No</td>
<td>5 to 15 monthly</td>
<td>Increase in frequency under monotherapy with naratriptan</td>
<td>Still to be determined</td>
</tr>
<tr>
<td>KM, 48, f</td>
<td>M, 19 y</td>
<td>Yes</td>
<td>sumatriptan</td>
<td>5 m, 20×2.5 mg monthly</td>
<td>Yes, daily TTH-like</td>
<td>2 to 12 monthly</td>
<td>Increase in frequency under various substances (NSAID, ergots, sumatriptan), under monotherapy with naratriptan worsen and increase in migraine attacks</td>
<td>Complete relief of daily headache, significant reduction in frequency</td>
</tr>
</tbody>
</table>

Naratriptan and Zolmitriptan can also cause MOH

Volker Limmroth, Zaza Kazarawa, Günther Fritsche, Hans-Christoph Diener

THE LANCET • Vol 353 • January 30, 1999
My Major Achievements

- The headache community became aware that the intake of triptans per month has to be restricted to 10 days
Alniditan in the acute treatment of migraine attacks: A subcutaneous dose-finding study

<table>
<thead>
<tr>
<th>Table 2. Effect of alniditan on several efficacy parameters and significance of difference with placebo. For each parameter the number of patients and percentage are presented.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
</tr>
<tr>
<td>Responders(^1) at 1 h</td>
</tr>
<tr>
<td>Responders(^1) at 2 h</td>
</tr>
<tr>
<td>Pain-free at 2 h</td>
</tr>
<tr>
<td>Recurrence(^1) within 24 h</td>
</tr>
<tr>
<td>Presence of associated symptoms at 2 h</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Photophobia</td>
</tr>
<tr>
<td>Photophobia</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Normal functioning at 2 h</td>
</tr>
<tr>
<td>Rescue medication</td>
</tr>
<tr>
<td>Would use trial medication again</td>
</tr>
</tbody>
</table>

Alniditan was effective for the treatment of migraine attacks

J&J’s Major Failure

- Johnson and Johnson decided that a triptan which is not superior to sumatriptan cannot be marketed.
- The manager responsible for this decision is now in charge of foot fungus in Outer Mongolia.
Lasmiditan is an effective acute treatment for migraine
A phase 3 randomized study

Bernice Kuca, BA, MS, Stephen D. Silberstein, MD, Linda Wietecha, BSN, MS, Paul H. Berg, MS, Gregory Dozier, MPH, and Richard B. Lipton, MD, on behalf of the COL MIG-301 Study Group

Neurology® 2018;91:e2222-e2232. doi:10.1212/WNL.0000000000006641

Correspondence
Ms. Wietecha
wietecha_linda_a@lilly.com

Figure 1 Study flow (first dose)

<table>
<thead>
<tr>
<th>Enrollment (N = 2,231)</th>
<th>Assessed for eligibility and randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>L200 (n = 745)</td>
<td>L100 (n = 744)</td>
</tr>
<tr>
<td>Allocation</td>
<td>Placebo (n = 742)</td>
</tr>
</tbody>
</table>

Safety population

<table>
<thead>
<tr>
<th></th>
<th>Lasmiditan 200 mg (n = 609)</th>
<th>Lasmiditan 100 mg (n = 630)</th>
<th>Placebo (n = 617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe headache (3), n (%)</td>
<td>148 (28.6)</td>
<td>132 (26.2)</td>
<td>145 (27.7)</td>
</tr>
<tr>
<td>Moderate headache (2), n (%)</td>
<td>355 (68.5)</td>
<td>366 (72.8)</td>
<td>370 (70.6)</td>
</tr>
<tr>
<td>Mild headache (1), n (%)</td>
<td>15 (2.9)</td>
<td>5 (1.0)</td>
<td>9 (1.7)</td>
</tr>
</tbody>
</table>
Lasmiditan zur Behandlung der Migräneattacke

MBS = Most bothersome symptom: (Übelkeit)
Zusammenfassung:

- Lasmiditan, ein 5-HT\textsubscript{1F}-agonist ist in der Behandlung akuter Migräneattacken wirksam
- Indiziert für Patienten mit Kontraindikationen für Triptane
- Wirksamkeit bei Triptanversagern unbekannt
i.v. ASS was as effective as s.c. sumatriptan

• Never managed to get i.v. ASS approved in the USA

• Migraine patients in US emergency rooms are still treated with neuroleptics and opioids
Trigeminovascular Migraine

Pain Pathways

1. Vasodilation
2. Neuropeptide Release (▲Neurokinin A, ●Substance P, ■CGRP)
   - Vasodilation
   - Neurogenic inflammation
3. Pain Signal Transmission
4. Central Pain Transmission
5. 5-HT1b Receptors
6. Trigeminal Ganglion

(Adapted from Hargreaves, Shepheard 1999)
Endothelin antagonist bosentan blocks neurogenic inflammation, but is not effective in aborting migraine attacks

Summary  Bosentan, a specific mixed antagonist of endothelin receptors with no vasoconstrictor activity, inhibits neurogenic plasma extravasation (NPE) within rat dura mater. This would predict efficacy in aborting migraine attacks, without causing cardiovascular side-effects. We investigated the efficacy of 250 mg i.v. bosentan in a randomized, double-blind, placebo-controlled, clinical trial. Improvement from moderate/severe to mild/no headache at 2 h (primary efficacy measure) occurred in 5/23 (22%) of bosentan-treated and in 9/25 (36%) of placebo-treated patients (effect difference −14%; 95% CI −52%, 24%). Thus, inhibition of NPE may not predict clinical efficacy of experimental antimigraine drugs. Vasoconstrictor action may be needed.

A drug which inhibits neurogenic inflammation is not effective in human migraine

A. May, H.J. Gijsman, A. Wallnöfer, R. Jones, H.C. Diener and MD Ferrari  

No Acute Antimigraine
Efficacy of CP-122,288, a
Highly Potent Inhibitor of
Neurogenic Inflammation:
Results of Two Randomized,
Double-Blind, Placebo-
Controlled Clinical Trials

K. I. Roon, MD,* J. Olesen, MD, PhD,†
H. C. Diener, MD, PhD,‡ P. Ellis, PhD,§
J. Hettiarachchi, MD, FRCP,§ P. H. Poole, CStat,§
I. Christianssen, MD,† D. Kleinermans, MD, PhD,¶
J. G. Kok, MD,# and M. D. Ferrari, MD, PhD*

Ann Neurol 2000;47:238–241
Plasma extravasation is not present in human migraine attacks
• Neurogenic inflammation is a good model to investigate analgesics, ergots and triptans in animal experiments

• Drugs which specifically inhibit neurogenic inflammation are not effective to treat migraine attacks in humans
Zolmitriptan and sumatriptan are not effective????

1058 patients were included

Primary endpoint: complete headache response (no recurrence)

39% zolmitriptan

38% sumatriptan

32% placebo
Clinical features of withdrawal headache following overuse of triptans and other headache drugs

Z. Katsarava, MD; G. Fritsche; M. Muessig; H.C. Diener, MD, PhD; and V. Limmroth, MD

Features of medication overuse headache following overuse of different acute headache drugs

V. Limmroth, MD; Z. Katsarava, MD; G. Fritsche, PhD; S. Przywara, MD; and H.-C. Diener, MD, PhD

Incidence and predictors for chronicity of headache in patients with episodic migraine

Z. Katsarava, MD; S. Schneeweiss, MD, ScD; T. Kurth, MD, ScD; U. Kroener, BS; G. Fritsche, PhD; A. Eikermann, MD; H.-C. Diener, MD, PhD; and V. Limmroth, MD

We learned a lot about MOH
Pathophysiology, prevention, and treatment of medication overuse headache

Hans-Christoph Diener, David Dodick, Stefan Evers, Dagny Holle, Rigmor Hoejland Jensen, Richard B Lipton, Frank Porreca, Stephen Silberstein, Todd Schwedt

Regular or frequent use of analgesics and acute antimigraine drugs can increase the frequency of headache, and induce the transition from episodic to chronic headache or medication overuse headache. The 1-year prevalence of this condition in the general population is between 1% and 2%. Medication overuse headache is more common in women and in people with comorbid depression, anxiety, and other chronic pain conditions. Treatment of medication overuse headache has three components. First, patients need education and counselling to reduce the intake of medication for acute headache attacks. Second, some patients benefit from drug withdrawal (discontinuation of the overused medication). Finally, preventive drug therapy and non-medical prevention might be necessary in patients at onset of treatment or in patients who do not respond to the first two steps. The optimal therapeutic approach requires validation in controlled trials.
Utility of topiramate for the treatment of patients with chronic migraine in the presence of absence of acute medication overuse.

Hypothesis was disproven by a randomized trial.
OnabotulinumtoxinA - treatment of chronic migraine

OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial

SK Aurora¹, DW Dodick², CC Turkel³, RE DeGryse³, SD Silberstein⁴, RB Lipton⁵, HC Diener⁶ and MF Brin³,⁷
on behalf of PREEMPT 1 Chronic Migraine Study Group

OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial

HC Diener¹, DW Dodick², SK Aurora³, CC Turkel⁴, RE DeGryse⁴, RB Lipton⁵, SD Silberstein⁶ and MF Brin⁴,⁷
on behalf of the PREEMPT 2 Chronic Migraine Study Group
We showed efficacy for migraine preventive therapy in patients with MOH for

- Topiramate
- Onabotulinumtoxin A
Topiramate in migraine prophylaxis

Results from a placebo-controlled trial with propranolol as an active control

![Graphs showing mean change in migraine frequency](image)

Similar efficacy for topiramate and propranolol
My major achievements

- New migraine preventive therapies should be investigated against placebo and an active comparator
- Reduction in migraine days is the most robust endpoint in clinical trials
A randomized trial to investigate what happens if prophylaxis is terminated
Erenumab in chronic migraine with medication overuse
Subgroup analysis of a randomized trial

Stewart J. Tepper, MD, Hans-Christoph Diener, MD, PhD, Messoud Ashina, MD, PhD, Jan Lewis Brandes, MD, Deborah I. Friedman, MD, MPH, Uwe Reuter, MD, Sunfa Cheng, MD, Jon Nilsen, PhD, Dean K. Leonardi, PhD, Robert A. Lenz, MD, PhD, and Daniel D. Mikol, MD, PhD

Correspondence
Dr. Tepper
shtepper@gmail.com


Table 1 Demographics and baseline disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Without medication overuse</th>
<th>Medication overuse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 169)</td>
<td>Erenumab 70 mg (N = 112)</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.8 (11.8)</td>
<td>41.1 (11.5)</td>
</tr>
<tr>
<td>Acute headache medication use at baseline, n (%)</td>
<td>165 (98)</td>
<td>112 (100)</td>
</tr>
<tr>
<td>Migraine specific</td>
<td>114 (68)</td>
<td>71 (63)</td>
</tr>
<tr>
<td>Not migraine specific</td>
<td>143 (85)</td>
<td>98 (88)</td>
</tr>
<tr>
<td>Baseline period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly migraine days</td>
<td>17.4 (4.7)</td>
<td>17.3 (4.2)</td>
</tr>
</tbody>
</table>
Erenumab bei chronischer Migräne und MOH

C. Without medication overuse

<table>
<thead>
<tr>
<th>Group</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 168)</td>
<td>13.1</td>
<td>23.2</td>
<td>27.4</td>
</tr>
<tr>
<td>70 mg (n = 111)</td>
<td>24.3</td>
<td>36.0</td>
<td>42.3</td>
</tr>
<tr>
<td>140 mg (n = 109)</td>
<td>31.2</td>
<td>40.4</td>
<td>45.9</td>
</tr>
</tbody>
</table>

Adjusted odds ratio (95% CI):
- 70 mg: 2.14 (1.14, 3.99) \( p = 0.016 \)
- 70 mg: 1.86 (1.10, 3.16) \( p = 0.020 \)
- 70 mg: 1.95 (1.17, 3.23) \( p = 0.010 \)
- 140 mg: 3.00 (1.64, 5.49) \( p < 0.001 \)
- 140 mg: 2.24 (1.32, 3.78) \( p = 0.002 \)
- 140 mg: 2.25 (1.36, 3.74) \( p = 0.002 \)

D. With medication overuse

<table>
<thead>
<tr>
<th>Group</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 113)</td>
<td>8.8</td>
<td>12.4</td>
<td>17.7</td>
</tr>
<tr>
<td>70 mg (n = 77)</td>
<td>23.4</td>
<td>42.9</td>
<td>36.4</td>
</tr>
<tr>
<td>140 mg (n = 78)</td>
<td>24.4</td>
<td>39.7</td>
<td>34.6</td>
</tr>
</tbody>
</table>

Adjusted odds ratio (95% CI):
- 70 mg: 3.26 (1.39, 7.67) \( p = 0.005 \)
- 70 mg: 5.31 (2.59, 10.91) \( p < 0.001 \)
- 70 mg: 2.67 (1.36, 5.22) \( p = 0.004 \)
- 140 mg: 3.21 (1.41, 7.30) \( p = 0.004 \)
- 140 mg: 4.65 (2.26, 9.54) \( p < 0.001 \)
- 140 mg: 2.51 (1.28, 4.94) \( p = 0.007 \)
A new era in migraine treatment

- A new principle in the treatment of migraine
- A positive trial
- A new trial design (up-and-down design)
- A migraine topic in the NEJM
• CGRP released during and triggers migraine attacks
• CGRP infusion triggers migraine
• CGRP levels normalized by triptans
• CGRP blockade at key sites (TNC, PAG, thalamus) effective in preclinical models of migraine pain
• 5 small molecule receptor antagonists effective for acute treatment


Durham, P. NEJM 2004; 350(11): 1073-1075
Telcagepant in menstrual migraine

Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine

**Figure 2.** Mean (+ standard error) monthly on-drug headache days among menstrually related migraine (MRM) patients who historically reported five or more moderate or severe migraine headaches per month (secondary endpoint).

**Development terminated**
CGRP-antibodies for migraine prevention

Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study

Marcelo E Bigal, Lars Edvinsson, Alan M Rapoport, Richard B Lipton, Egilkes L H Spierings, Hans-Christoph Dienes, Rami Burstein, Pippa S Loupe, Yuju Ma, Ronghao Yang, Stephen D Silberstein  
Lancet Neurol 2015

Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study

David W Dodick, Peter J Goadsby, Egilkes L H Spierings, Joel C Scherer, Steven P Sweeney, David S Grayzel  
Lancet Neurol 2014

Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial

David W Dodick, Peter J Goadsby, Stephen D Silberstein, Richard B Lipton, Joes Olsen, Messoud Ashina, Ken Wilks, David Kukla, Robin Kroll, Bruce Kohrman, Robert Barger, Joel Hurman, Jeff Smith, for the ALD403 study investigation  
Lancet Neurol 2014

Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study

Marcelo E Bigal, David W Dodick, Alan M Rapoport, Stephen D Silberstein, Yuju Ma, Ronghao Yang, Pippa S Loupe, Rami Burstein, Lawrence C Neuman, Richard B Lipton  
Lancet Neurol 2015
The Future

• Antibodies against CGRP or the CGRP receptor are effective in the preventive therapy of migraine and cluster headache

• They have a favorable AE profile

• What happens if the BBB gets leaky?

• Who can afford these drugs
Patent foramen ovale (PFO) and migraine

Patent foramen ovale, stroke, and cardiovascular disease in migraine
Hans-Christoph Diener, Tobias Kurth and David Dodick

Purpose of review
We will review the literature on the association between migraine with patent foramen ovale, stroke, and coronary heart disease.

Recent findings
The prevalence of patent foramen ovale in patients with migraine with aura is significantly higher than in normotensive controls and migraineurs without aura. However, there is currently no evidence to support a causal relationship. Migraine with aura has been consistently associated with increased risk of ischemic stroke in several epidemiologic studies. Migraine with aura is associated with a more unfavourable cardiovascular risk profile and recent data suggest that the association between migraine with aura and stroke may extend to overall cardiovascular disease. Identification of migraine patients at particular risk for stroke or other vascular events is impossible based on current knowledge.

Summary
Migraine with aura and patent foramen ovale have higher coincidences than expected by chance only. It is possible that both conditions are inherited together. Until now there has been no evidence from placebo-controlled randomized trials that closure of patent foramen ovale improves migraine with aura. There is increasing evidence that migraine with aura is not only a risk factor for ischemic stroke but also for myocardial infarction and other ischemic vascular events.

Keywords
aura, migraine, myocardial infarction, patent foramen ovale, stroke, vascular risk factors

Introduction
An emerging body of evidence indicates that patent foramen ovale (PFO) is more common in migraineurs with aura, and migraine with aura is more common in patients with PFO. In addition, studies, mostly retrospective and uncontrolled, have examined the effect of PFO closure on migraine headache frequency and severity. This review will evaluate the evidence that PFO and migraine are comorbid conditions and the evidence that PFO closure has an effect on migraine outcomes.

Changes in cerebral blood flow during migraine aura, evidence of platelet aggregation, elevated procoagulants (e.g. vWF), increased T2 hyperintensities on brain magnetic resonance imaging (MRI), and the elevated frequency of ischemic stroke among young women with migraine have led to speculation that migraine may be a risk factor for ischemic stroke. Indeed, several studies have found associations between migraine, particularly migraine with aura, and increased risk of ischemic stroke. This review will also report the most recent studies establishing a link between migraine and other ischemic vascular events including coronary heart disease.

Patent foramen ovale in patients with migraine
Several studies have investigated a possible link between PFO and migraine. Using transcranial Doppler, Del Sette et al. [1] evaluated and compared 44 patients with migraine with aura, 73 patients under 50 years with focal cerebral ischemia, and 50 control individuals without cerebrovascular disease or migraine. The prevalence of right-to-left shunt was significantly higher in patients
Migraine with aura and PFO

Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFO closure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD), (N), [min, max]</td>
<td>44.1 ± 10.7 (53) [21–61]</td>
<td>42.7 ± 11.0 (54) [20–62]</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8/53 (15%)</td>
<td>9/54 (17%)</td>
</tr>
<tr>
<td>Female</td>
<td>45/53 (85%)</td>
<td>45/54 (83%)</td>
</tr>
</tbody>
</table>

European Heart Journal (2016) 37, 2029–2036
doi:10.1093/eurheartj/ehw027

Occlusion of a PFO in migraine with aura is not effective

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Thank you

In Essen
- Volker Limmroth
- Zaza Katsarava
- Arne May
- Holger Kaube
- Günther Fritsche
- Cornelius Weiller
- Christian Büchel
- Tobias Kurth
- Markus Schürks
- Markus Gerwig
- Charly Gaul
- Kasja Solbach
- Dagny Holle
- Steffen Nägel

In the rest of the world
- Peter Goadsby
- Michel Ferrari
- David Dodick
- Richard Lipton
- Jean Schoenen
- Stephen Silberstein
- Jes Olesen
- Friends in industry
- And many more
Meilensteine in der Therapie von Migräne und Kopfschmerz: 35 Jahre Kopfschmerzforschung