Migraine and Vascular Disease

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Essen Germany
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Berlin
Conflict of Interest Statement (last 3 years)

• German Research Council
• German Ministry of Education and Research
• European Union

• Allergan
• Amgen
• Electrocore
• Lilly
• Novartis
• Teva
• Weber & Weber
Overview

• Migraine and stroke
• Migraine and vascular disease
• Are triptans dangerous?
Background

- Migraine is one of the most common neurological diseases in adulthood
  - The one-year prevalence of migraine is 6% in men and 18% in women
- Close physiological connection between migraine and the (cerebral) vascular system known for a long time
- Influence of migraine on peripheral vascular system unclear

Migraine and cardiovascular risk factors

- Population-based cross-sectional study (American Migraine Prevalence and Prevention, AMPP)
- 5227 women and 1496 men with episodic migraine, age ≥ 22 years


Risk factors among patients with migraine

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent with 1-2 CV risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 risk factor</td>
<td></td>
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<tr>
<td>2 risk factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Migraine and cardiovascular events

• Associations between migraine and ischemic stroke known for decades

• Stronger associations for
  • Migraine with aura
  • Younger women
  • Increased by smoking and use of certain hormonal contraception

• Association with other cardiovascular events only apparent through cohort studies with long follow-up
  • Myocardial infarction, coronary artery procedures, cardiovascular death
  • Intracerebral hemorrhage
Migraine and cardiovascular events: Meta-analysis

Most recent meta-analysis (2018) of 16 cohort studies
394,942 patients* with migraine; 757,465 people without migraine

• Stroke (13 studies)
  Adjusted HR 1.42 (95% CI, 1.25–1.62)

• Myocardial infarction (7 studies)
  Adjusted HR 1.23 (95% CI, 1.03–1.43)

• Combined outcome (4 studies)
  Adjusted HR 1.42 (95% CI, 1.26–1.69)

HR: hazard ratio; CI: confidence interval
### Migraine and stroke: Meta-analysis, by sex

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Follow-up</th>
<th>total 1</th>
<th>Total 0</th>
<th>HR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke (Males)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Merikangas et al</td>
<td>1997</td>
<td>10</td>
<td>1108</td>
<td>10982</td>
<td>1.40 (1.10, 1.70)</td>
<td>18.49</td>
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<tr>
<td>Kurth et al (PHS)</td>
<td>2007</td>
<td>16</td>
<td>1449</td>
<td>18635</td>
<td>1.12 (0.84, 1.50)</td>
<td>16.07</td>
</tr>
<tr>
<td>Gudmundsson et al</td>
<td>2010</td>
<td>26</td>
<td>571</td>
<td>7068</td>
<td>1.55 (1.10, 2.18)</td>
<td>14.38</td>
</tr>
<tr>
<td>Kuo et al</td>
<td>2013</td>
<td>2</td>
<td></td>
<td></td>
<td>2.38 (1.72, 3.30)</td>
<td>14.90</td>
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<tr>
<td>Peng et al</td>
<td>2016</td>
<td>3.6</td>
<td></td>
<td></td>
<td>1.16 (0.94, 1.42)</td>
<td>18.86</td>
</tr>
<tr>
<td>Lantz et al</td>
<td>2017</td>
<td>11.9</td>
<td>8635</td>
<td>44769</td>
<td>1.06 (0.82, 1.36)</td>
<td>17.31</td>
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<tr>
<td><strong>Subtotal (I-squared = 74.1%, p = 0.002)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.36 (1.10, 1.69)</td>
<td>100.00</td>
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<tr>
<td><strong>Stroke (Females)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Kurth et al (WHS)</td>
<td>2006</td>
<td>10</td>
<td>5125</td>
<td>22715</td>
<td>1.22 (0.88, 1.68)</td>
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<td>5130</td>
<td>22730</td>
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<td>1.20 (0.91, 1.59)</td>
<td>13.41</td>
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<td>Kuo et al</td>
<td>2013</td>
<td>2</td>
<td>20925</td>
<td>104625</td>
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<td>Kurth et al (NHS)</td>
<td>2016</td>
<td>20</td>
<td>17531</td>
<td>98010</td>
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<tr>
<td>Peng et al</td>
<td>2016</td>
<td>3.6</td>
<td>119017</td>
<td>119017</td>
<td>1.31 (1.10, 1.57)</td>
<td>17.82</td>
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<tr>
<td>Rambarat et al</td>
<td>2017</td>
<td>6.5</td>
<td>219</td>
<td>669</td>
<td>2.33 (1.16, 4.68)</td>
<td>4.21</td>
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<tr>
<td>Lantz et al</td>
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<td>11.9</td>
<td>8635</td>
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<td>16.19</td>
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<tr>
<td><strong>Subtotal (I-squared = 61.5%, p = 0.011)</strong></td>
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<td>1.38 (1.17, 1.61)</td>
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</table>

Outcome better with migraine  Outcome worse with migraine
Migraine and myocardial infarction: Meta-analysis, by sex

Migraine and mortality: meta-analysis, by sex

Adjusted absolute effects

• To date, several population-based studies have shown that migraine increases the relative risk of cardiovascular events.

• Unclear to what extent absolute risk plays a role versus other vascular risk factors.

• New analysis from the Women's Health Study (USA)
  • Women 45 years and older
  • Information on migraine and other vascular risk factors collected with questionnaires, blood lipid profiles
  • Cardiovascular events according to medical record review
  • > 22 years follow-up

Adjusted absolute effects Women's Health Study

• Total study population: 27 858 women
  • 1435 (5.2%) migraine with aura
  • 26 423 without (2177 migraine without aura, 24 246 without migraine)
  • 1666 major cardiovascular events (myocardial infarction, stroke, cardiovascular death)
  • Total unadjusted incidence: 2.87 per 1000 person years

  * Adjusted for all other vascular risk factors

• Migraine with aura: 3.36 per 1000 person years*
• Migraine without aura: no increased incidence compared with women without migraine
Adjusted incidences for major cardiovascular events per 1000 women per year.

Vertical red line: adjusted incidence for migraine with aura

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of participants</th>
<th>No. of events</th>
<th>Person-years</th>
<th>Adjusted IR (95% CI)</th>
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<tbody>
<tr>
<td>Migraine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No migraines or migraine without aura</td>
<td>26,412</td>
<td>1,556</td>
<td>550,656</td>
<td>2.68 (1.95–2.21)</td>
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<td>Migraine with aura</td>
<td>1,435</td>
<td>110</td>
<td>29,956</td>
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<td>Cholesterol, mg/dL</td>
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<td>&lt;160</td>
<td>2,272</td>
<td>97</td>
<td>48,707</td>
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<td>160–199</td>
<td>902</td>
<td>417</td>
<td>191,573</td>
<td>1.96 (1.77–2.16)</td>
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<td>200–229</td>
<td>10,416</td>
<td>657</td>
<td>216,228</td>
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<td>240–279</td>
<td>447</td>
<td>116</td>
<td>9,100</td>
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<td>≥280</td>
<td>1,645</td>
<td>163</td>
<td>33,094</td>
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<td>Smoking status</td>
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<td>Never</td>
<td>14,408</td>
<td>778</td>
<td>305,008</td>
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<td>Past</td>
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<td>Current</td>
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<td>HDL cholesterol, mg/dL</td>
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<tr>
<td>≤50</td>
<td>830</td>
<td>411</td>
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<td>50–59</td>
<td>715</td>
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<td>40–49</td>
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<td>469</td>
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<td>≥40</td>
<td>4,822</td>
<td>413</td>
<td>95,299</td>
<td>2.76 (2.45–3.11)</td>
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<td>Diabetes</td>
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<tr>
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<td>1,532</td>
<td>569,226</td>
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<tr>
<td>Yes</td>
<td>602</td>
<td>134</td>
<td>113,078</td>
<td>5.52 (4.58–6.65)</td>
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<td>Triglycerides, mg/dL</td>
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<td>≤77</td>
<td>5,032</td>
<td>308</td>
<td>1,121,134</td>
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<td>77–104</td>
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<td>105–137</td>
<td>5,439</td>
<td>311</td>
<td>1,118,13</td>
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<td>138–193</td>
<td>5,658</td>
<td>363</td>
<td>1,16,122</td>
<td>2.07 (1.84–2.31)</td>
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<tr>
<td>≥194</td>
<td>5,546</td>
<td>517</td>
<td>1,105,83</td>
<td>2.47 (2.19–2.77)</td>
</tr>
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<td>Body mass index</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;25</td>
<td>14,913</td>
<td>733</td>
<td>303,175</td>
<td>2.15 (1.96–2.33)</td>
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<tr>
<td>25–29</td>
<td>8,566</td>
<td>717</td>
<td>1,17,193</td>
<td>2.14 (1.95–2.35)</td>
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<tr>
<td>30–34</td>
<td>8,576</td>
<td>248</td>
<td>88,845</td>
<td>2.09 (1.82–2.41)</td>
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<tr>
<td>≥35</td>
<td>1,563</td>
<td>112</td>
<td>31,431</td>
<td>3.52 (2.73–4.35)</td>
</tr>
<tr>
<td>Family history of MI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>23,913</td>
<td>1,599</td>
<td>458,068</td>
<td>2.65 (1.92–3.16)</td>
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<tr>
<td>Yes</td>
<td>2,945</td>
<td>267</td>
<td>82,544</td>
<td>2.62 (2.23–2.99)</td>
</tr>
</tbody>
</table>

Adjusted absolute effects

• Migraine with aura is an important absolute vascular risk marker for cardiovascular events

• After diabetes, elevated systolic blood pressure, and smoking, migraine is the next most important risk marker

• In interaction with other vascular risk factors, the presence of migraine with aura increases the incidence of cardiovascular events

Summary

- Migraine, especially migraine with aura, is a relevant marker of increased risk of cardiovascular events, also measured as absolute risk increase
- Association also with vascular risk factors
- Impact on acute therapy and prophylaxis
- Complex patterns of association with genetic markers that may even show protective effects of these markers in causal analyses
  - Might argue against a direct causal effect
- Unclear whether treatment of migraine has a beneficial effect on cardiovascular risk
Are triptans dangerous?
Treatment Considerations

Hans-Christoph Diener
University Duisburg-Essen
Germany
Agenda

• Treatment of migraine in patients with coronary artery disease
CONTRAINDICATIONS

IMITREX Tablets should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort, vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia.

Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because IMITREX Tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension.
Plaque rupture with local thrombus formation and vessel occlusion
In >99% of patients no role of vasoconstriction
N = 130,000 - No increased risk of vascular events with triptans

Quote in a recent publication

Triptans also are either contraindicated or must be used with caution in an estimated 3.5 million of the 40 million Americans with migraine because of concerns about cardiovascular effects.8,9
The dominant pathophysiology of acute coronary syndrome is plaque rupture and local thrombosis.

Triptans play no role in this process.

In Prinzmetal angina vasoconstriction plays a role and triptans are contraindicated.
Agenda

• Treatment of migraine in patients with coronary artery disease
• Migraine and stroke
### Odds Ratio: 1.4

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of migraine attack</td>
<td>Aspirin</td>
<td>Triptans</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lasmiditan „Gepants“</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine prevention Medication</td>
<td>Beta-blockers Botulinumtoxin (CM) Aspirin 300 mg</td>
<td>CGRP-MOABs Memantine SSRIs</td>
<td>SSRIs should not be used in patients with ICH</td>
</tr>
<tr>
<td>Migraine prevention Non-medical</td>
<td>Exercise and sport</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Differentiate between ischemic and hemorrhagic stroke**
Safety findings from Phase 3 lasmiditan studies for acute treatment of migraine: Results from SAMURAI and SPARTAN

John H Krege¹, Paul B Rizzoli², Emily Lifick¹, Erin G Doty¹, Sherie A Dowsett¹, Jianing Wang¹ and Andrew S Buchanan¹
While triptans have affinity for 5-HT$_{1B}$, located on vascular smooth muscle receptors and mediating vasoconstrictor effect, lasmiditan has a high affinity for the 5-HT$_{1F}$ receptor and is not a vasoconstrictor (10–12). Due to the increased risk of cardiovascular disease in patients with migraine (13,14), the vasoconstrictive effects of triptans as well as ergotamines (12,15–17), and warnings concerning rare serious cardiovascular events with triptans, ergotamines, and NSAIDS (17–19), we evaluated the cardiovascular safety of lasmiditan. No TEAEs related to vasoconstriction, including angina pectoris, cerebral infarction, hypertensive crisis, and ischemic stroke, were reported in either SAMURAI or SPARTAN. In addition, available information sug-
Risk of triptan use after ischemic stroke

**Ischaemic stroke**

- **25% large-artery atherosclerotic**
- **20% cardioembolic**
- **25% lacunar**
- **5% other/rare**
  - (e.g. dissections, arteritis, etc.)
- **25% Cryptogenic**
  - (not investigated, multiple causes, truly cryptogenic)

**Triptan**

- Triptan
- Triptan
- Triptan
- Triptan
- ?
Are triptans safe?

Views and Perspectives

Consensus Statement: Cardiovascular Safety Profile of Triptans (5-HT\textsubscript{1B/1D} Agonists) in the Acute Treatment of Migraine

David Dodick, MD; Richard B. Lipton, MD; Vincent Martin, MD; Vasilios Papademetriou, MD; Wayne Rosamond, PhD; Antoinette MaassenVanDenBrink, PhD; Hassan Loutfi, MD; K. Michael Welch, MD; Peter J. Goadsby, MD, PhD; Steven Hahn, MD; Susan Hutchinson, MD; David Matchar, MD, FACP; Stephen Silberstein, MD; Timothy R. Smith, MD; R. Allan Purdy, MD, FRCP; Jane Saiers, PhD, The Triptan Cardiovascular Safety Expert Panel

Dodick et al, Headache 2004
Are triptans safe?

Triptans should not be taken during the presence of aura
   Not effective
   Theoretical risk of stroke

Basilar type and hemiplegic migraine attacks should only be treated by a triptan when symptoms have resolved
• Tritpans have no increased risk of vascular events in patients with CHD and ischemic stroke
• Some patients with cluster headache and multiple vascular risk factors inject sumatriptan s.c. 3 x daily for 10 years without adverse events
• Number of reported acute coronary syndromes and ischemic strokes after use of triptans in Germany/year?
Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study

Mercede Rigal, Lars Edvinsson, Alan M. Rapoport, Richard E. Lipton, Eugenie L. Spiersings, Hans-Christoph Diener, Rami Burstein, Pippa S. Lowe, Yiju Ma, Ronghui 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. Goodfob, Eugenie L. Spiersings, Joel C. Schene, Steven P. Sweeney, David S. Glasper  

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


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

Mercede Rigal, David W. Dodick, Alan M. Rapoport, Stephen D. Silberstein, Yiju Ma, Ronghui Yang, Pippa S. Lowe, Rami Burstein, Lawrence C. Neumeier, Richard E. Lipton  

Lancet Neurol 2015
• Pregnancy
• Acute ischemic stroke
• Subarachnoidal hemorrhage
• Acute coronary syndrome

• Disruption of the blood-brain barrier
• Wound healing
• Integrity of the mucosa of the GI tract
• Pregnancy
• Acute ischemic stroke
• Subarachnoidal hemorrhage
• Acute coronary syndrome

• Disruption of the blood-brain barrier
• Wound healing
• Integrity of the mucosa of the GI tract
Vasospasm after SAH
Monoclonal antibodies against CGRP or the CGRP receptor should not be prescribed in patients with:

- A history of ischemic stroke or TIA
- A high risk of stroke (e.g. AF)
- Prolonged aura in combination with risk factors
- History of subarachnoidal hemorrhage
- Familial multiple aneurysms
- Reversible cerebral vasoconstriction syndrome
- Raynauds syndrome
Agenda

• Treatment of migraine in patients with coronary artery disease
• Migraine and stroke
Thank you for your attention
thank you