Headache Update 2016

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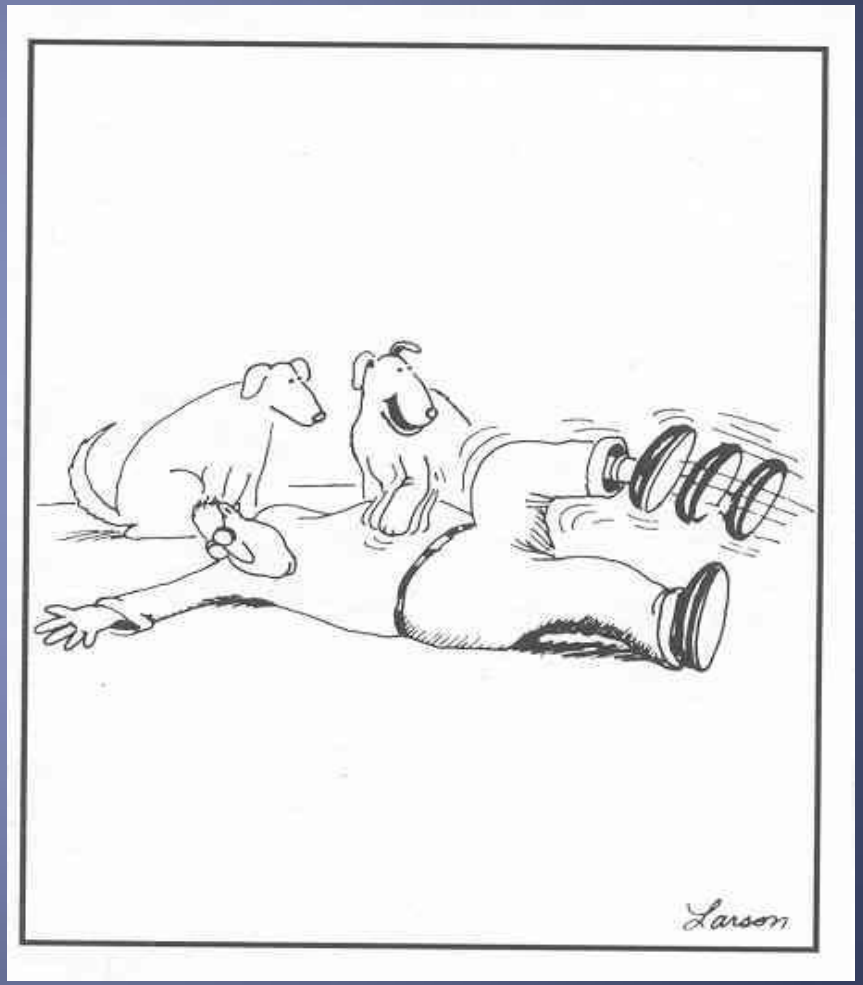
Disclosures

- No pharmaceutical company grants, honoraria, or advisory boards
- Work to support my dogs – Buck and Satchel



What's New

- Migraine is a risk factor for cardiovascular disease
- Preventive therapy
  - Some cardiovascular drugs may be effective migraine prevention
  - Is CGRP blockade the answer for migraine prevention?
- Acute therapy
  - Different formulations for sumatriptan
  - CV risks include NSAIDs

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CV Disease in Women

- Women's Health Study – 40,000 female health care professionals over age 45 w/out CV disease; 10 year follow-up
- 18.4% prevalence of migraine
- 40% w/ migraine in the past year reported aura
- Women with migraine w/out aura did not differ from women w/out migraine in CV risk

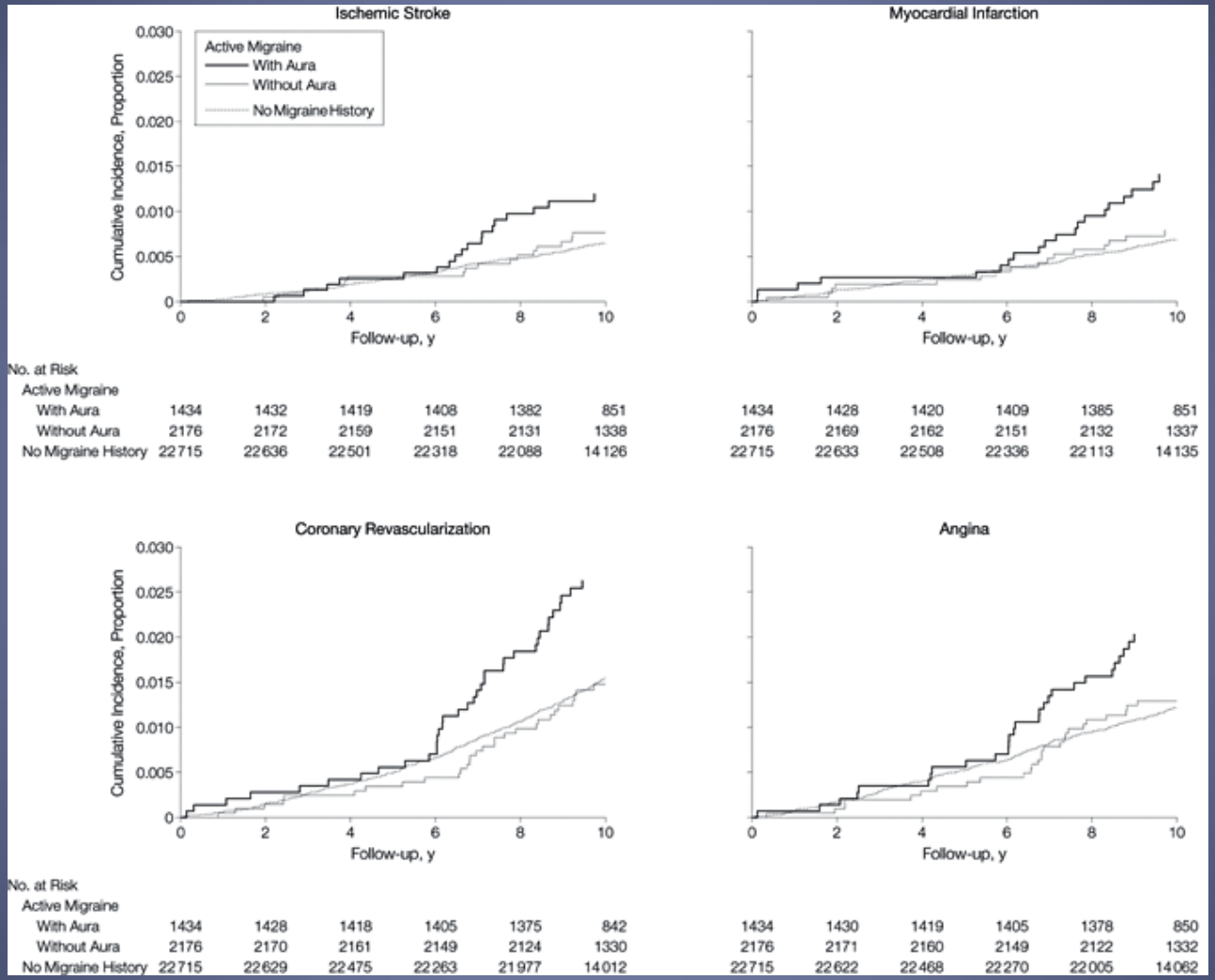
CV Disease in Women

Active migraine w/ aura compared w/ no migraine

Disease	Hazard ratio
Major CV disease	2.15
Ischemic stroke	1.91
MI	2.08
Coronary revascularization	1.74
Angina	1.17
Ischemic CV death	2.33

Kurth T, et al. JAMA. 2006; 296:283-291

Age-Adjusted Cumulative Incidence of Ischemic Stroke, Myocardial Infarction, Coronary Revascularization, and Angina According to Migraine Status



Kurth, T. et al. JAMA 2006;296:283-291.

JAMA

Hazard ratios for cardiovascular disease outcomes according to migraine status in Nurses' Health Study II (n=115 541)

- Major cardiovascular disease event (n=1329):
  - 1.84 (1.64 to 2.06) <0.01
- Myocardial infarction (n=678):
  - 1.79 (1.52 to 2.10) <0.01
- Stroke (n=651):
  - 1.89 (1.60 to 2.22) <0.01
- Angina/coronary revascularization (n=203):
  - 2.35 (1.77 to 3.12) <0.01
- Cardiovascular mortality (n=223):
  - 1.66 (1.25 to 2.21) <0.01

Kurth et al. BMJ 2016:353:i2610

Implications

- History of migraine is a marker for increased risk of any cardiovascular disease event
- No mechanisms explain the increased risk
- No data exist on whether prevention of migraine attacks reduces these risks

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When Should Prophylaxis be Considered:

- Quality of life, business duties, or school attendance are severely impaired
- Frequency of attacks per month is ≥ 2
- Migraine attacks do not respond to acute drug treatment
- Frequent, very long, or uncomfortable auras occur

EFNS Guideline on the drug treatment of migraine
Eur J Neurol 2006, 13: 560-572

US Headache Consortium Guidelines for Migraine Prophylaxis

Group 1: Medium to high efficacy, good strength of evidence, mild to moderate side effects

Amitriptyline (10-150 mg/day)

Divalproex sodium (125-200 mg/day)

Timolol (10-30 mg/day)

Propranolol (20-160 mg/day)

Topiramate (50-150 mg/day)*

* Based on evidence not available at the time of Guideline publication

US Headache Consortium Guidelines for Migraine Prophylaxis

Group 2: Lower efficacy, limited strength of evidence, mild to moderate side effects

Aspirin (325 mg/day)
Atenolol (25-100 mg/day)
Fenoprofen (600 mg three times a day [tid])
Flurbiprofen (100 mg bid-tid)
Fluoxetine (10-80 mg/day)
Gabapentin (300-2,400 mg/day)
Ketoprofen (75 mg tid)
Metoprolol (50-200 mg/day)
Nadolol (20-120 mg/day)
Naproxen (200-550 mg two times a day [bid])
Nimodipine (30 mg tid)
Verapamil (120-480 mg/day)
Botulinum toxin type A (25-100 units/3 months)*

* Based on evidence not available at the time of Guideline publication

US Headache Consortium Guidelines for Migraine Prophylaxis

Group 3: No scientific evidence of efficacy, but clinically efficacious based on consensus of experience

Low to moderate adverse events

Frequent or severe adverse events (or safety concerns); complex management issues

Cyproheptadine

Antidepressants such as nortriptyline, paroxetine, venlafaxine, doxepin, sertraline, and phenelzine

Methylergonovine

US Headache Consortium Guidelines for Migraine Prophylaxis

Group 4: Medium to high efficacy, good strength of evidence, but side effect concerns

Methysergide

Group 5: Evidence indicating no efficacy over placebo

Acebutolol
Pindolol
Carbamazepine
Nicardipine
Nifedipine
Indomethacin

Scottish Intercollegiate Guidelines Network (SIGN)

- Recommendations based on systematic review of the literature
- Grades recommendations based on strength of literature

Scottish Intercollegiate Guidelines Network (SIGN)

Pharmacological Prophylaxis

Beta Blockers

- **A** - Propranolol 80-240 mg per day is recommended as first line therapy for prophylaxis in patients with migraine.
- **D** - Timolol, atenolol, nadolol and metoprolol can be used as alternatives to propranolol as prophylaxis in patients with migraine.

Antiepileptics

- **A** - In patients with episodic migraine and chronic migraine topiramate 50-200 mg per day is recommended to reduce headache frequency and severity.
- **A** - In patients with episodic migraine sodium valproate 800-1,500 mg per day is recommended to reduce headache frequency and severity.
- **C** - Patients with episodic and chronic migraine can be treated with gabapentin 1,200 -2,400 mg per day to reduce headache frequency.

Antidepressants

- **B** - Selective serotonin reuptake inhibitors (SSRIs) are not recommended in the prophylaxis of migraine.
- **B** - Amitriptyline 25-150 mg per day is recommended for patients requiring prophylaxis of migraine.
- **B** - Venlafaxine 75-150 mg per day is an effective alternative to tricyclic antidepressants for prophylaxis of migraine.

Other Therapies

- **A** - Botulinum toxin A is not recommended for the prophylactic treatment of migraine.

European Federation of Neurological Societies (EFNS)

- Drugs of first choice
- Drugs of second choice: less effective or more side effects than first choice drugs
- Drugs of third choice: only probable efficacy

EFNS Drugs of First Choice for the prophylactic drug treatment of migraine

Substances	Daily dose	Level
Beta blockers		
Metoprolol	50–200 mg	A
Propranolol	40–240 mg	A
Calcium channel blockers		
Flunarizine	5–10 mg	A
Antiepileptic drugs		
Valproic acid	500–1800 mg	A
Topiramate	25–100 mg	A

EFNS Drugs of Second Choice

(evidence of efficacy, but less effective or more side effects than first choice drugs)

Substances	**Daily dose (mg)**	**Level**
Amitriptyline	50–150	B
Naproxen	2 × 250–500	B
Petasites	2 × 75	B
Bisoprolol	5–10	B

EFNS Drugs of Third Choice (only probable efficacy)

Substances	Daily dose	Level
Acetylsalicylic acid	300 mg	C
Gabapentin	1200–1600 mg	C
Magnesium	24 mmol	C
Tanacetum parthenium	3 × 6.25 mg	C
Riboflavin	400 mg	C
Coenzyme Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	C
Methysergide	4–12 mg	C

	US Headache Consortium	Scottish Intercollegiate Guidelines Network	European Federation of Neurological Societies
First Line	Amitriptyline Divalproex sodium Timolol Propranolol Topiramate	Propranolol Topiramate Valproic Acid Amitriptyline	Propranolol Metoprolol Flunarizine Valproic Acid Topiramate
Second line	Aspirin Atenolol Fenoprofen Flurbiprofen Fluoxetine Gabapentin Ketoprofen Metoprolol Nadolol Naproxen Nimodipine Verapamil Botulinum toxin type A	Timolol Atenolol Nadolol Metoprolol Gabapentin Venlafaxine	Amitriptyline Naproxen Petasites Bisoprolol
Third Line	Cyproheptadine Antidepressants: nortriptyline, paroxetine, venlafaxine, doxepin, sertraline, and phenelzine Methylergonovine		ASA Gabapentin Magnesium Riboflavin Coenzyme Q10 Tanecetum Candesartan Lisinopril Methysergide

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Simvastatin and Vitamin D for Migraine Prevention

- Simvastatin 20 mg + vitamin D3 1000 IU BID
- Baseline 12 weeks Intervention 24 weeks (n=57)
- 50% reduction in migraine days at 12 weeks
  - Placebo 1 (3%) Active drug 8 (25%) $p<0.03$
- Number of migraine days (baseline - week 12)
  - Placebo +1 Active drugs -8 $p<0.001$

Candesartan vs Propranolol vs Placebo for Migraine Prophylaxis

- Candesartan 16 mg vs propranolol 160 mg qd
- Triple blind, double cross-over study with 3X 12 week treatment periods
- Days with migraine per 4 weeks:
  - Candesartan 2.95 Propranolol 2.91 Placebo 3.53
- Responders >50% reduction in migraine days from baseline:
  - Candesartan 43% Propranolol 40% Placebo 23%

Candesartan vs Propranolol vs Placebo for Migraine Prophylaxis

- Candesartan 16 mg is effective for migraine prevention
- Candesartan is non-inferior to propranolol (and vice versa)
- Adverse effects were similar in number between the active drugs, but were different from each other – pain with propranolol, dizziness with candesartan, tiredness with both

Cochrane Systematic Review

Acupuncture for the prevention of episodic migraine

Authors: Klaus Linde, Gianni Allais, Benno Brinkhaus, Yutong Fei, Michael Mehring, Emily A. Vertosick, Andrew Vickers, Adrian R White

First published: 28 June 2016

Acupuncture

- Acupuncture was associated with a moderate reduction of headache frequency over no acupuncture
- Acupuncture was associated with a small but statistically significant frequency reduction over sham
- Acupuncture reduced migraine frequency significantly more than drug prophylaxis after treatment, but the significance was not maintained at follow-up

Acupuncture

- Authors' conclusions:

The available evidence suggests that adding acupuncture to symptomatic treatment of attacks reduces the frequency of headaches. Contrary to the previous findings, the updated evidence also suggests that there is an effect over sham, but this effect is small. The available trials also suggest that acupuncture may be at least similarly effective as treatment with prophylactic drugs. Acupuncture can be considered a treatment option for patients willing to undergo this treatment. As for other migraine treatments, long-term studies, more than one year in duration, are lacking.

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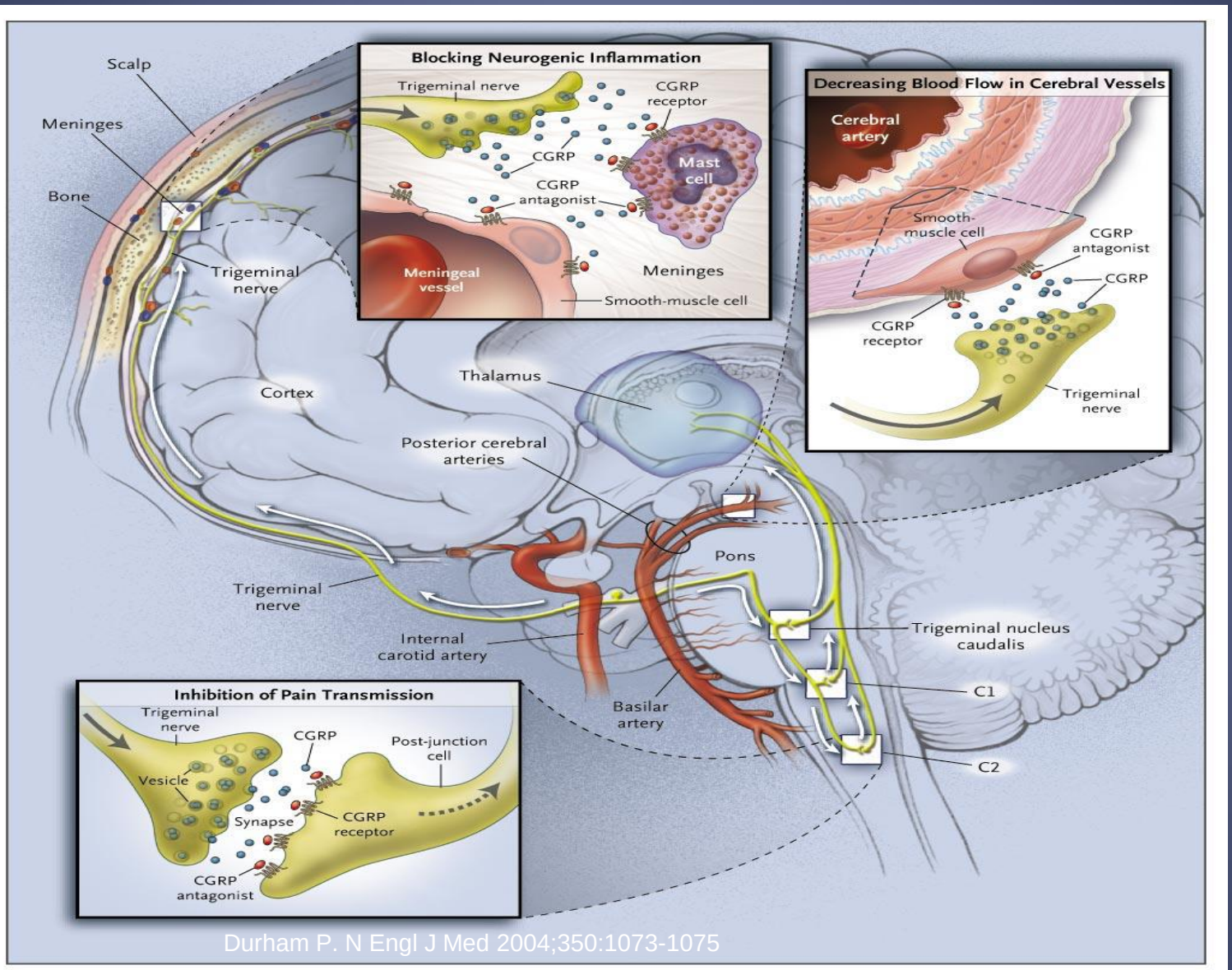
Calcitonin-Gene Related Peptide

- Calcitonin-gene related peptide (CGRP) is a 37 amino acid neuropeptide
- Potent vasodilator
- Maintenance of vascular homeostasis
- CNS: pain modulation, perception, and central sensitization
- Periphery: vasodilation and mast cell degranulation

Possible Sites of Possible Sites of Action of the Nonpeptide CGRP-Receptor Antagonist of the CGRP-Receptor Antagonist BIBN 4096 BS



Durham P. N Engl J Med 2004;350:1073-1075

ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lynna M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group

ABSTRACT

BACKGROUND

Calcitonin gene–related peptide (CGRP) may have a causative role in migraine. We therefore hypothesized that a CGRP-receptor antagonist might be effective in the treatment of migraine attacks.

METHODS

In an international, multicenter, double-blind, randomized clinical trial of BIBN 4096 BS, a highly specific and potent nonpeptide CGRP-receptor antagonist, 126 patients with migraine received one of the following: placebo or 0.25, 0.5, 1, 2.5, 5, or 10 mg of BIBN 4096 BS intravenously over a period of 10 minutes. A group-sequential adaptive treatment-assignment design was used to minimize the number of patients exposed.

RESULTS

The 2.5-mg dose was selected, with a response rate of 66 percent, as compared with 27 percent for placebo (P=0.001). The BIBN 4096 BS group as a whole had a response rate of 60 percent. Significant superiority over placebo was also observed with respect to most secondary end points: the pain-free rate at 2 hours; the rate of sustained response over a period of 24 hours; the rate of recurrence of headache; improvement in nausea, photophobia, phonophobia, and functional capacity; and the time to meaningful relief. An effect was apparent after 30 minutes and increased over the next few hours. The overall rate of adverse events was 25 percent after the 2.5-mg dose of the drug and 20 percent for the BIBN 4096 BS group as a whole, as compared with 12 percent for placebo. The most frequent side effect was paresthesia. There were no serious adverse events.

CONCLUSIONS

The CGRP antagonist BIBN 4096 BS was effective in treating acute attacks of migraine.

From the Department of Neurology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark (J.O.); the Department of Neurology, University of Essen, Essen, Germany (H.-C.D.); the Department of Neurology, University Hospital, Münster, Germany (I.W.H.); the Institute of Neurology, London (P.J.G.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, Conn. (D.H., L.M.L.); and Boehringer Ingelheim Pharma, Ingelheim, Germany (U.M., S.P.). Address reprint requests to Dr. Olsen at the University of Copenhagen, Department of Neurology, Glostrup Hospital, 2600 Glostrup, Copenhagen, Denmark, or at jeol@glostruphosp.kbhamt.dk.

N Engl J Med 2004;350:1104-10.

CGRP Receptor Antagonists

- Olcegepant
- Telcagepant

CGRP Monoclonal Antibodies

- Long half-life injectable medications (IV or SQ)
- Developed for migraine prevention
- 4 in development
  - 3 target the CGRP ligand
    - Eli Lilly and Co.
    - Alder Biopharmaceuticals
    - Teva Pharmaceuticals
  - 1 targets the CGRP receptor
    - Amgen

Concerns About CGRP Blockade

- CGRP is a vasodilator peptide
  - ? Medication-induced hypertension
  - ? Inhibition of cardio-protective mechanisms during ischemia
- Cochlear function
- Reduced expression of CGRP – cisplatin-induced renal injury
- Bone differentiation

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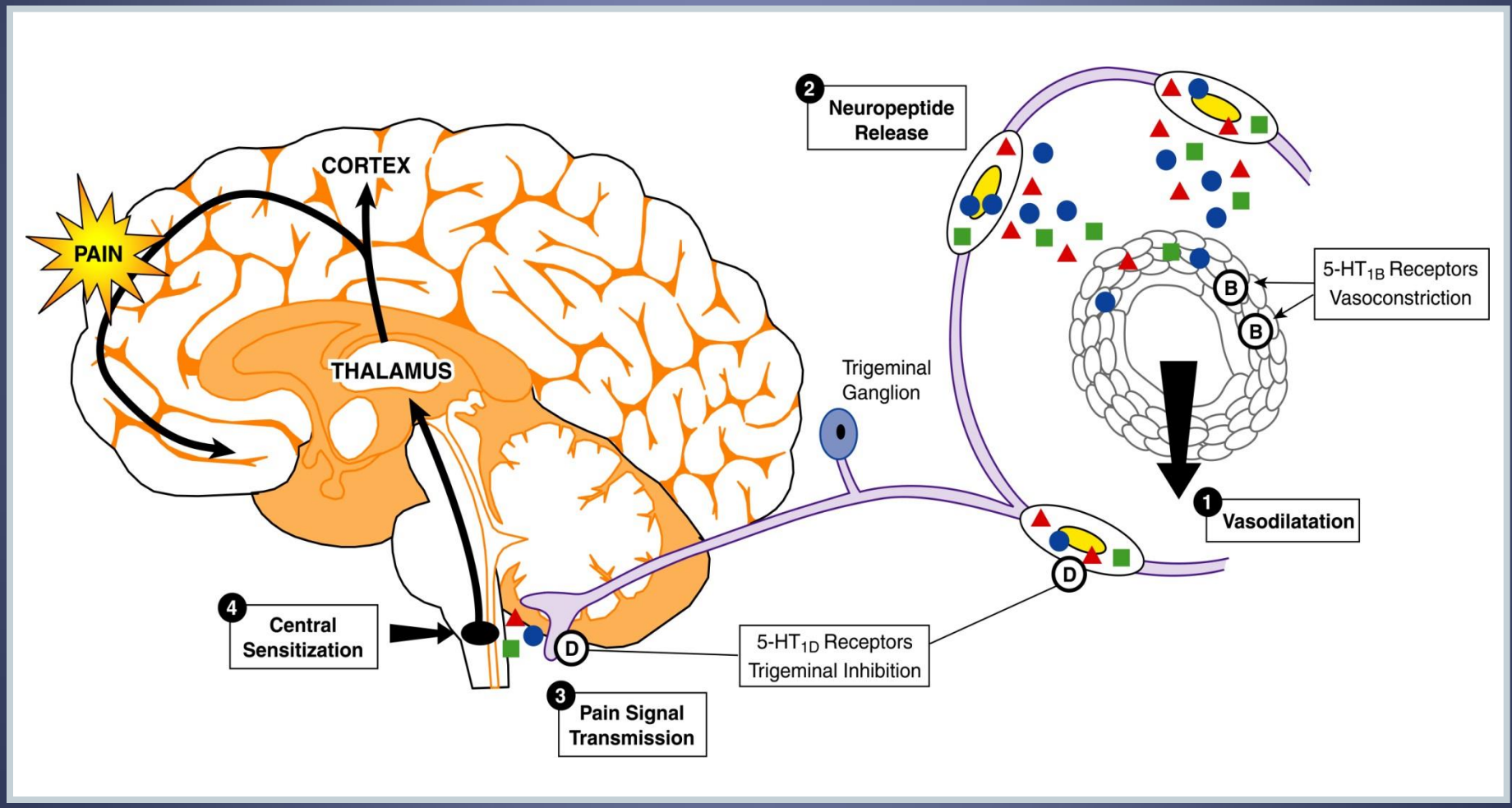
Migraine : Abortive Therapy

- Serotonin agonists - triptans & ergots
- Isometheptene mucate combination
- NSAIDs
- Antiemetics
- Lidocaine
- Corticosteroids
- Analgesics

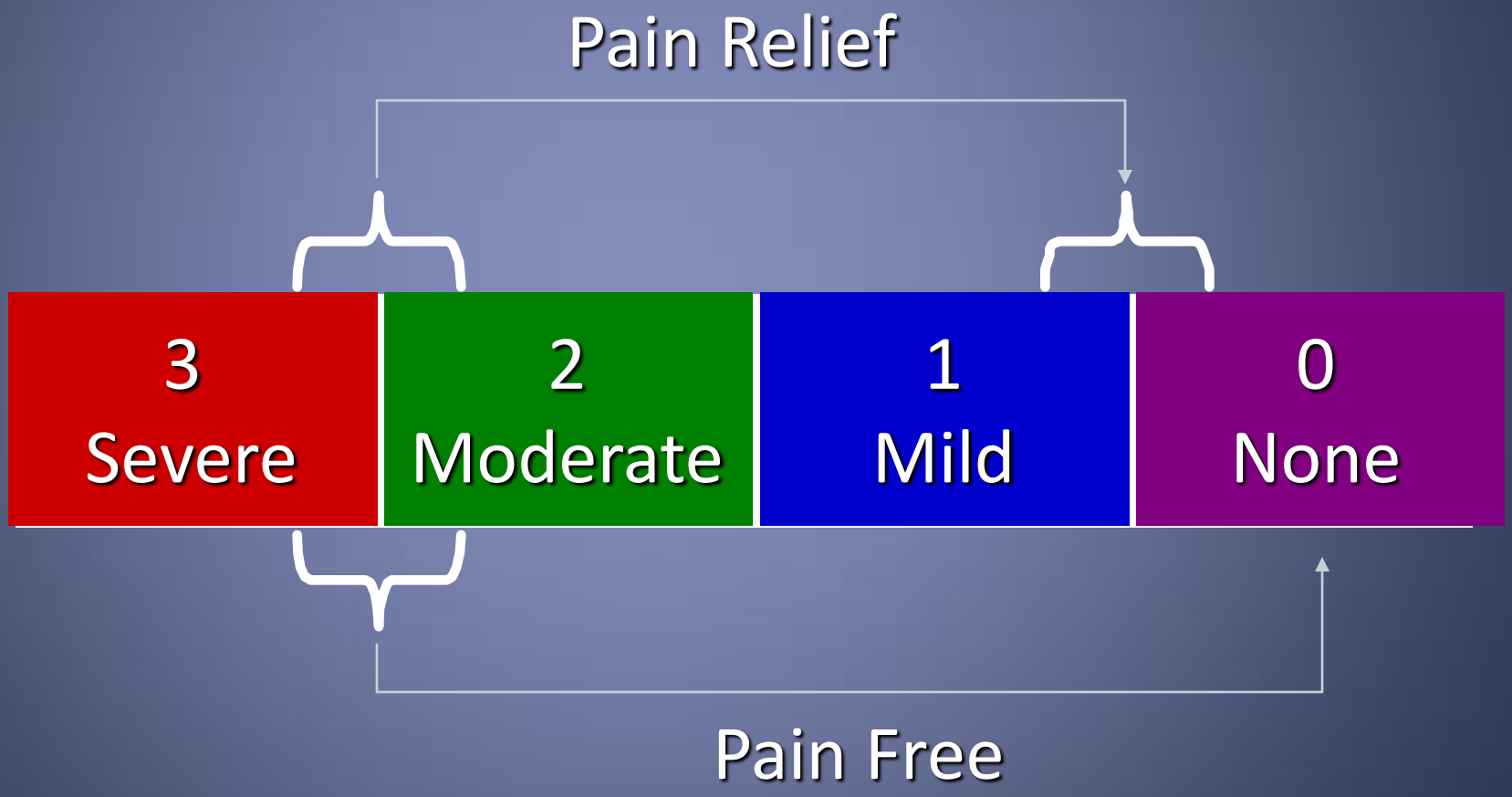
Key Questions

- Are there differences among the triptans?
- When should patients take triptans?
- How should patients take triptans?
- What are the alternatives to triptans?
- Should I start with an NSAID?
- What about opioids?

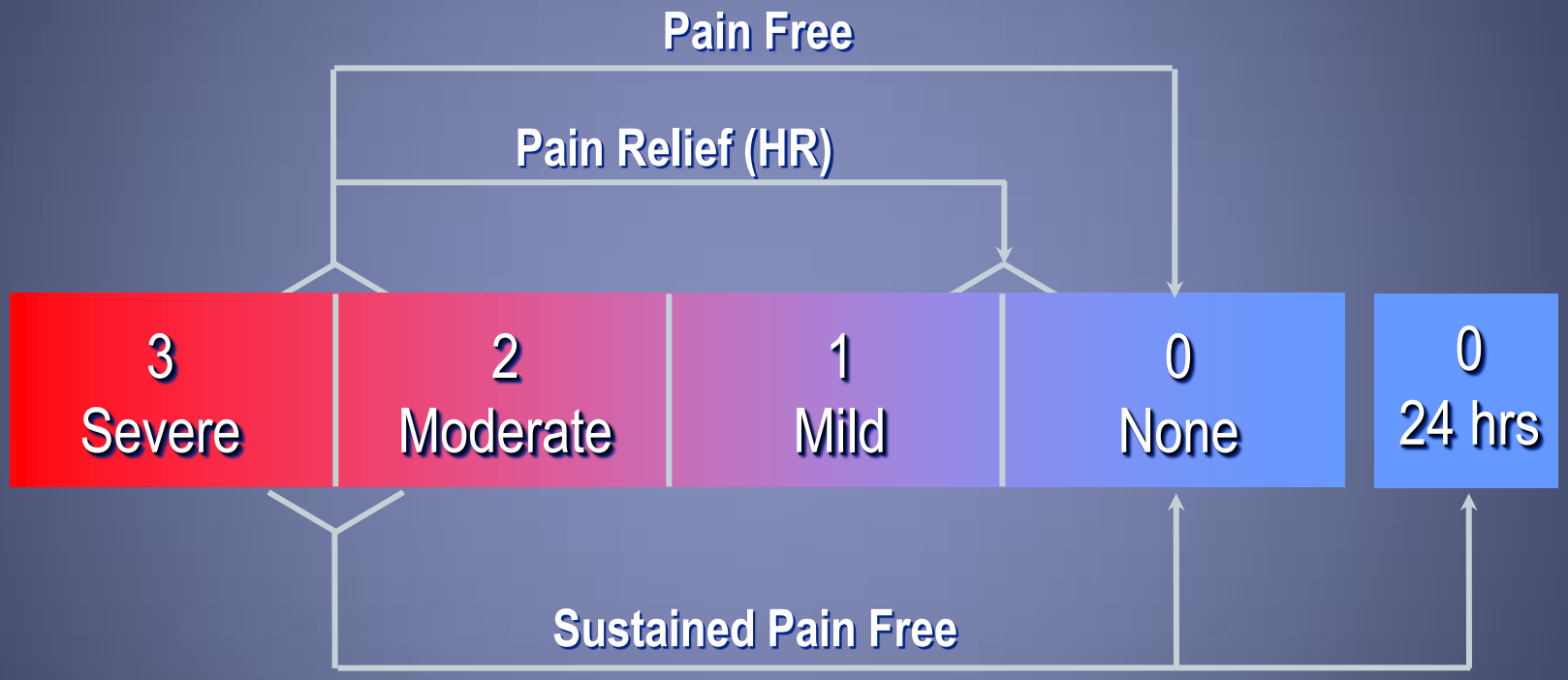
Trigeminovascular Migraine Pain Pathways



Migraine Study Terminology

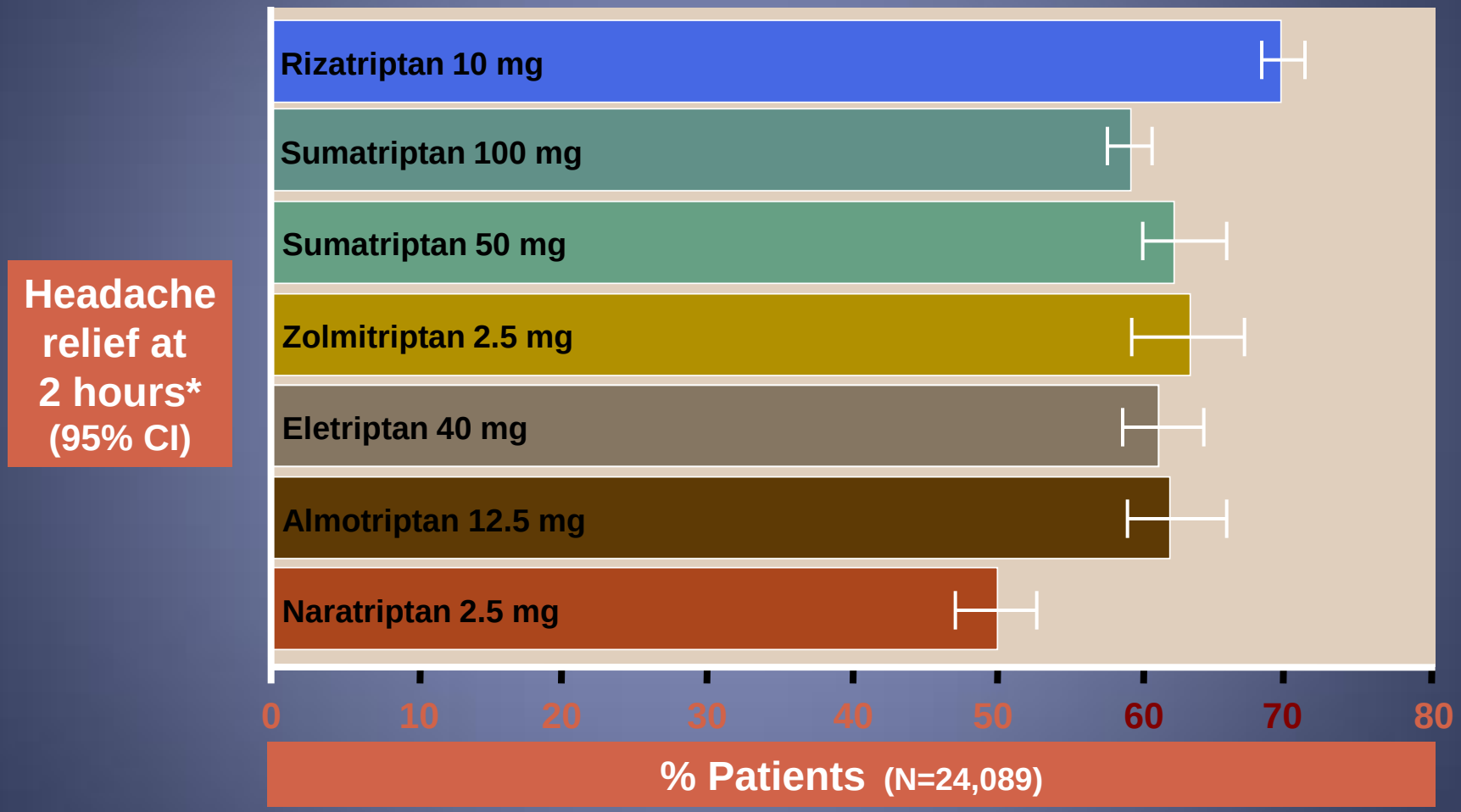


Definition of Sustained Pain Free



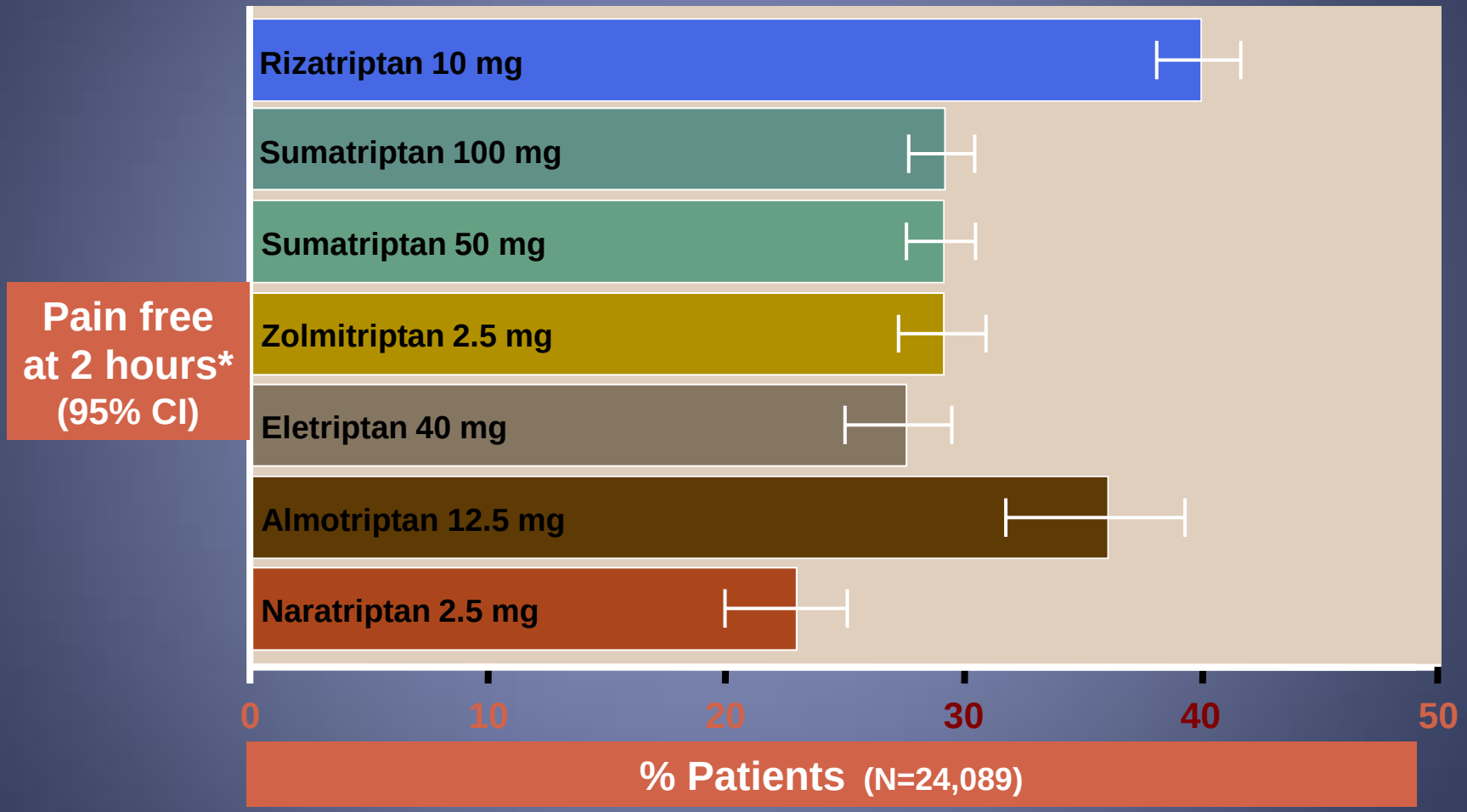
- Pain free at 2 hours
- No recurrence
- No use of additional medications between 2–24 hours

Pain Relief
(Meta-Analysis)



Adapted from Ferrari MD et al. *Lancet* 2001;358:1668-1675.
*Comparison of recommended initial doses in SPC and standard comparator in the meta-analysis (sumatriptan 100 mg)

Pain Free
(Meta-Analysis)



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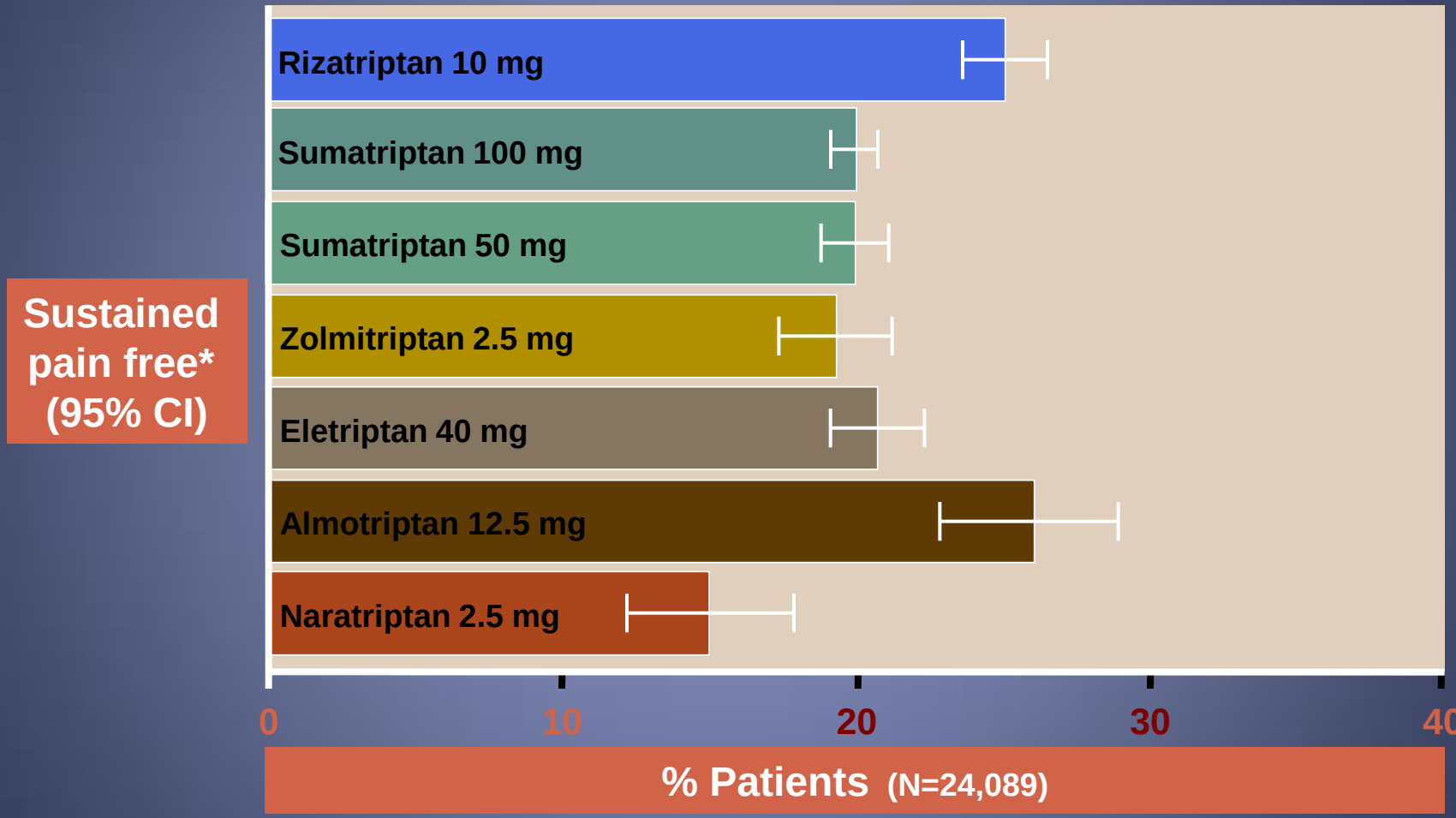
Sustained Pain Free
(Meta-Analysis)



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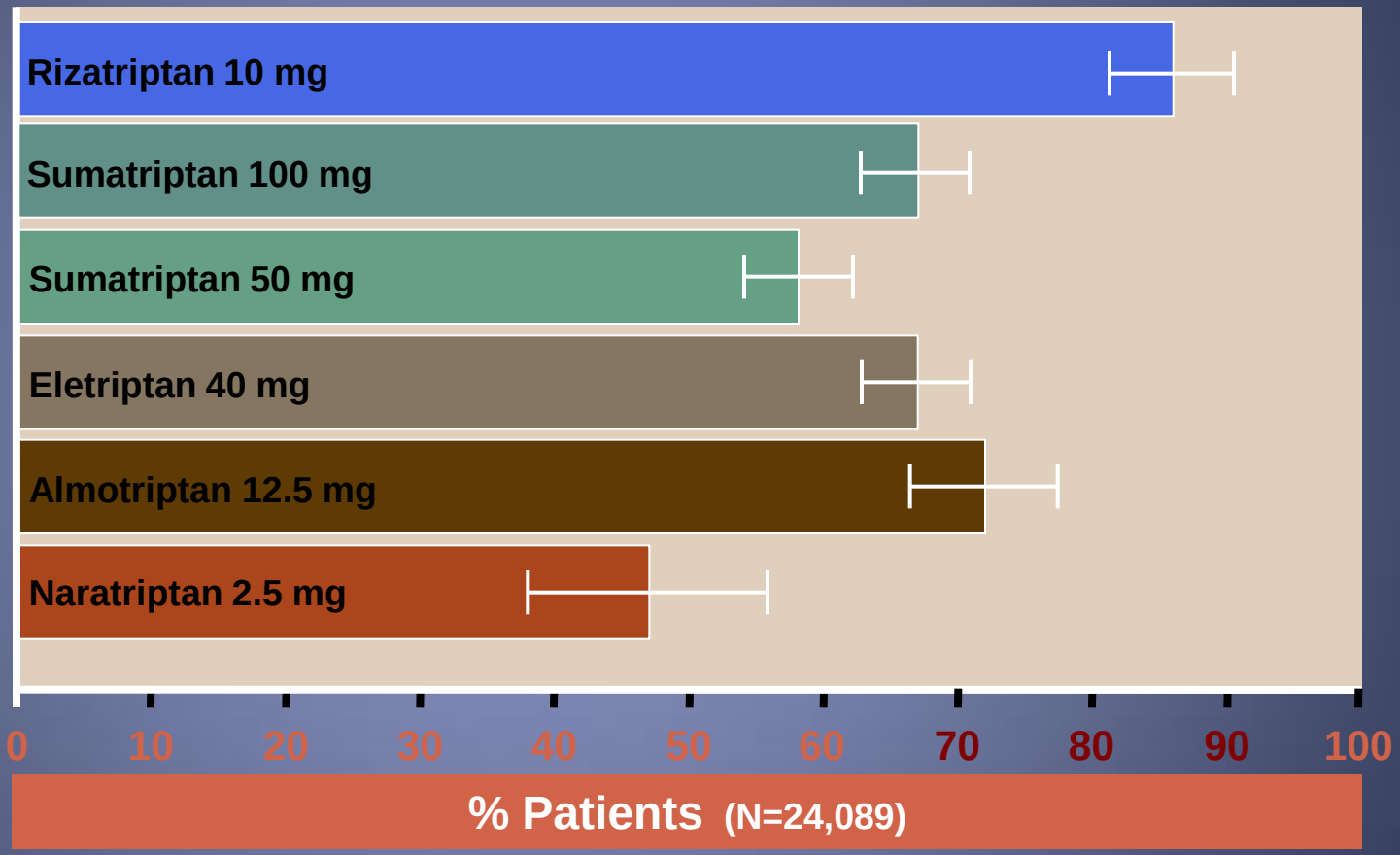
Consistency of Migraine Treatment (Meta-Analysis)

Headache relief at 2 hours in at least 2 out of 3 attacks* (95% CI)



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*Comparison of recommended initial doses in SPC and standard comparator in the meta-analysis (sumatriptan 100 mg)

Triptan Efficacy

If taken for a moderate or severe migraine

- **60-70%** will have mild or no pain at 2 hrs
- **30-40%** will be pain free at 2 hrs
- **20-30%** will be pain free at 2 hrs and remain pain free for 24 hrs w/o additional medications

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Sumatriptan Needle-Free Injection

Table 2. Sumatriptan Products[1]

Formulations	Onset of Action	Usual Dosage	Cost[2]
Tablets			
(25, 50, 100 mg tabs) generic	30-60 min	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	$22.22
Imitrex			28.15
Nasal Spray (5, 20 mg/spray) *Imitrex Nasal Inhaler*	10-15 min	5, 10 or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)	55.49
Subcutaneous injection (4, 6 mg/0.5 mL) generic	~10 min	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	79.99
Imitrex			108.58
Needle-free injection (6 mg/0.5 mL) *Sumavel DosePro*	~10 min	6 mg; can be repeated once after 1 hr (max 12 mg/d)	83.00[3]

1. Sumatriptan is also available as the combination tablet *Treximet* (85 mg sumatriptan/500 mg naproxen sodium)
2. Cost of one dose at the lowest usual dosage based on prices at drugstore.com. Accessed June 21, 2010. Subcutaneous sumatriptan is marketed in boxes of 2 prefilled, single-dose syringe cartridges. *Sumavel DosePro* is marketed in a package containing 6 single-dose units.
3. Wholesale Acquisition Cost (WAC) according to the manufacturer.

Sumatriptan Needle-Free Injection

- *Sumavel DosePro*, the new needle-free formulation of sumatriptan, can be used by patients who require parenteral administration of a triptan for acute attacks of migraine or cluster headache, but are afraid of needles. It is at least as painful, however, as a subcutaneous injection through a needle and may cause a somewhat more severe local reaction.

Sumatriptan Nasal Powder

- **PHARMACOKINETICS —** A single-dose, crossover study in 20 healthy subjects compared sumatriptan 22-mg nasal powder, 20-mg liquid nasal spray, 100-mg oral tablets, and 6-mg SC injection. Compared with the nasal spray, use of the nasal powder resulted in a faster rise in plasma concentrations of sumatriptan and a 27% higher peak serum concentration (Cmax). The Cmax and systemic exposure (AUC) with the nasal powder were significantly lower than with the oral tablet or SC injection.

Sumatriptan Nasal Powder

Table 1. Pharmacology	
Route	Intranasal
Cmax	21 ng/mL (22-mg dose)
Tmax	45 minutes (range 10 mins - 2 hrs)
Bioavailability	19% (relative to SC injection)
Metabolism	Monoamine oxidase (MAO), predominantly A isoenzyme
Half-life	3 hours
Elimination (nasal spray)	Urine (42% as the major metabolite indole acetic acid; 3% unchanged)

Sumatriptan Nasal Powder

- In a randomized, double-blind, crossover trial, 185 patients were treated for multiple migraine attacks with either sumatriptan nasal powder or 100 mg of oral sumatriptan. Rates of pain relief and pain freedom were significantly higher with the nasal powder than with the oral tablets from 15 to 90 minutes post-dose, but were similar in the two groups from 2 to 48 hours

Intranasal Therapies

Table 2. Intranasal Triptans for Acute Treatment of Migraine

Drug	Formulations	Usual Dosage	Cost[1]
Sumatriptan – *Imitrex* (GSK)	5, 20 mg/0.1 mL nasal spray	5, 10, or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)	$69.20
Onzetra Xsail (Avanir)	11 mg nasal powder capsules	22 mg intranasally, can be repeated once after 2 hrs (max 44 mg/d)	61.00
Zolmitriptan – *Zomig* (Impax)	2.5, 5 mg/0.1 mL nasal spray	2.5 or 5 mg intranasally; can be repeated once after 2 hrs (max 10 mg/d)	56.90

1. Approximate WAC for one dose at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. July 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.

Sumatriptan Formulations

Table 1. Some Sumatriptan Products for Acute Treatment of Migraine

Drug	Some Available Formulations	Usual Adult Dosage	Cost[1]
generic	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	$2.10
	6 mg/0.5 mL vial, prefilled syringe, auto-injector	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	25.50[2]
Imitrex (GSK)	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	48.20
	5, 20 mg/0.1 mL nasal spray	5, 10 or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)	60.10
	6 mg/0.5 mL vial; 4, 6 mg/0.5 mL cartridges, auto-injectors	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	140.50[2]
Alsuma (Pfizer)	6 mg/0.5 mL auto-injector	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	98.90
Sumavel DosePro (Endo)	4, 6 mg/0.5 mL needle-free injector	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	150.60
Zecuity (Teva)	6.5 mg transdermal patch	6.5 mg transdermally; a second patch can be applied after 2 hrs (max 2 patches/d)	289.00

1. Approximate WAC for one dose at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. October 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015 www.fdbhealth.com/policies/drug-pricing-policy.
2. Cost of 1 vial.

Sumatriptan Iontophoretic Patch

- The iontophoretic patch formulation of sumatriptan *(Zecuity)* for acute treatment of migraine provides relief of headache pain in about 50% of patients after 2 hours, but it requires some assembly by the patient, has a slower onset of action than injectable or intranasal formulations, and frequently causes application-site reactions. It is much more expensive than other sumatriptan formulations, but causes few triptan-associated adverse events. It might be worth trying in patients who are unable to tolerate or unwilling to use other triptan formulations.

Sumatriptan Iontophoretic Patch

- 06/02/2016 - FDA is investigating the risk of serious burns and potential permanent scarring with the use of Zecuity (sumatriptan iontophoretic transdermal system) patch for migraine headaches. Since marketing of the Zecuity patch began in September 2015, a large number of patients have reported they experienced burns or scars on the skin where the patch was worn. The reports included descriptions of severe redness, pain, skin discoloration, blistering, and cracked skin.

Sumatriptan Iontophoretic Patch

- **UPDATED 06/13/2016:** Zecuity manufacturer Teva Pharmaceuticals has decided to temporarily suspend sales, marketing, and distribution to investigate the cause of burns and scars associated with the Zecuity patch. Health care professionals should discontinue prescribing Zecuity, and patients should stop using any remaining patches and contact their prescribers for an alternative migraine medicine.

Zembrace 3 mg Injection

Dose	3 mg	6 mg
2 hrs efficacy	60%	70%
Adverse events	77%	83%

Cost of Sumatriptan

2010

Table 2. Sumatriptan Products[1]

Formulations	Onset of Action	Usual Dosage	Cost[2]
Tablets			
(25, 50, 100 mg tabs) generic	30-60 min	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	$22.22
Imitrex			28.15
Nasal Spray (5, 20 mg/spray) *Imitrex Nasal Inhaler*	10-15 min	5, 10 or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)	55.49
Subcutaneous injection (4, 6 mg/0.5 mL) generic	~10 min	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	79.99
Imitrex			108.58
Needle-free injection (6 mg/0.5 mL) *Sumavel DosePro*	~10 min	6 mg; can be repeated once after 1 hr (max 12 mg/d)	83.00[3]

1. Sumatriptan is also available as the combination tablet *Treximet* (85 mg sumatriptan/500 mg naproxen sodium)
2. Cost of one dose at the lowest usual dosage based on prices at drugstore.com. Accessed June 21, 2010. Subcutaneous sumatriptan is marketed in boxes of 2 prefilled, single-dose syringe cartridges. *Sumavel DosePro* is marketed in a package containing 6 single-dose units.
3. Wholesale Acquisition Cost (WAC) according to the manufacturer.

2015

Table 1. Some Sumatriptan Products for Acute Treatment of Migraine

Drug	Some Available Formulations	Usual Adult Dosage	Cost[1]
generic	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	$2.10
	6 mg/0.5 mL vial, prefilled syringe, auto-injector	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	25.50[2]
Imitrex (GSK)	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	48.20
	5, 20 mg/0.1 mL nasal spray	5, 10 or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)	60.10
	6 mg/0.5 mL vial; 4, 6 mg/0.5 mL cartridges, auto-injectors	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	140.50[2]
Alsuma (Pfizer)	6 mg/0.5 mL auto-injector	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	98.90
Sumavel DosePro (Endo)	4, 6 mg/0.5 mL needle-free injector	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)	150.60
Zecuity (Teva)	6.5 mg transdermal patch	6.5 mg transdermally; a second patch can be applied after 2 hrs (max 2 patches/d)	289.00

1. Approximate WAC for one dose at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. October 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015 www.fdbhealth.com/policies/drug-pricing-policy.
2. Cost of 1 vial.

What's New

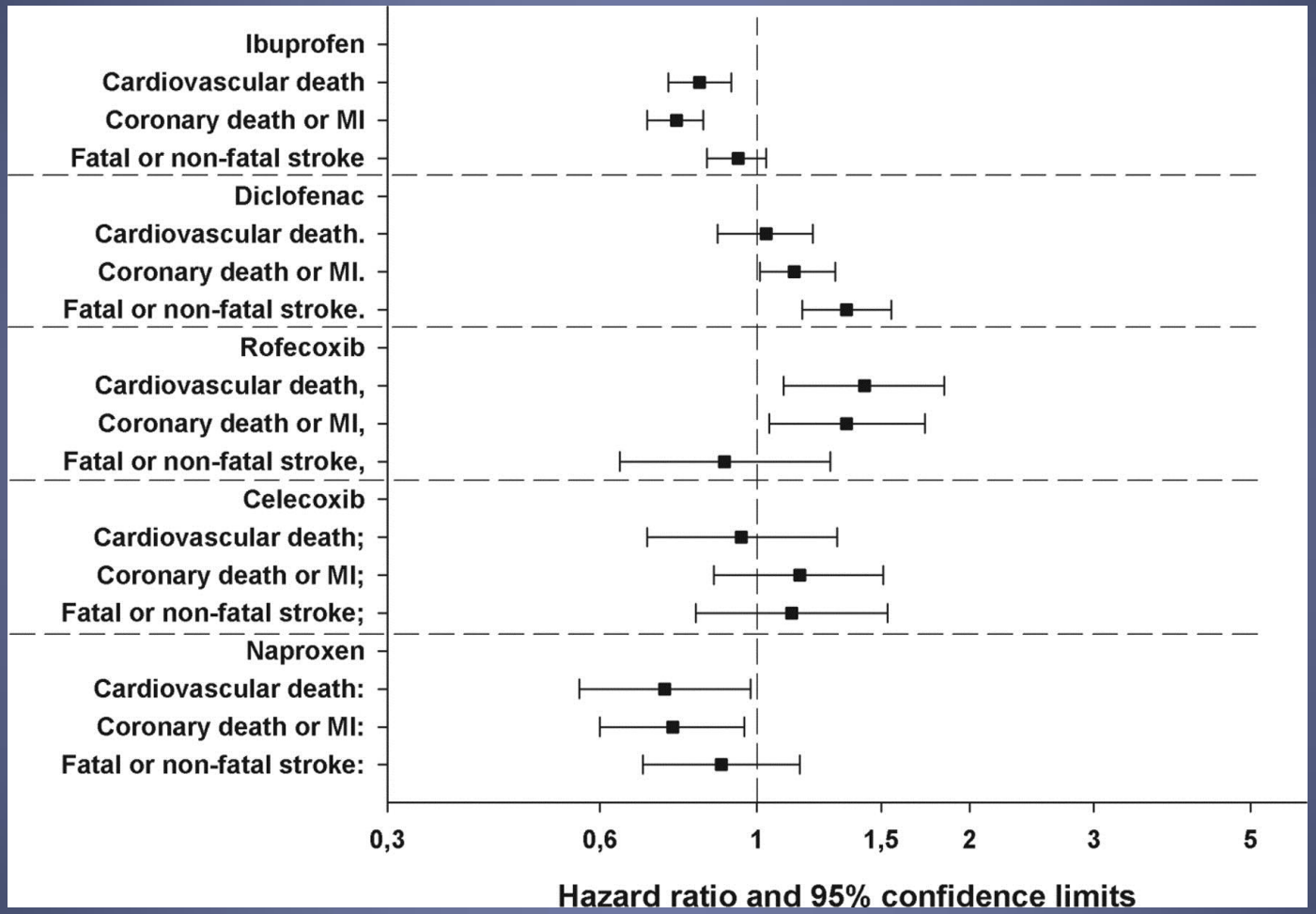
- Migraine is a risk factor for cardiovascular disease
- Preventive therapy
  - Some cardiovascular drugs may be effective migraine prevention
  - Is CGRP blockade the answer for migraine prevention?
- Acute therapy
  - Different formulations for sumatriptan
  - CV risks include NSAIDs

CV Risk of NSAIDs

Drug	Relative Risk
Rofecoxib >25mg/d	2.19
Diclofenac	1.40
Indomethacin	1.30
Meloxicam	1.25
Ibuprofen	1.07
Celecoxib <200mg/d	1.06
Piroxicam	1.06
Naproxen	0.97

McGettigan P, et al. JAMA. 2006;296:1633-44

Cox proportional hazard analysis



Fosbol, E. L. et al. Circ Cardiovasc Qual Outcomes 2010;3:395-405

Circulation:
Cardiovascular Quality and Outcomes

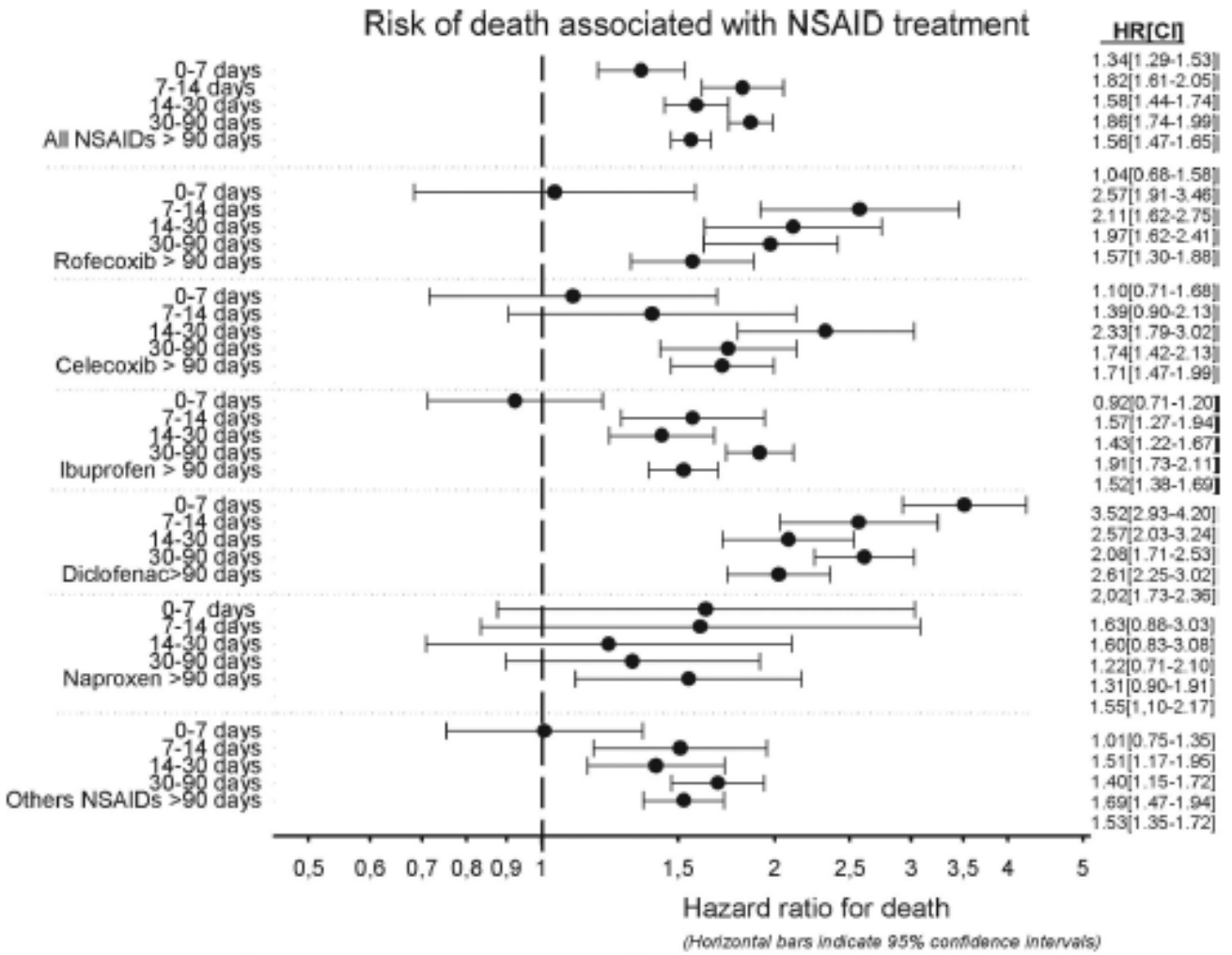


Figure 3. Time-dependent Cox proportional hazard analysis of risk of death according to duration of nonsteroidal antiinflammatory drug (NSAID) treatment in patients with prior myocardial infarction. HR indicates hazard ratio; CI, confidence interval.

(*Circulation*. 2011;123:2226-2235.)

Do Opioids Have a Role?

Cons

- Limited efficacy: ~30% pain relief at 2 hours
- Risk of habituation
- Reduced function after use

Pros

- Safe for patients w/ coronary risk factors
- Little habituation risk with infrequent use
- Valued as rescue therapy