Le traitement de la migraine chez le patient avec maladie neurovasculaire

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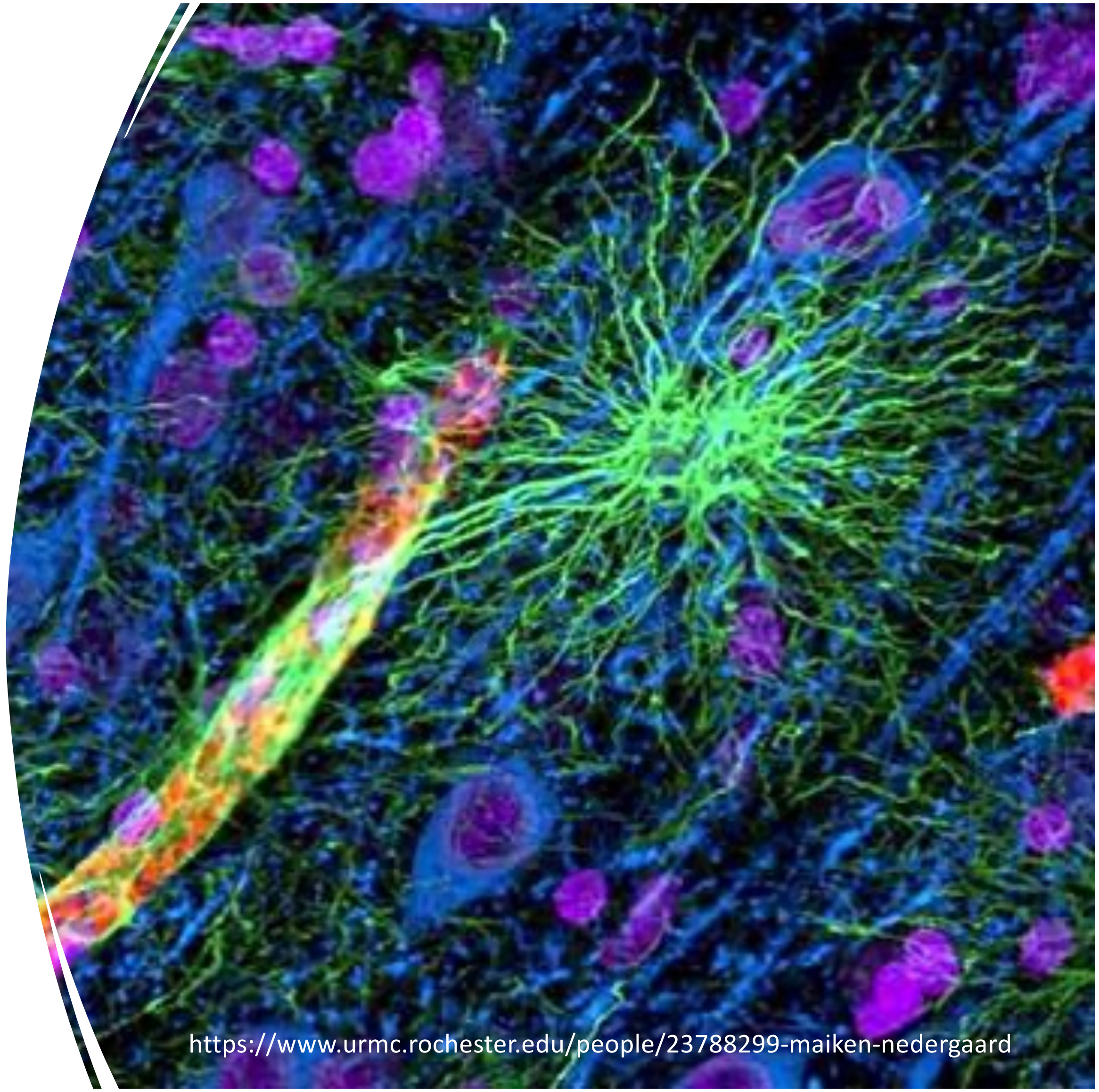
Colloque de la SSVQ

21 octobre 2022



Divulgation des conflits d'intérêts potentiels

Dr Leroux a reçu des honoraires professionnels en tant que conférencière, membre du comité aviseur et consultante des compagnies suivantes:

- Allergan/Abbvie
- Aralez Pharmaceuticals
- Eli Lilly Canada
- Lundbeck Canada
- Medscape
- McKesson Canada
- Miravo
- Novartis
- Teva Neuroscience
- Lin-pharmaceuticals
- Paladin pharma
- Impel Neuropharma

mastermind
Advancing Migraine Management in Primary Care

Calendrier Canadien des Migraines

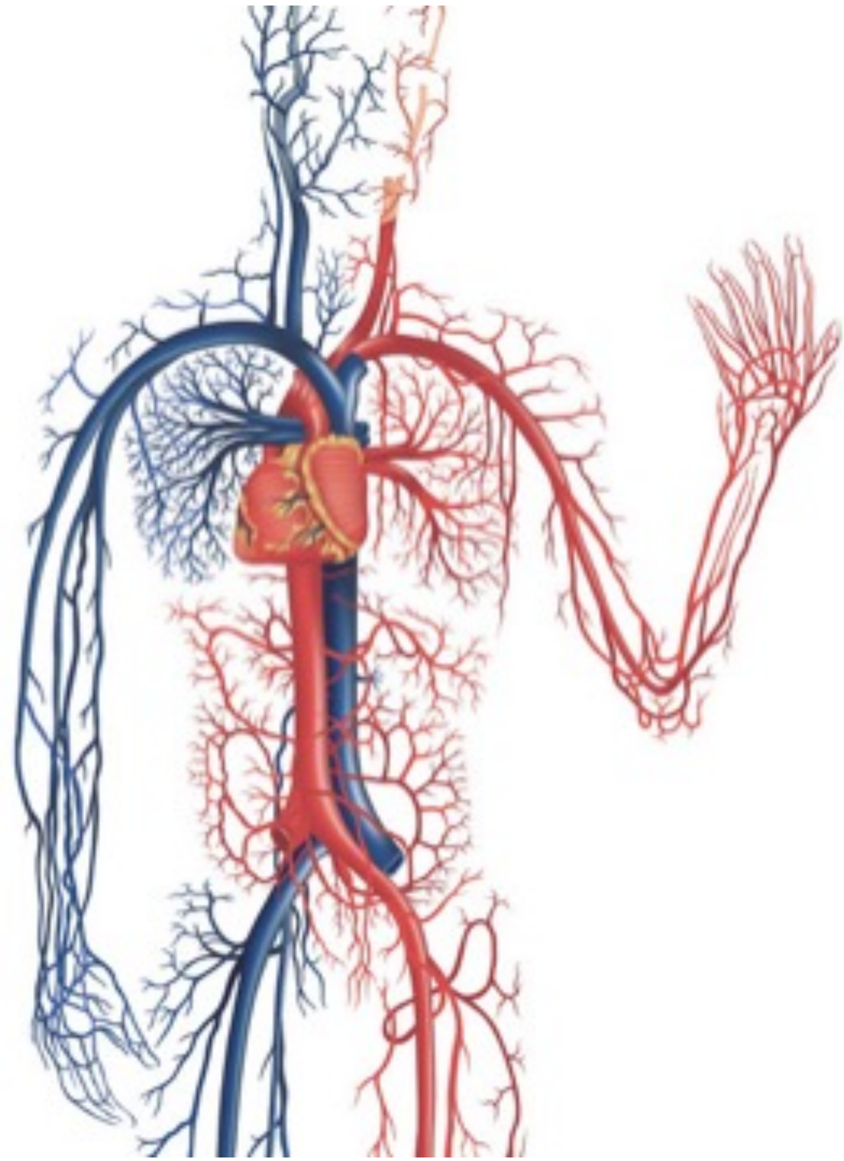
Canadian Headache Society

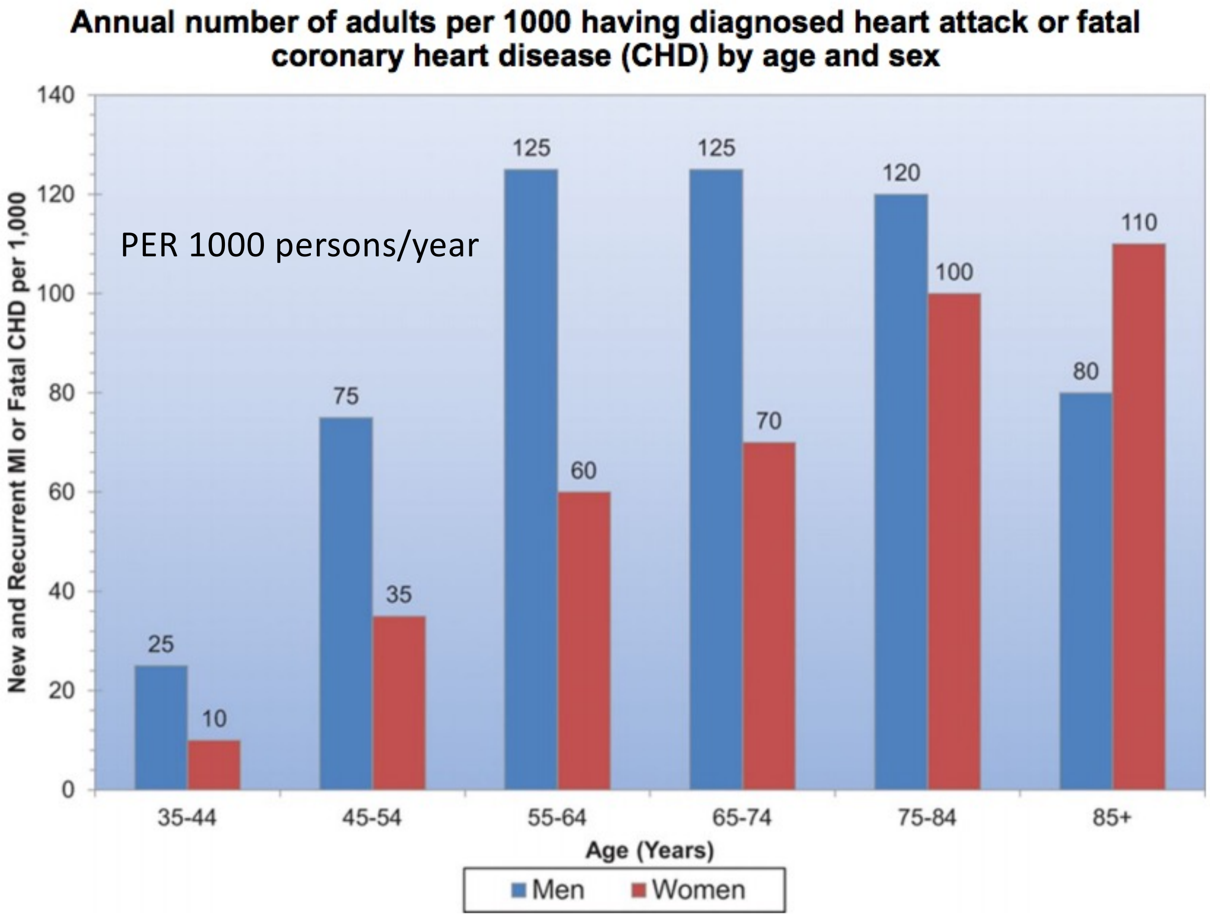
Migraine Canada

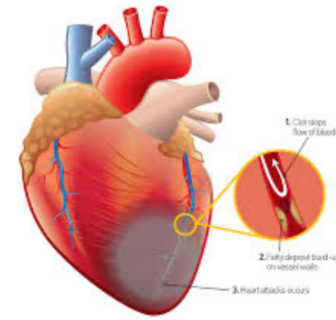
Migraine Québec
Mieux comprendre

Objectifs d'apprentissage

1. Réviser l'association entre migraine et maladie vasculaire.
2. Présenter les liens entre l'aura et l'AVC.
3. Discuter de l'utilisation des triptans, anticorps CGRP et gepants chez le patient avec maladie neurovasculaire.







Risque annuel d'évènement coronarien

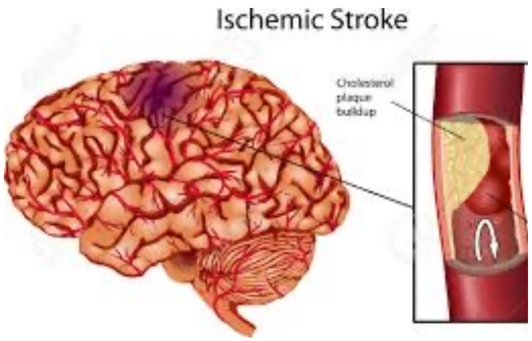
1-2% des adultes 35-44

3-12% des adultes 50-60-70

Atherosclerosis Risk in Communities Surveillance: 2005–2011 and Cardiovascular Health Study.

American Heart Association

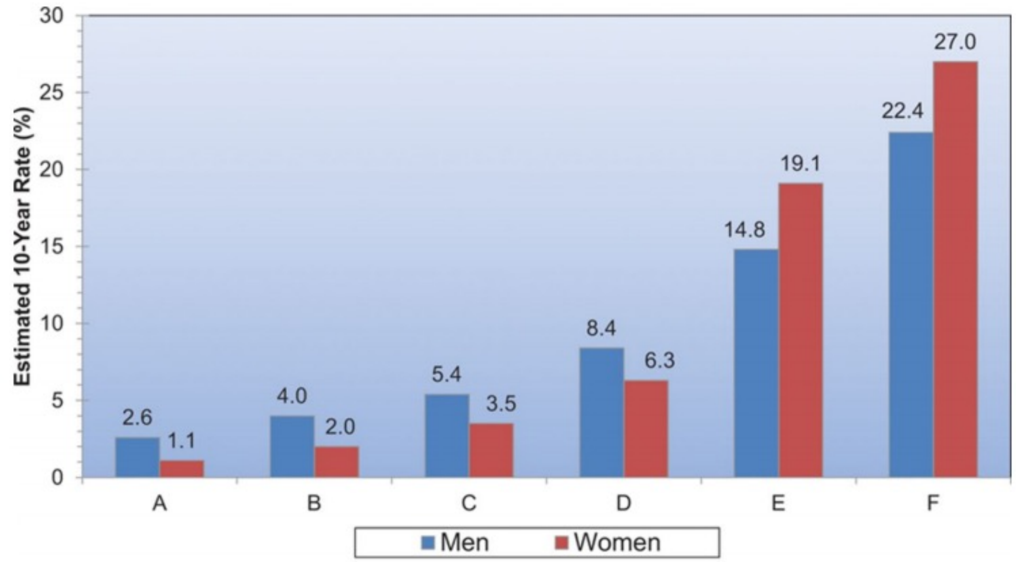
Mozaffarian D et al. Circulation. 2015;131:e29-e322



50aine en santé
Risque annuel/10 ans
1% à 2%

Tous les facteurs:
Risque annuel/10 ans
22 à 27%
F > M

Estimated 10-year stroke risk in adults 55 years of age according to levels of various risk factors (Framingham Heart Study).



	A	B	C	D	E	F
Blood Pressure*	95-105	138-148	138-148	138-148	138-148	138-148
Diabetes	No	No	Yes	Yes	Yes	Yes
Cigarette Smoking	No	No	No	Yes	Yes	Yes
Prior AF	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

* - Closest ranges for women are : 95-104 and 115-124.

American Heart Association.

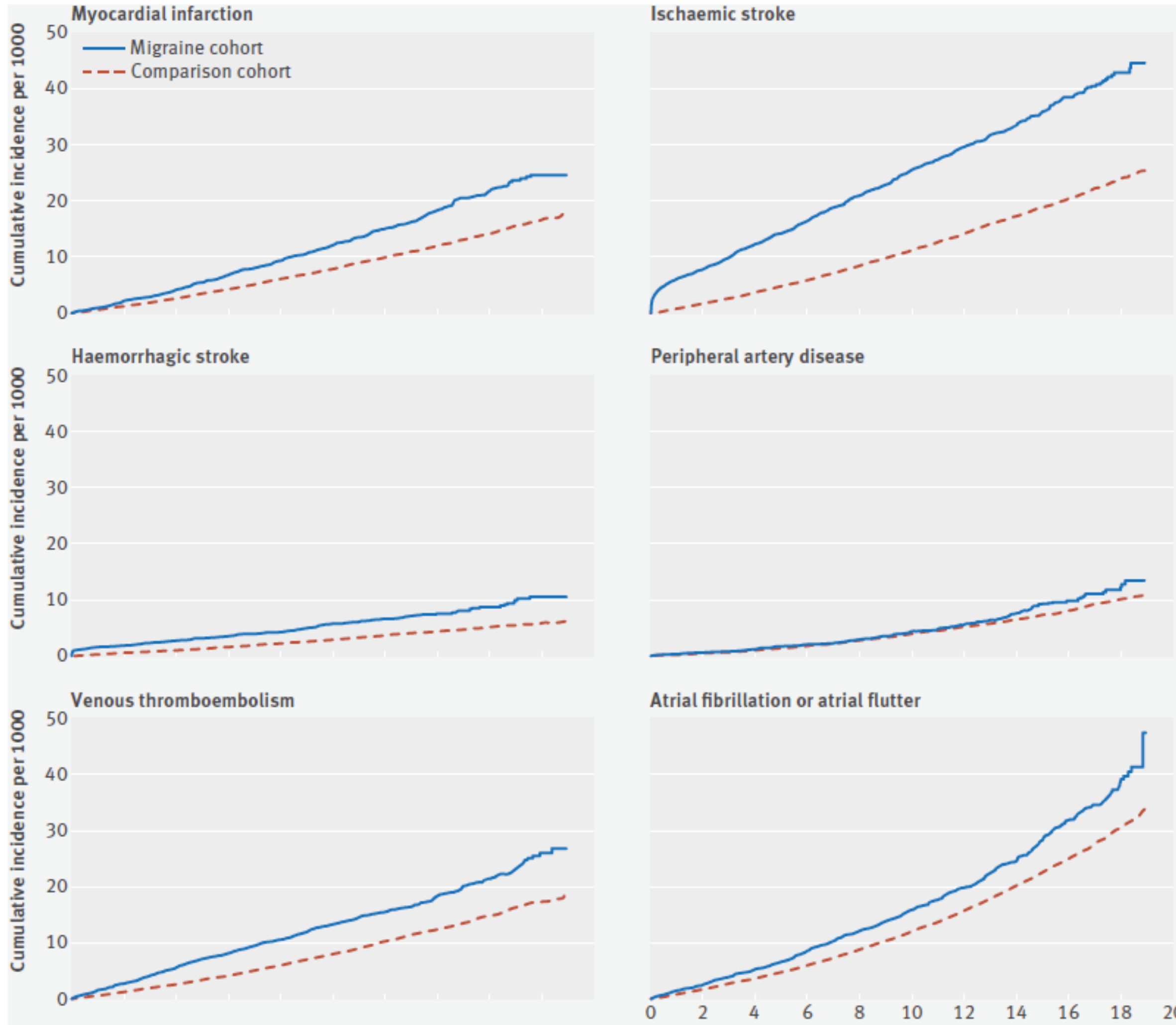
Mozaffarian D et al. Circulation. 2015;131:e29-e322

Migraine et maladie vasculaire

- Une méta-analyse de 2009 n'a trouvé aucune association entre la migraine et l'IDM (OR 1,12 ; IC à 95 % : 0,95-1,32), alors que les méta-analyses de 2015 et 2018 ont toutes deux montré une association, bien que modeste (1,23-1,33).

- Le risque d'IM associé à la migraine était cependant plus robuste (1,74 à 2,61) lorsque la migraine avec aura était considérée séparément.

Adelborg K, Szépligeti SK, Holland-Bill L, Ehrenstein V, Horváth-Puhó E, Henderson VW, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. Bmj. 2018;360:k96.



Migraine et maladie cardiovasculaire

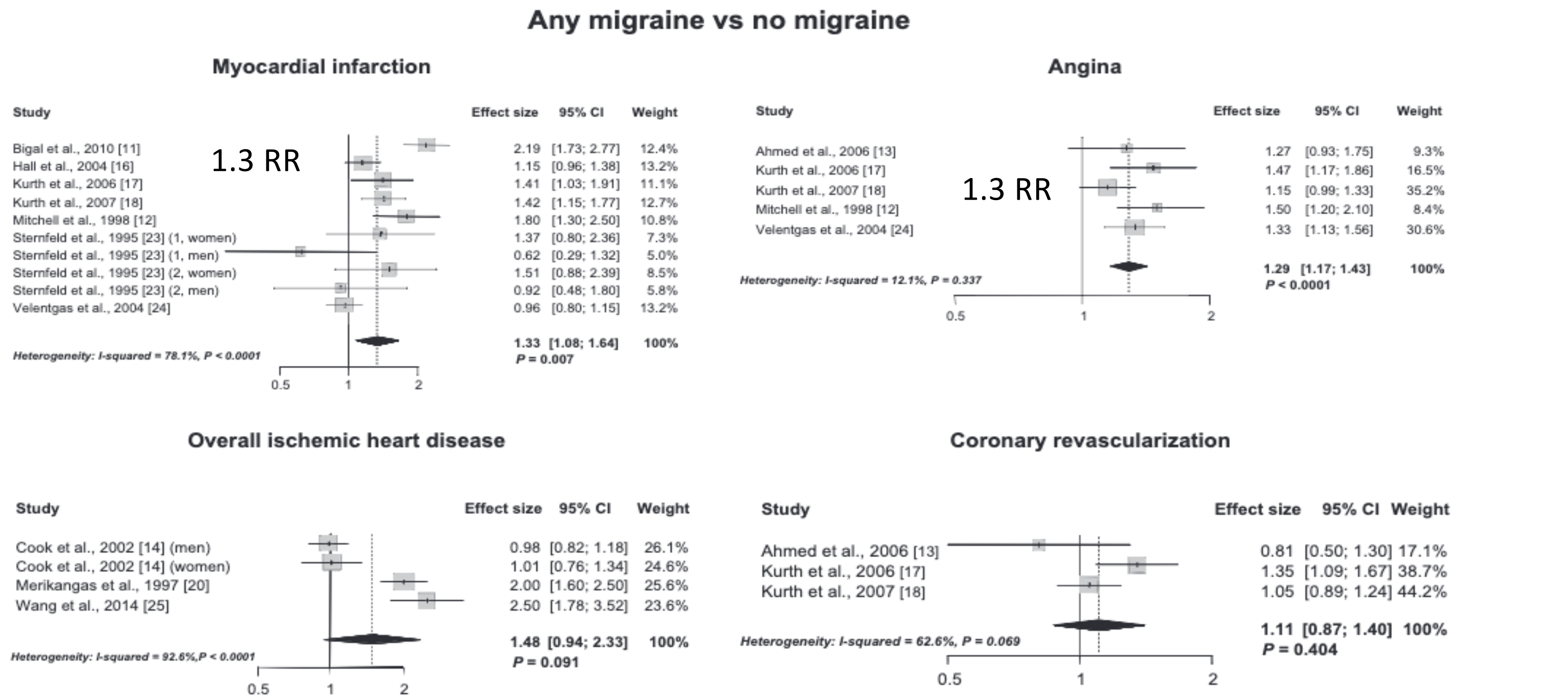
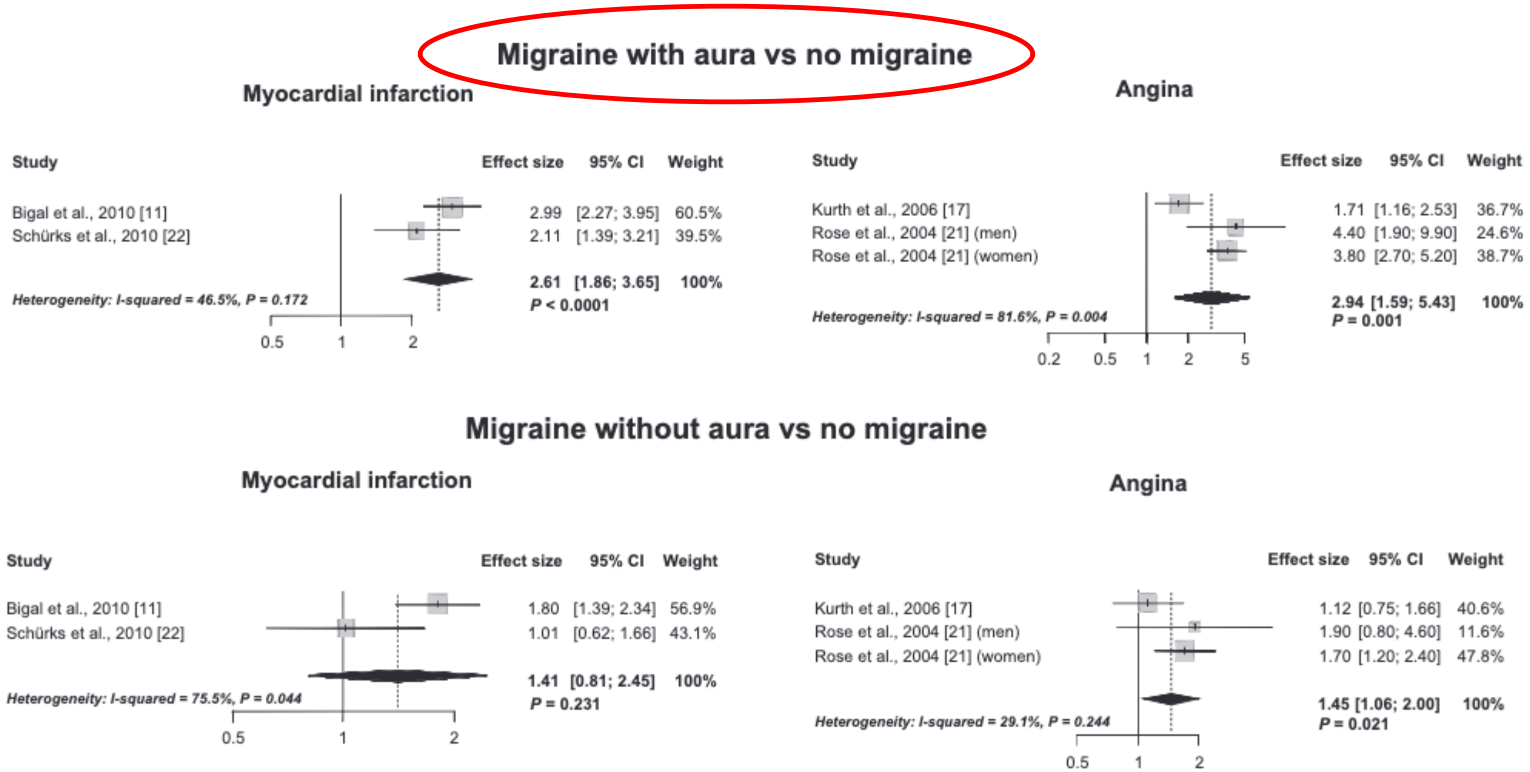


Figure 2 Adjusted effect estimates of myocardial infarction, angina, ischaemic heart disease and coronary revascularization in migraineurs versus non-migraineurs.

Sacco S, Ornello R, Ripa P, Tiseo C, Degan D, Pistoia F, et al. Migraine and risk of ischaemic heart disease: a systematic review and meta-analysis of observational studies. Eur J Neurol. 2015;22(6):1001-11.

Migraine et maladie cardiovasculaire



2-3 RR

Figure 3 Adjusted effect estimates of myocardial infarction and angina in subjects with migraine with aura or migraine without aura versus non-migraineurs.

Sacco S, Ornello R, Ripa P, Tiseo C, Degan D, Pistoia F, et al. Migraine and risk of ischaemic heart disease: a systematic review and meta-analysis of observational studies. Eur J Neurol. 2015;22(6):1001-11.

Risque annuel d'AVC chez la jeune femme

Facteurs de risque	Schürks BMJ Risque relatif	Incidence AVC ischémique /an/100 000
Femme	1	10
Femme migraineuse <45 >45	2 1.2 NS 3.6	20 36
Migraine avec aura	2-4	20-40
Migraine et tabac	9	90
Migraine et CO	7	70
Migraine + aura + tabac	10-17	100-170 disons 200 2% / 10 ans

Schwartz, Ann Int Med 1997, Kristensen, Stroke 1997, Groppo Neurol Sci 2011, Lidegaard NEJM 2012
Tietjen GE, Maly EF. Migraine and Ischemic Stroke in Women. A Narrative Review. Headache.2020;60(5):843-63.

Migraine et AVC ischémique

- La vaste majorité des publications recensées dans la littérature tendent à indiquer que la migraine sans aura n’est pas associée à l’AVC ischémique
- Une revue systématique a révélé que la migraine avec aura est associée à un risque de 2 à 3 fois plus élevé d’AVC ischémique
- L’augmentation du risque est particulièrement marquée chez :
  - les femmes
  - les personnes de moins de 45 ans
  - les fumeurs
  - les personnes prenant des contraceptifs oraux
- Des antécédents de migraine avec aura ne sont pas associés à une hausse du risque d’AVC chez les personnes plus âgées (> 60 ans)
- Une fréquence élevée d’auras (> 1/semaine) peut représenter un risque accru

Øie LR, *et al. J Neurol Neurosurg Psychiatry.* 2020;91:593-604.

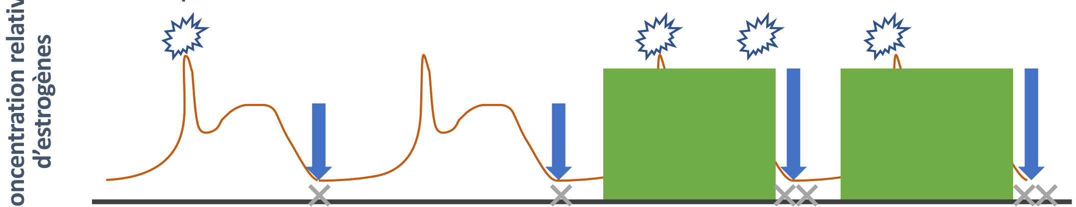
Choix de contraceptifs chez les femmes atteintes de migraines avec aura : justification

- L'allégation selon laquelle les contraceptifs oraux avec estrogènes sont contre-indiqués chez les femmes atteintes de migraines avec aura repose sur des **études peu récentes portant sur des doses relativement élevées d'éthinylestradiol**
- **Les données probantes à l'appui du risque d'AVC associé à une dose d'éthinylestradiol < 20 mcg sont peu convaincantes**
- Cela dit, dans une étude récente, un rapport de cotes de 6 a été attribué à la survenue d'AVC ischémiques chez les femmes atteintes de migraines avec aura utilisant des contraceptifs oraux combinés
- Même s'il est statistiquement significatif, **le risque absolu d'AVC associé à l'utilisation de contraceptifs oraux combinés demeure très faible :**
  à la base, les jeunes femmes sont en effet peu exposées aux AVC
  - De 15 à 19 ans = 1/100 000
  - De 40 à 49 ans = 30/100 000

Champaloux SW, *et al. Am J Obstet Gynecol.* 2017;216:489.e1-7; Øie LR, *et al. J Neurol Neurosurg Psychiatry.* 2020;91:593-604 1. Calhoun A. Combined hormonal contraceptives: is it time to reassess their role in migraine? Headache. 2012;52(4):648-60.

Supplément : utilisation d’un anneau vaginal chez les femmes atteintes de migraines menstruelles et de migraines avec aura

N = 23, anneau vaginal, 8 mois d’observation en moyenne, étude rétrospective



2 cycles menstruels suivis de la prise d’un contraceptif oral combiné à faible dose (contenant 35 mcg d’éthinylestradiol) **pendant 2 mois**

3 auras par mois, migraine menstruelle

Suppression de l’ovulation par la prise en continu d’un contraceptif hormonal combiné à très faible dose

0,23 aura par mois, diminution de 90 % de la fréquence des migraines menstruelles

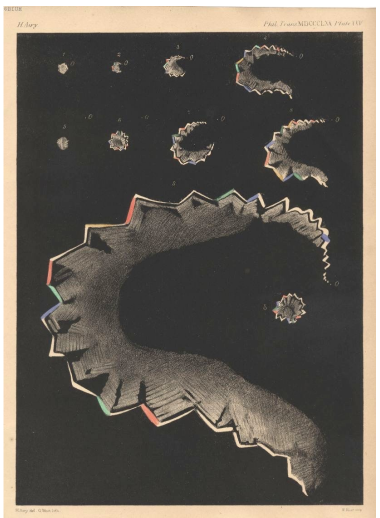
La stabilisation des taux d’estrogènes est bénéfique.

- Supprime les pics = moins d’auras
- Supprime les creux = moins de migraines menstruelles

Il s’agit d’une petite étude, mais elle est néanmoins intéressante.

Calhoun A. *Headache.* 2012;52(8):1246-53.

L’aura visuelle typique



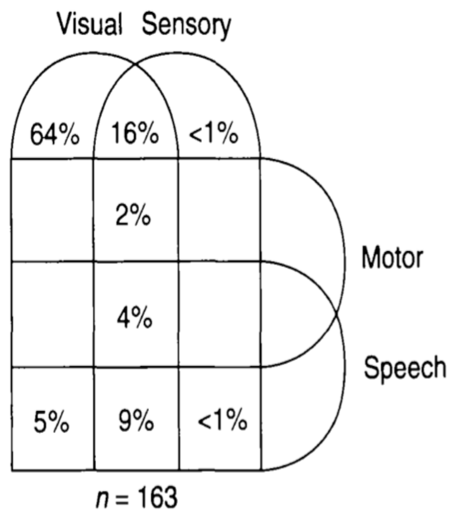
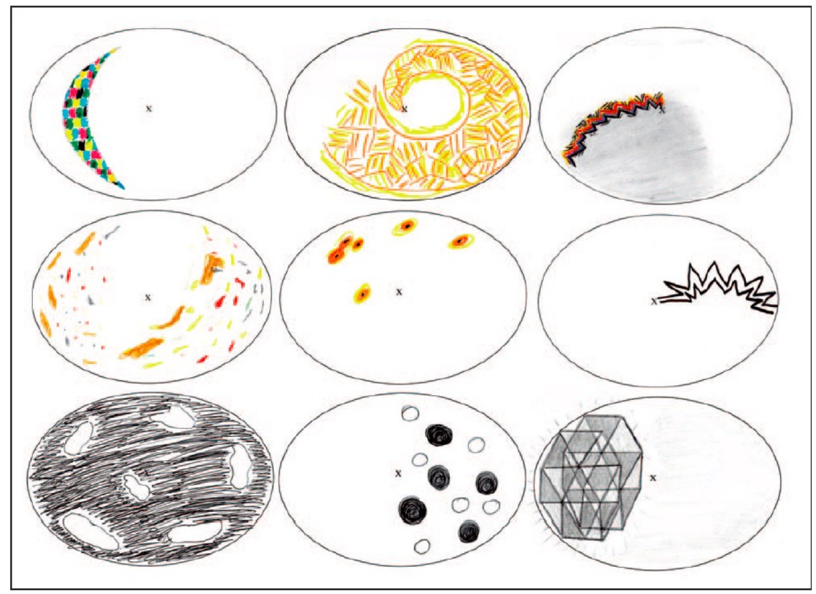


Fig. 1 Venn diagram illustrating the distribution of the various aura symptoms.

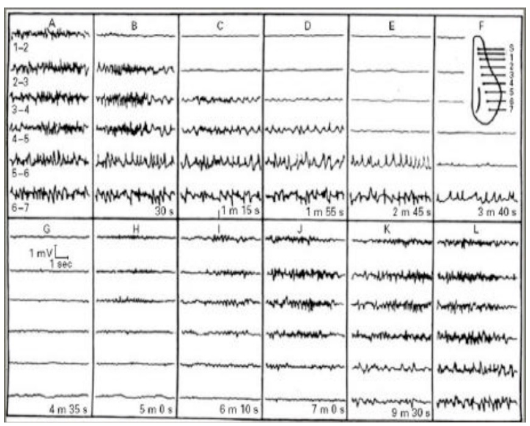


Typical fortification
Airy, 1870

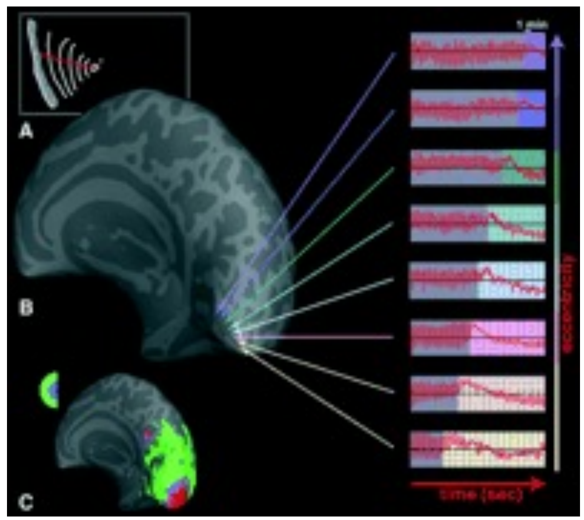
Visual and sensory sx
Russell, Brain 1996

Diversity of visual sx
Queiroz, 2001

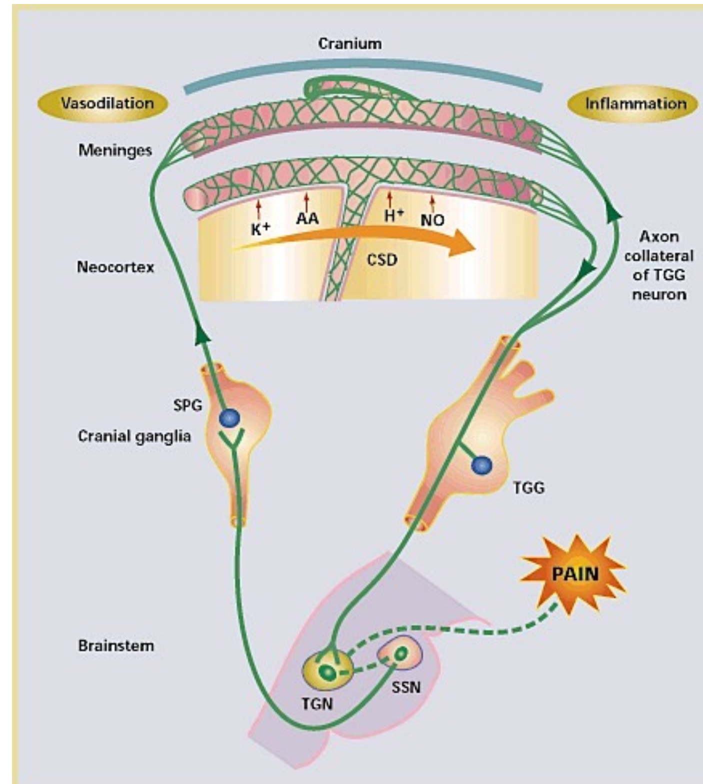
CSD = cortical spreading depression



CSD on a rabbit brain
Leao 1944



Evolution of BOLD signal during an aura, Hadjikhani 2001



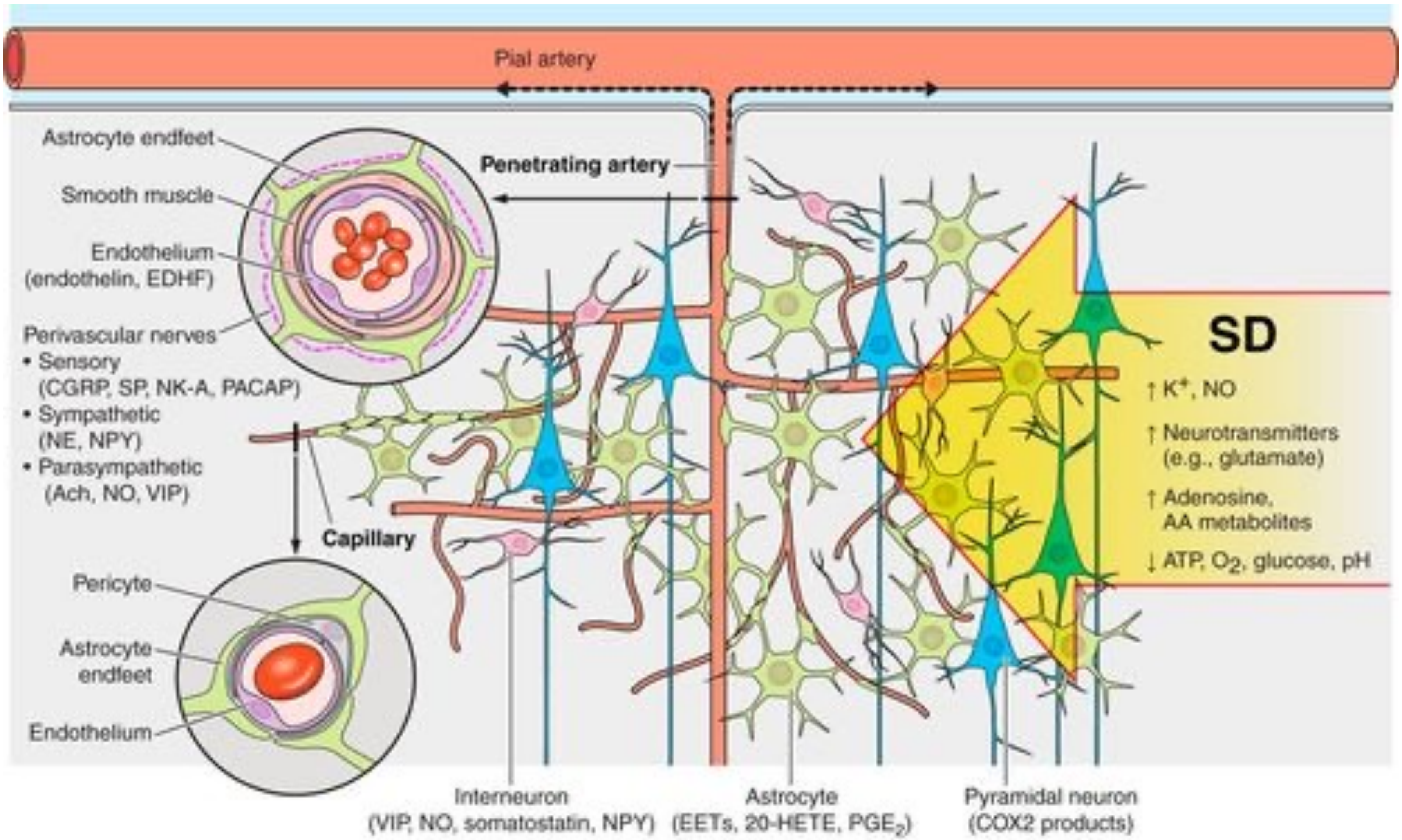
CSD activates the TNC
Bolay, Nature Med 2002

Conséquences de la CSD
(modèles animaux)

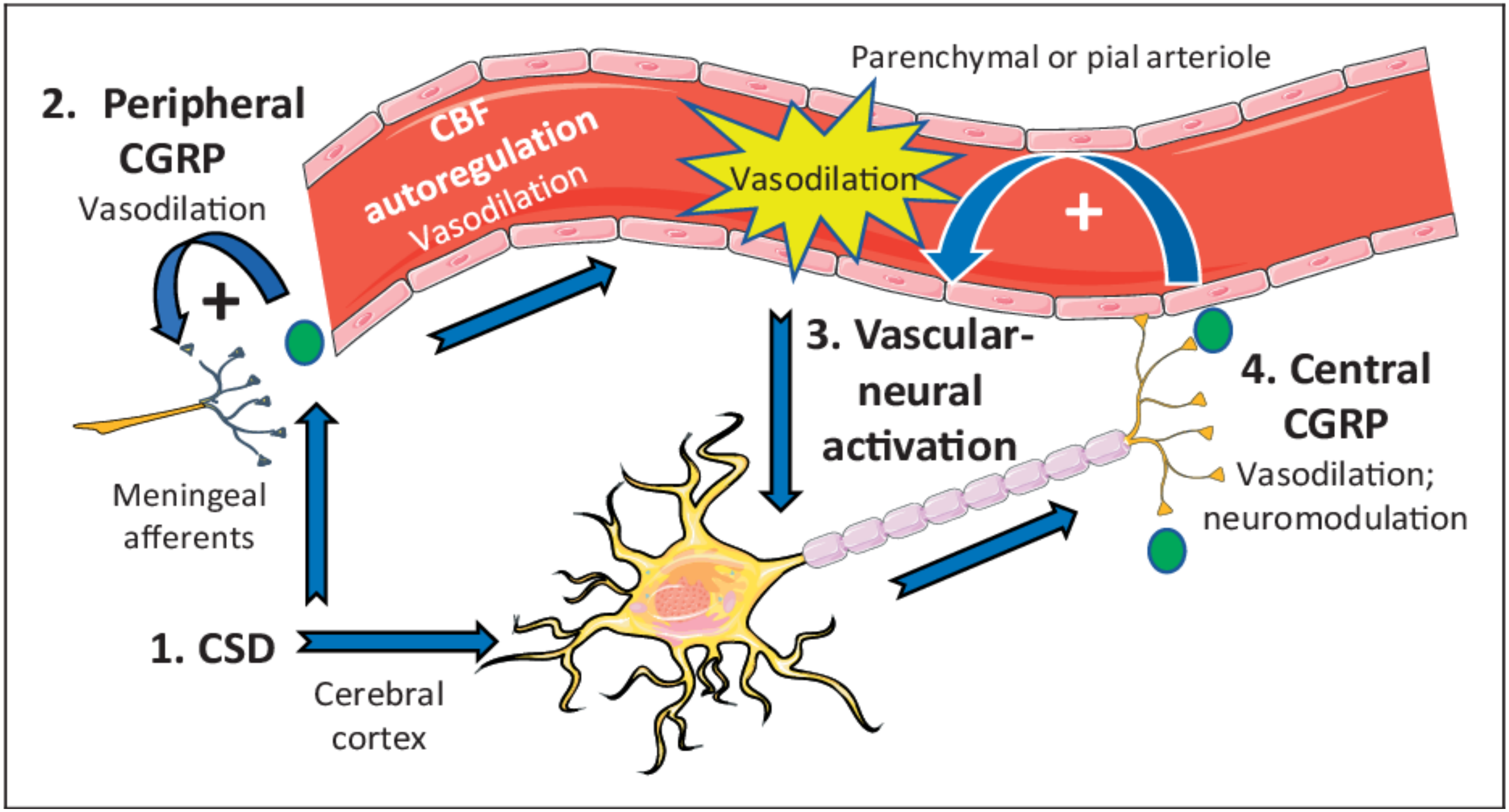
- Perte des gradients ioniques
- Œdème cellulaire
- Bris de la barrière hémo-encéphalique
- Extravasation de protéines
- Activation des afférents nociceptifs
- Diminution de l’activité neuronale
- Modification du flot sanguin

- Baisse du flot sanguin
  - (Lauritzen 1983, Sanchez Del Rio Cephalalgia 1999)
- Besoins en glucose non comblés
  - (Hashemi J Cereb Blood Flow 2009)
- Extraction O2 augmentée
  - (Friberg Stroke 1994, Piilgaard J Cereb Blood Flow 2009)

Obrenovitch, Neuroimage 2009 Ayata, Cephalalgia 2009 Busija, Prog Neurobiol 2009



https://journals.physiology.org/doi/full/10.1152/physrev.00027.2014



Close LN, Eftekhari S, Wang M, Charles AC, Russo AF. Cortical spreading depression as a site of origin for migraine: Role of CGRP. *Cephalalgia*. 2019;39(3):428-434. doi:[10.1177/0333102418774299](https://doi.org/10.1177/0333102418774299)

Présenter les liens entre l’aura migraineuse et l’AVC.

La migraine avec aura est associée à de multiples facteurs de risque d’AVC

- Hypertension
- Hyperlipidémie
- Diabète sucré
- Tabagisme
- Fibrillation auriculaire
- Foramen ovale perméable

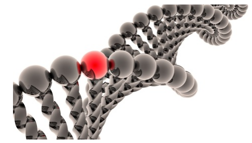
Tietjen GE, Maly EF. Migraine and Ischemic Stroke in Women. A Narrative Review. Headache.2020;60(5):843-63

Table 1.—Factors Independently Associated With Migraine With Aura and With Migraine With Aura-Associated Ischemic Stroke

Migraine With Aura	Migraine With Aura-Associated Ischemic Stroke
Venous thromboembolism	Female sex
Elevated cholesterol	Visual aura
Diabetes mellitus	Increased migraine frequency
Hypertension	Age < 45 years old
Cigarette smoking	Cigarette smoking
Combined hormonal contraception use	Combined hormonal contraception use
Pregnancy, preeclampsia	Pregnancy, preeclampsia
Patent foramen ovale, atrial septal aneurysm	Patent foramen ovale, atrial septal aneurysm
Atrial fibrillation (incident)	Non-PFO related cardioembolic stroke
Endothelial activation markers	Thrombophilia
Subclinical brain lesions	Perioperative state

Différentes sortes de CSD

Gènes



PHACTR1

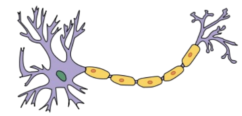
NOTCH3
(arteriopathie)

MELAS
(mitochondriopathie)

FHM
(channelopathie)

Dissection
Risque x 2 si migraine

Stress oxydatif



Dysfonction endothéliale

FOP embolie
Pop 25%
Crypto stroke 50%
MA 50%

Hypercoagulabilité

Aggrégation plaquettaire

Facteurs de risque
vasculaires

CSD: augmente les besoins énergétiques
Active les métalloprotéinases, ouvre la BBB, ferme le système glymphatique

Aura

«AVC migraineux»

Crise migraineuse

AVC

PHACTR1 may link migraine, CAD and dissection

Coronary artery disease
C4D

Study	Cases	Controls
PROCARDIS	5,720	4,381
HPS	2,704	2,887
PROMIS	4,255	4,098
LOLIPOP	2,741	3,696
Total	**15,420**	**15,062**

↔

Migraine
IHGC

For comparison with C4D			For comparison with CARDIoGRAM	
Cases	Controls	Study	Cases	Controls
		Clinic-based studies		
1,032	3,513	Finnish MA	1,032	3,513
997	1,105	German MA	997	1,105
1,208	2,564	German MO	1,208	2,564
820	4,774	LUMINA MA	820	4,774
1,118	2,016	LUMINA MO	1,118	2,016
		Population-based studies		
3,134	5,103	ALSPAC	3,134	5,103
1,683	2,383	Australia ATM	1,683	2,383
2,139	34,617	deCODE		
330	1,216	ERF	330	1,216
189	580	FinnTwin	189	580
1,608	1,097	HUNT	1,608	1,097
757	4,399	NFBC1966	757	4,399
282	2,260	NTR&NESDA	282	2,260
351	1,647	Rotterdam III	351	1,647
972	3,837	TWINS UK	972	3,837
5,122	18,108	WGHS	5,122	18,108
378	2,065	YoungFinns	378	2,065
22,120	**91,284**	**Total**	**19,981**	**56,667**

↔

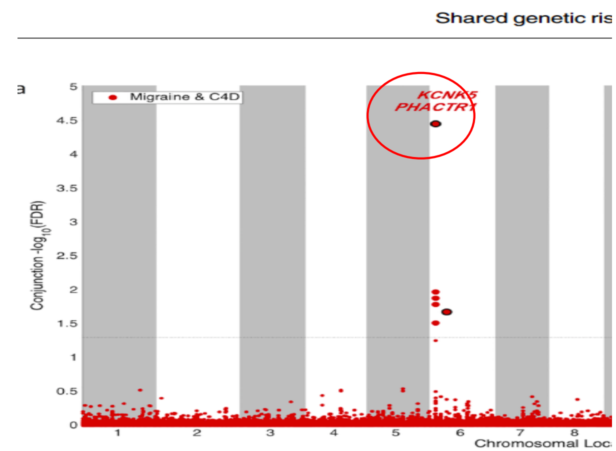
Coronary artery disease
CARDIoGRAM

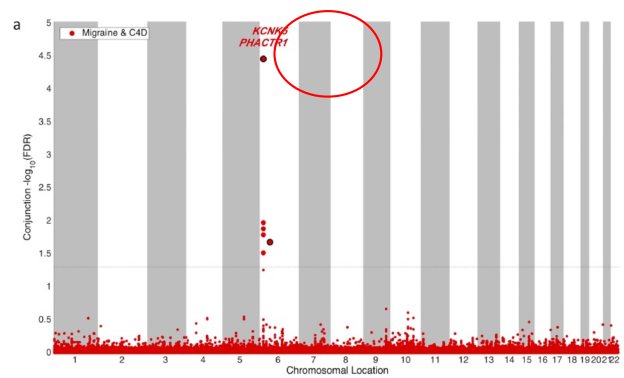
Study	Cases	Controls
ADVANCE	278	312
CADomics	2,078	2,952
CHARGE	2,287	22,024
deCODE CAD	6,640	27,611
GERMIFS I	884	1,604
GERMIFS II	1,222	1,287
GERMIFS III (KORA)	1157	1748
LURIC/ AtheroRemo 1	652	213
LURIC/ AtheroRemo 2	486	296
MedStar	874	447
MIGen	1,274	1,407
OHGS1	1,542	1,455
PennCATH	933	468
WTCCC	1,926	2,938
Total	**22,233**	**64,762**

Fig 1. Overview of the included studies.

https://doi.org/10.1371/journal.pone.0185663.g001

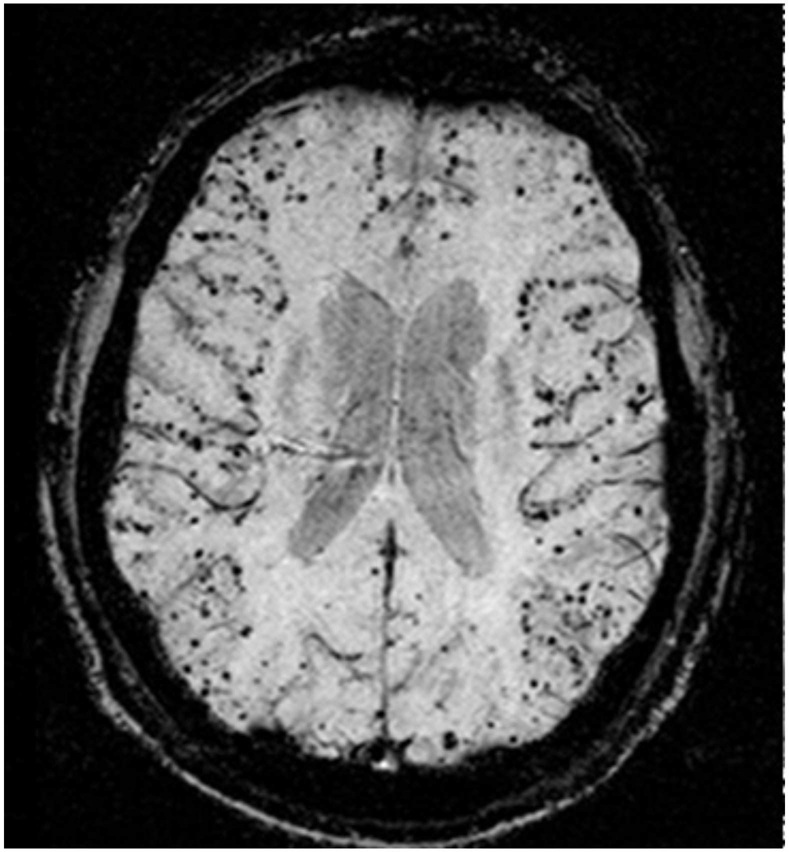
Winswold, Shared genetic risk between migraine and coronary artery disease: A genome-wide analysis of common variants, PLOS One 2017





Pathologies aigües associées aux auras (En clinique)

- Angiographie (Whitty 1986)
- Dissection (Olesen 1993, Silverman 1998)
- Thrombose veineuse (Bousser 2007)
- Echo avec microbulles
- HSA corticale (Dodick 2009)
- Interventions cardiaques



CSD, embolies, ischémie: une étude majeure

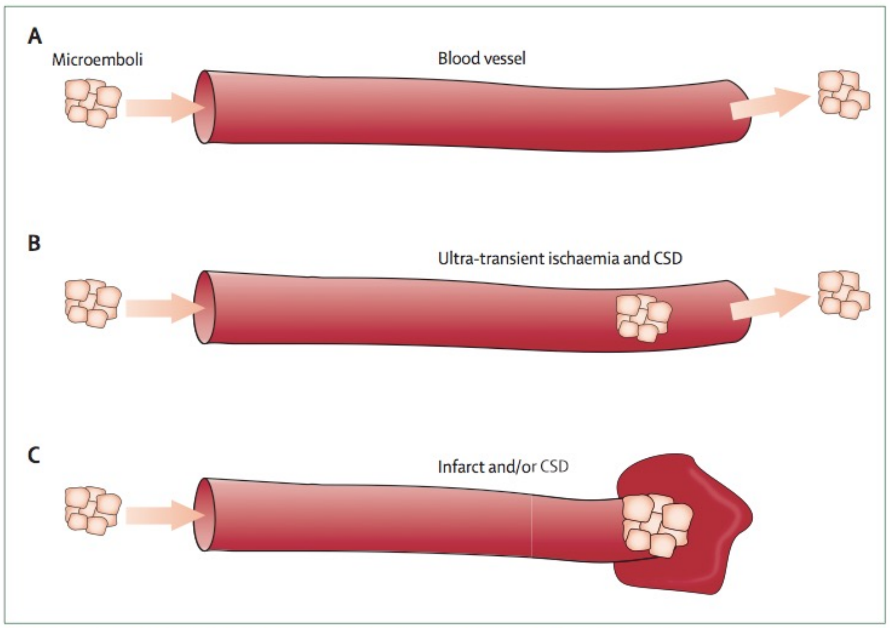


***Figure 3:* The risk of developing CSD after microembolisation partly depends on the location, size, and duration of vascular occlusion**
Although some microemboli can traverse the brain microcirculation without pathophysiological consequence (A), other microemboli can transiently occlude the circulation to a critical volume of tissue to initiate CSD (B) followed by recovery; more prolonged occlusion (C) will cause tissue microinfarction. CSD=cortical spreading depression.

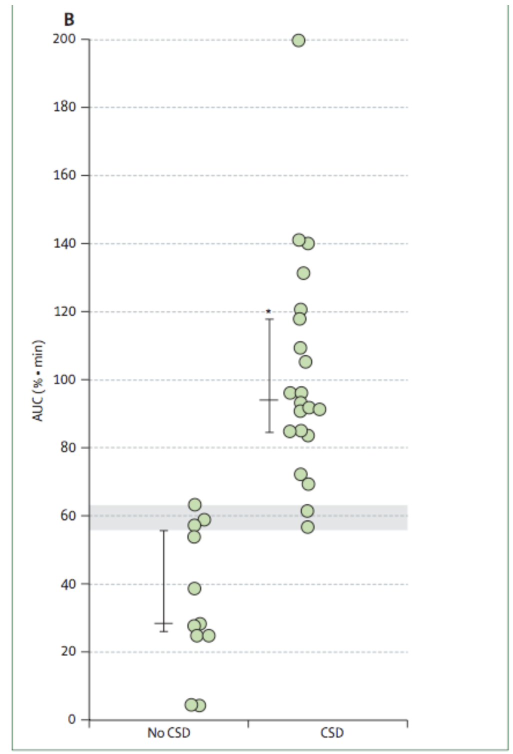


***Figure 2:* Association between CSD and CBF**

Dalkara, Lancet Neurology 2010

Aura ou ICT?

	Aura	ICT
Patient	Puberté, jeune adulte	Plus âgé Facteurs risque vasculaire
Progression	Evolue lentement	Soudain
Durée	< 1h (20-30 min typique)	En général <60 min
Relation avec la céphalée	Précède	Non spécifique
Symptômes visuels	99% des auras Sx POSITIFS	% des ICT Sx NÉGATIFS
Symptômes sensori-moteurs	Associés à sx visuels	Peuvent être isolés
Fréquence	Multiples stéréotypés Tempête d'auras	Un épisode ou plusieurs différents (embolies)

MacGregor, Dodick, ABC of headache, Blackwell 2009

La migraine avec aura augmente le risque d'évènements neurovasculaires de différents types

		MA	MO
Any stroke	Mahmoud 2018	1.56 (1.30-1.87)	1.11 (0.94-1.31)
Ischemic stroke	Etminan Schurks Spector	2.27 (1.61-3.19) 2.16 (1.53-3.03) 2.25 (1.53-3.33)	1.83 (1.06-3.15) 1.23 (0.90-1.69) 1.24 (0.86-1.79)

Magalhaes, Headache Current 2018

Incidence /100/year	**MA 463**	**MO 1 159**	**No headache 10 053**
Any stroke	0.4	0.2	0.3
Thrombotic	0.2	0.14	0.14
Cardioembolic	0.13	0.039	0.09
Lacunar	0.065	0.03	0.066
Unadjusted HR	1.4 (1.0-2.0)	1.47 (1.0-2.0)	
Adjusted HR	1.67 (1.1-2.4)	1.2 (0.8-1.7)	

Androulakis, Neurology 2016

Aura sans céphalée dans l’étude Framingham

- 2110 patients, questionnaire ciblé sur les sx visuels
- 186 patients: AVC, ICT, ophtalmologique, inconnu etc.
- 1.2% dx “migraine” (n = 26)
- Age moyen 56 years, 65% femmes
- 60% sans aucune céphalée
- Durée 15-60 min (50%) ou moins (27%)
- > 10 épisodes chez 70% des patients

Wijman CA, Wolf PA, Kase CS, Kelly-Hayes M, Beiser AS. Migrainous visual accompaniments are not rare in late life: the Framingham Study. Stroke. 1998;29(8):1539-43.

Pronostic des auras sans céphalées vs ICT

	Dennis **JNNP 1992**	**Wijman** **Stroke 1998**	**Tuna** **October 2013 abstract**
N patients (aura/stroke) Lenght of FU	50/50 Mean 4,5 years	26/87 2,2 years	158 > 3 months
Stroke risk (Aura)	2%	11,5%	1,2% 1.1% / pt / year
Stroke risk (TIA)	10%	33%	Aura/ICT HR 0,23
Risk in the whole cohort	NA	13%	0,4% /pt / year NS

Qui sont ces patients ? (hx de migraine, facteurs de risque vasculaire, etc.)
Doit-on les investiguer ? Doit-on les traiter ?

Ce ne sont PAS des auras

- Prodrome: symptômes prémonitoires
  - Envie de sucré, bâillements, irritabilité
- Photophobie
- Symptômes visuels autres
  - Points blancs, points noirs, brefs (secondes)
  - Taches de couleur…les yeux fermés
  - Flottants
  - Vison brouillée
  - Neige visuelle (visual snow)

- ICT
- Épisodes fonctionnels
- Symptômes vestibulaires
- Symptômes neurologiques autres

Migraine avec et sans aura…
S'agit-il de catégories bien séparées?

- La majorité des patients ont aussi MO
- Les deux coexistent en proportion variable
- Les patients MA peuvent avoir des auras isolées
- L'aura sans mal de tête existe

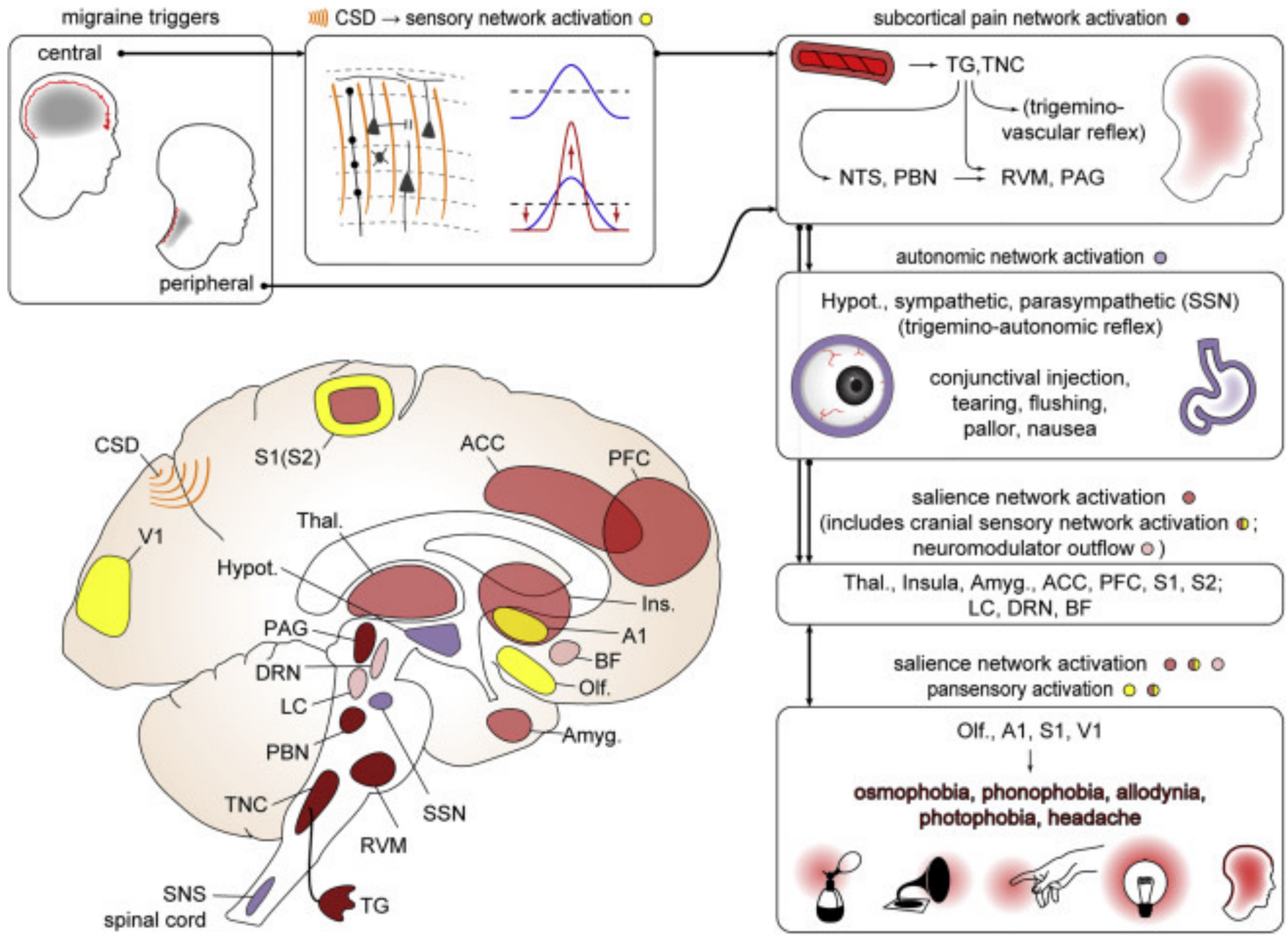
Que trouverions-nous si nous étudiions la « migraine pure avec aura » ?

	Observations from studies	
Coexistence or MO and MA	4% 13% 35%	Russell 1996 Launer 1999 Kelman 2004
Aura without headache in MA patients	12% 44% 6% 30% 37%	Alvarez 1960 Ziegler 1990 Stang 1992 Kelman 2004 Eriksen 2004
Aura without headache in the population	1% 1.23%	Rassmussen 1991 Wijman 1998

Physiologie de la CSD et aura: typique et atypique

Clinical manifestations CONSISTENT with the CSD physiology	Clinical manifestations NOT consistent with the CSD physiology
Matches retinotopic organization of visual cortex	Bilateral aura symptoms
Gradual progress of aura symptoms	No progression Visual + sensory simultaneous
Contralateral headache	Ipsilateral headache
The aura precedes the headache in a typical fashion	The occurrence of aura and headache without any temporal relationship
Spreading hypoperfusion at a rate within established CSD limits	CSD associated vascular reactivity changes do not match the rCBF/BOLD alterations detected in migraine patients

Bolay H, Vuralli D, Goadsby PJ. Aura and Head pain: relationship and gaps in the translational models.
J Headache Pain. 2019;20(1):94.



Brennan KC, Pietrobon D. A Systems Neuroscience Approach to Migraine. Neuron. 2018;97(5):1004-21.

Discuter de l'utilisation des triptans, anticorps CGRP et gepants chez le patient avec maladie neurovasculaire.

Médication
AINS
Triptans
DHE
Anticorps CGRP
(Ditans)
Gepants

Patient
Facteurs de risque vasculaires
Évènements vasculaires
Malformations vasculaires
Auras complexes, hémiplégiques
SVCR / ATCD de SCVR
CADASIL
Hypercoagulabilité

Devrais-je prescrire le medicament X au patient Y?

- Quel est le risque d’évènement vasculaire chez ce patient?
- Est-ce que la migraine influence ce risque?
- Est-ce que le traitement influence le risque?
- Est-ce que le bénéfice en vaut la peine?
- Qui prend la decision?
- Quel est mon type de gestion du risque?
- Quel est le type de gestion de risque du patient?

AINS
Risque vasculaire coronarien

87 studies
27 million patients

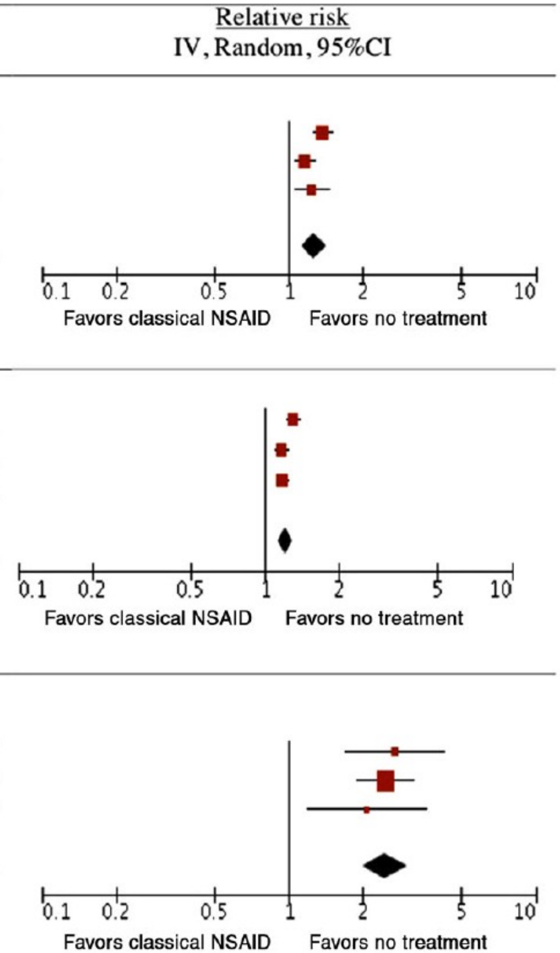
Confirm (modest) risk of coxibs

Also a risk of classical NSAIDs

Risk is dose dependent.
Occasional use unlikely to increase risk.

NO risk associated with «low» dose of
- Celecoxib
- Etoricoxib
- Ibuprofen
- Naproxen

COX 2 inhibitor	N° of studies	Relative risk (95% CI)
Cerebrovascular events		
Diclofenac	12	1.37 (1.26-1.49)
Ibuprofen	14	1.16 (1.05-1.29)
Naproxen	13	1.24 (1.05-1.47)
Subtotal	15	1.26 (1.12-1.41)
Heterogeneity: Tau²=0.04; Chi²=231.22, df=44 (P<0.00001); I²=81%		
Test for overall effect: Z=5.84 (P<0.00001)		
Cardiac events		
Diclofenac	27	1.30 (1.23-1.37)
Ibuprofen	30	1.17 (1.10-1.23)
Naproxen	31	1.17 (1.11-1.23)
Subtotal	31	1.21 (1.13-1.30)
Heterogeneity: Tau²=0.01; Chi²=421.37, df=106 (P<0.00001); I²=75%		
Test for overall effect: Z=11.48 (P<0.00001)		
Vascular events		
Diclofenac	3	2.68 (1.70-4.22)
Ibuprofen	3	2.46 (1.89-3.20)
Naproxen	3	2.07 (1.19-3.59)
Subtotal	3	2.44 (1.98-3.02)
Heterogeneity: Tau²=0.04; Chi²=28.42, df=8 (P=0.0004); I²=72%		
Test for overall effect: Z=9.75 (P<0.00001)		



Martin Arias, Cardiovascular Risk of Nonsteroidal Anti-inflammatory Drugs and Classical and Selective Cyclooxygenase-2 Inhibitors:A Meta-analysis of Observational Studies, J Clin Pharm 2018

Les triptans et les artères coronaires

- Induisent une VC coronaire modeste
- Études de cas rapportés, même chez patients sans ATCD
- Incidence d'évènements dans les études: 1/100 000 (pts choisis)
- Études de cohorte = risque minimal (risque visible pour ergotamine) même chez pts avec FRV
- Étude récente: risque plus élevé pour opioïdes et AINS

Conclusion: risque coronarien minimal mais existant

** Voir diapos supplémentaires en fin de présentation

Leroux E, Rothrock J. Triptans for Migraine Patients With Vascular Risks: New Insights, New Options. Headache. 2019;59(9):1589-96.

Triptans: effets sur la vasculature cérébrale

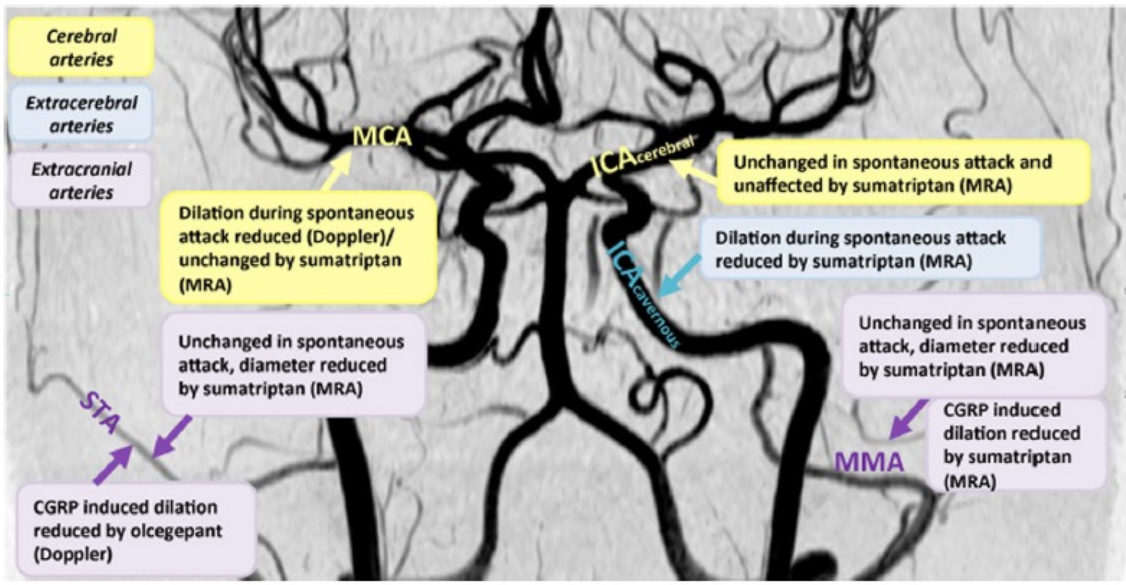


Fig. 1 Effects of sumatriptan and olcegepant on cranial vessels in migraine patients. The intracerebral vessels, the middle cerebral artery (MCA) and the cerebral part of the internal carotid artery ($ICA_{cerebral}$), are both shown in yellow. The extracerebral artery, the cavernous part of the internal carotid artery ($ICA_{cavernous}$), is shown in blue. The extracranial vessels, the middle meningeal artery (MMA) and the superficial temporal artery (STA), are both shown in purple. Boxes include description of vessel reactivity during spontaneous and/or CGRP induced attacks as well as vessel response to sumatriptan and/or olcegepant. Imaging modality indicated in parentheses in boxes; magnetic resonance angiography (MRA) or transcranial ultrasound Doppler (Doppler). Image from MRA of healthy volunteer kindly provided by Faisal M Amin

Benemei, JHP 2017

Triptans et AVC: résumé

- Effet sur circulation cérébrale controversé
- Pas d'étude de cas dans la littérature

Conclusion: la contre-indication en lien avec l'AVC peut être remise en question.

Leroux E, Rothrock J. Triptans for Migraine Patients With Vascular Risks: New Insights, New Options. Headache. 2019;59(9):1589-96.

Agoniste 5HT1F : Lasmiditan

Triptans with similar 5HT1F affinity:
Suma, Zolmi, Nara, Almo

Triptans/ergots with lower 5HT1F affinity:
Ergotamine, Riza, Frova

5HT1B:
In blood vessels, vasoconstrictive, not the only mechanism

5HT1D:
Pure agonist does NOT treat acute migraine
Lasmiditan inhibits CGRP release in mouse (AHS 2018 abstract)

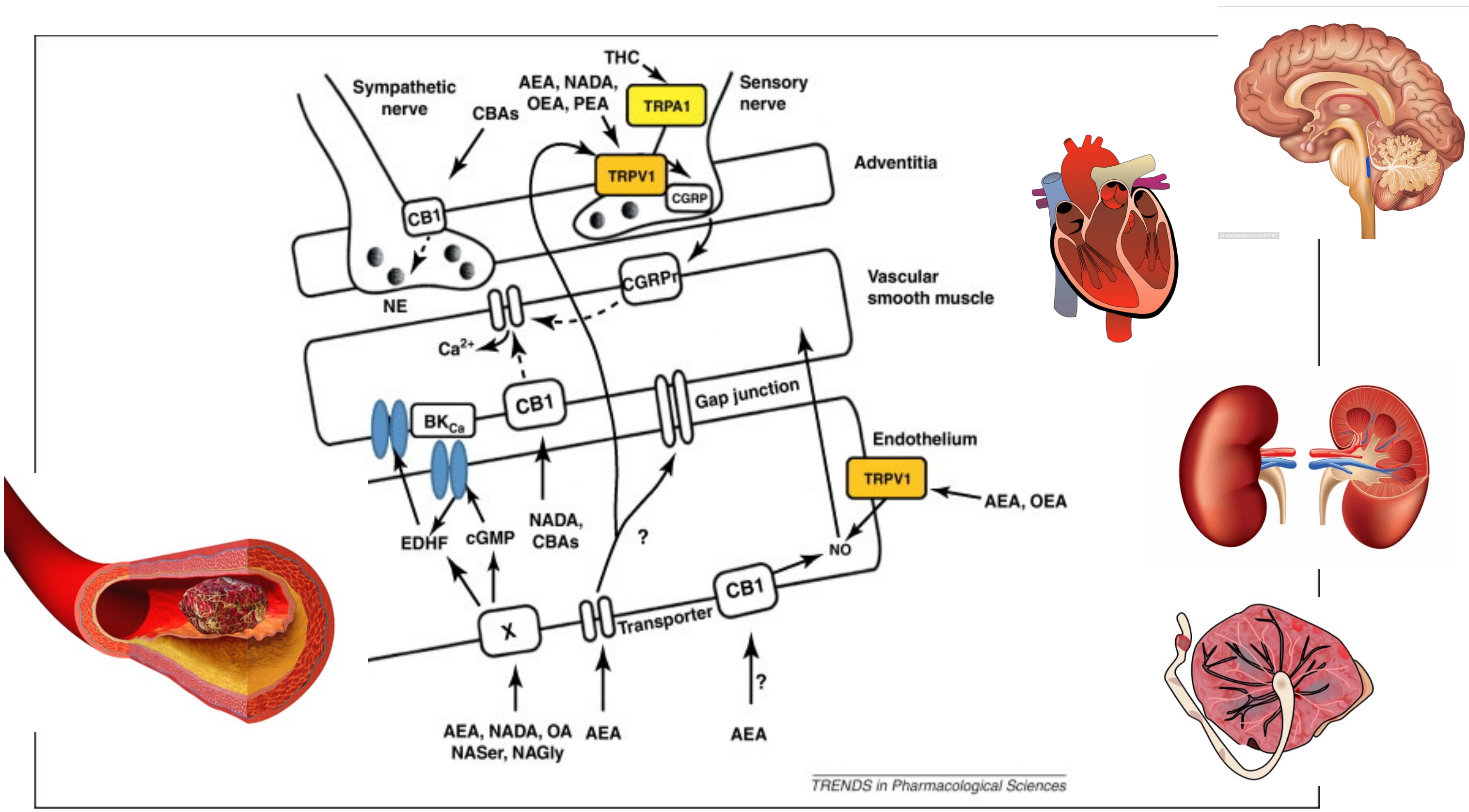
5HT1F:
CNS and cerebral arteries, inhibit protein extravasation and modulate TGV system

Challenge	Will provide an advantage?
Triptan non responders and failure	Unlikely
Medication overuse	?
Vascular contra-indication	Probably SAFE No vasoconstriction
Drug coverage issues	Probably more costly
Administered with CGRP MABs	Act on serotonin Cross BBB

MaassenvandenBrink abstract AHS 2018

Rubio-Beltran 2018, SAMURAI, SPARTAN

CGRP et la vasorégulation
Un système complexe avec de nombreux acteurs



Montecucco at al., Trends in Pharmacol Sciences 2012; 33(6):331-40

De nombreux essais cliniques sur les AcM CGRP avaient des critères d'exclusion spécifiques aux maladies et facteurs de risque cardiovasculaires (CV)

	Critères d'exclusion CV
Érénumab	
Essais de phase 2 (migraine épisodique/chronique)[1] Essai de phase 2a (capacité d'exercice)[1–2] ARISE/STRIVE[3–4]	*Tous les essais :* Infarctus du myocarde (IM), accident vasculaire cérébral, accident ischémique transitoire (AIT), angine instable, pontage aortocoronarien ou autre intervention de revascularisation dans les 12 mois précédant la sélection L'essai de phase 2a incluait seulement des patients à risque CV élevé (100 % des patients présentaient une maladie cardiovasculaire; 40 % des patients avaient des antécédents d'infarctus du myocarde).
Galcanézumab	
EVOLVE-1[5] EVOLVE-2[6]	Avoir subi des ECG montrant des anomalies associées à des événements CV aigus et/ou à un risque CV important, avoir subi un infarctus du myocarde, une angine instable, une intervention coronarienne percutanée, un pontage aortocoronarien, un AVC ou une thrombose veineuse profonde (TVP)/embolie pulmonaire (EP) dans les 6 mois de la sélection, ou avoir une chirurgie cardiovasculaire ou une angioplastie coronarienne percutanée planifiée.
REGAIN[7]	Antécédents d'accident vasculaire cérébral ou être à risque d'événements CV aigus selon les résultats d'ECG
Frémanézumab	
HALO-EM[8] HALO-CM[9]	Antécédents de maladie CV ou d'ischémie vasculaire cliniquement significatifs ou d'événements thromboemboliques, tels qu'un accident vasculaire cérébral (y compris des accidents ischémiques transitoires), une TVP ou une EP.
Eptinézumab	
PROMISE-1[10]	Maladie cardiovasculaire (hypertension, cardiopathie ischémique), maladie cérébrovasculaire
PROMISE-2[11]	Antécédents connus ou signes d'artériosclérose, de cardiomyopathie, de coronaropathie, de graves anomalies du rythme cardiaque, de maladie cérébrovasculaire ou de tout trouble cardiovasculaire actif, évolutif ou instable

Ce tableau se veut un résumé des données d'essais cliniques individuels accessibles seulement; il ne permet pas de comparaison directe entre les essais.

1. Données internes. 2. Depre, C. et al. *Headache*, 2018;58:715-723. 3. Dodick DW et al. *Cephalalgia*. 2018;38(6):1026-1037. 4. Goadsby PJ et al. *The New England Journal of Medicine*. 2017;377:2123-2132. 5. Stauffer VL et al. *JAMA Neurology*. 2018;75(9):1080-1088. 6. Skljarevski V et al. *Cephalalgia*. 2018;38(8):1442-1454. 7. Detke HC et al. *Neurology*. 2018;91(24):e2211-e2221. 8. Dodick DW et al. *JAMA*. 2018;319(19):1999-2008. 9. Silberstein SD, et al. *The New England Journal of Medicine*. 2017;377(22):2113-2122. 10. Ashina M et al. *Cephalalgia*. 2020;40(3):241-254. 11. Lipton RB et al. *Neurology*. 2020;94:e1365-1377.

Les AcM CGRP n’augmentent pas le risque de résultats CV négatifs chez les patients sans maladie cardiovasculaire

Résultats CV dans la classe des AcM CGRP	
Érénumab[1]	**Dans une étude de prolongation ouverte de 1 an d’un essai de phase 2, il n’y a pas eu de différence cliniquement significative dans les cardiopathies ischémiques/ effets indésirables cérébrovasculaires présentant un intérêt pour l’érénumab au fil du temps[1]** **L’érénumab n’a pas eu d’effet négatif sur la durée de l’exercice dans une population de patients à risque CV élevé[2]** • Dans un test sur tapis roulant incluant 88 patients avec une angine stable (44 ont reçu l’érénumab et 44 ont reçu le placebo)
Galcanézumab[2]	**Aucune différence cliniquement significative n’a été observée pour les effets indésirables CV apparus durant le traitement, la pression artérielle, le pouls ou le QTcF entre les patients traités par le galcanézumab ou le placebo[3]** • La durée maximale du traitement était de 6 mois
Frémanézumab[3]	**Aucun signe relatif à l’innocuité CV n’était apparent, les effets indésirables CV apparaissant peu fréquemment et à des taux similaires dans tous les groupes traités par le frémanézumab[4]** • La durée maximale du traitement était de 15 mois
Eptinézumab[4–6]	**Aucun événement CV indésirable apparu durant le traitement n’a été déterminé lors des essais cliniques sur l’eptinézumab pendant un an de traitement**

Ce tableau se veut un résumé des données d’essais cliniques individuels accessibles seulement; il ne permet pas de comparaison directe entre les essais.

1. Ashina M et al. *Neurology*. 2017;89:1-7. 2. Depre, C. et al. *Headache*, 2018;58:715-723. 3. Oakes T et al. *Neurology*. 2019;92(Suppl 15):P1.10-010. 4. Ning X et al. *Neurology*. 2019;92(Suppl 15):S17.005. 4. Ashina M et al. *Cephalalgia*. 2020;40(3):241-254. 5. Lipton RB et al. *Neurology*. 2020;94:e1365-1377. 6. Smith TR et al. *Clinical Therapeutics*. 2020;42(12):2254-2265.

Sécurité des anticorps CGRP
Différents points de vue

Prudence/alarmiste	Rassurant/optimiste
Le CGRP joue un rôle clé dans la vasorégulation et la protection contre l'ischémie.	De nombreux autres acteurs de ce réseau complexe. Des mécanismes alternatifs/de compensation peuvent exister. Les risques théoriques ne se sont pas toujours avérés vrais dans la pratique clinique.
Les migraineux ont un risque plus élevé d'événements vasculaires.	Les migraineux prennent des AINS, des triptans et des ergots depuis des années. Un traitement préventif efficace diminue l'utilisation de tx de crise.
La sécurité a été étudiée principalement à court terme et chez les animaux.	Les données disponibles à ce jour sur des centaines de patients ne démontrent pas un risque accru d'événements vasculaires.
La recherche future doit nous éclairer	

MaassenVanDenBrink et al., Trends in Pharmacol Sci 2016; 37(9):779-788

RESEARCH SUBMISSIONS

Risk of hypertension in erenumab-treated patients with migraine: Analyses of clinical trial and postmarketing data

David W. Dodick MD[1] | Stewart J. Tepper MD[2] | Jessica Ailani MD[3] | Nicola Pannacciulli MD, PhD[4] | Marco S. Navetta MD[4] | Brett Loop MPH[5] | Feng Zhang MS[4] | Ani C. Khodavirdi PhD[4] | Allison Mann MD[6] | Ahmad Abdrabboh PharmD, MPH[6] | Jawed Kalim MD, MSc[6]

Y'a-t-il un risque d'HTA associé aux anticorps CGRP?

Clinical trial program

	Placebo (N = 1043)	Erenumab 70 mg (N = 893)	Erenumab 140 mg (N = 507)
Hypertension AEs, n (%)	9 (0.9)	7 (0.8)	1 (0.2)
Serious hypertension AEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Exposure-adjusted incidence rates of hypertension, per 100 patient-years	3.6	3.3	0.8
Patients without antihypertensive medication at baseline, n	972	859	485
Patients initiating antihypertensive medication[a] during 12-week DBTP, n (%)[b]	12 (1.2)	7 (0.8)	1 (0.2)

The incidence of hypertension AEs, exposure-adjusted incidence rates of hypertension AEs, and percentage of patients initiating medication to treat hypertension, were similar across treatment groups during the DBTP

Postmarketing surveillance data

- A total of 362 hypertension AEs in 355 cases were reported in the postmarketing setting during the specified time frame (a total of >245,000 patient-years of exposure).
  - 26.2% (95/362) of hypertension AEs were classed as serious AEs.
- The exposure-adjusted incidence rate was 0.144 per 100 patient-years, meaning that hypertension AEs were reported for 1.4 (approximately 2) patients out of every 1000 patients treated annually.
- The majority of patients with hypertension were female (73.5%), and the median age (range) was 53 (24–87) years.

Need longitudinal data to determine prevalence, risk factors, drug/class specificity

!

Diapo de Dr David W. Dodick

Dodick DW, et al. *Headache* 2021;61:1411-1420.

Résumé pratique: les anticorps CGRP

- La plupart des experts ne les utilisent pas si
  - Prinzmetal
  - SVCR
  - Maladie vasculaire active, FR non-contrôlés
- La toxine botulinique reste un meilleur choix chez les patients vasculopathes avec migraine chronique
- Les anticorps CGRP sont à utiliser avec prudence chez les patients vasculopathes ayant échoué les tx de première ligne
- Le suivi de la TA est de mise
- La longue demi-vie influence la décision
  - Est-ce que les gépants seront préférables?

Avis d’expert

Les gépants à l'étude

Compound	Atogepant*	Rimegepant*	Ubrogepant*	Zavegepant*
Company	AbbVie	Pfizer	AbbVie	Pfizer
Approved US indications	Preventive Treatment of EM	Preventive Treatment of EM	**Acute Treatment of Migraine**	**Acute Treatment of Migraine**
Indications in development	Preventive Treatment of CM	**Acute Treatment of Migraine**		
Mechanism of Action	CGRP Receptor Antagonist	CGRP Receptor Antagonist	CGRP Receptor Antagonist	CGRP Receptor Antagonist
Formulation	Oral tablet	Oral tablet ODT	Oral tablet	Nasal spray

* These compounds are investigational and not yet approved by Health Canada.
CGRP: calcitonin gene-related peptide; CM: chronic migraine; EM: episodic migraine; ODT: orally disintegrating tablet

Gepants:
Antagonistes oraux du récepteur CGRP

- Traversent la BBB?
- Ont une affinité pour le récepteur AMY1
- Non vasoconstricteurs
- Inhibent la vasodilation
- Tx de crise ou préventif (continuum?)

Challenge	Will provide an advantage?
Triptan non responders and failure	?
Medication overuse	Favorable
Vascular contra-indication	< Triptans? > Ditans?
Drug coverage issues	Probably more costly
Administered with CGRP MABs	Probablement have therapeutic activity

Article for Fast Track Review

Cephalalgia
An International Journal of Headache
International Headache Society

Atogepant – an orally-administered CGRP antagonist – attenuates activation of meningeal nociceptors by CSD

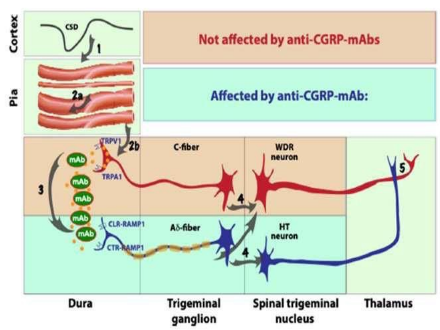
Cephalalgia
0(0) 1–11

DOI: 10.1177/03331024221083544
journals.sagepub.com/home/cep
SAGE

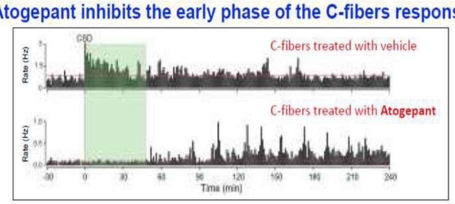
Andrew M Strassman[1,2], Agustin Melo-Carrillo[1,2], Timothy T Houle[3], Aubrey Adams[3], Mitchell F Brin[4,5] and Rami Burstein[1,2]

Anti-CGRP-mAbs Block Activation of Aδ-fibers by CSD

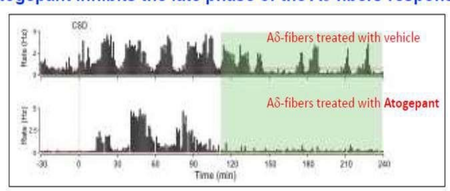
Anti-CGRP-mAbs Do Not Block Activation of C-fibers by CSD



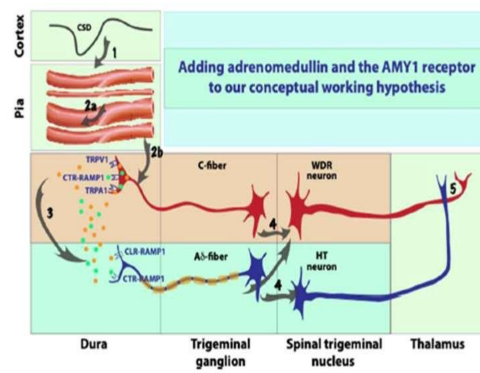
Atogepant inhibits the early phase of the C-fibers response



Atogepant inhibits the late phase of the Aδ-fibers response

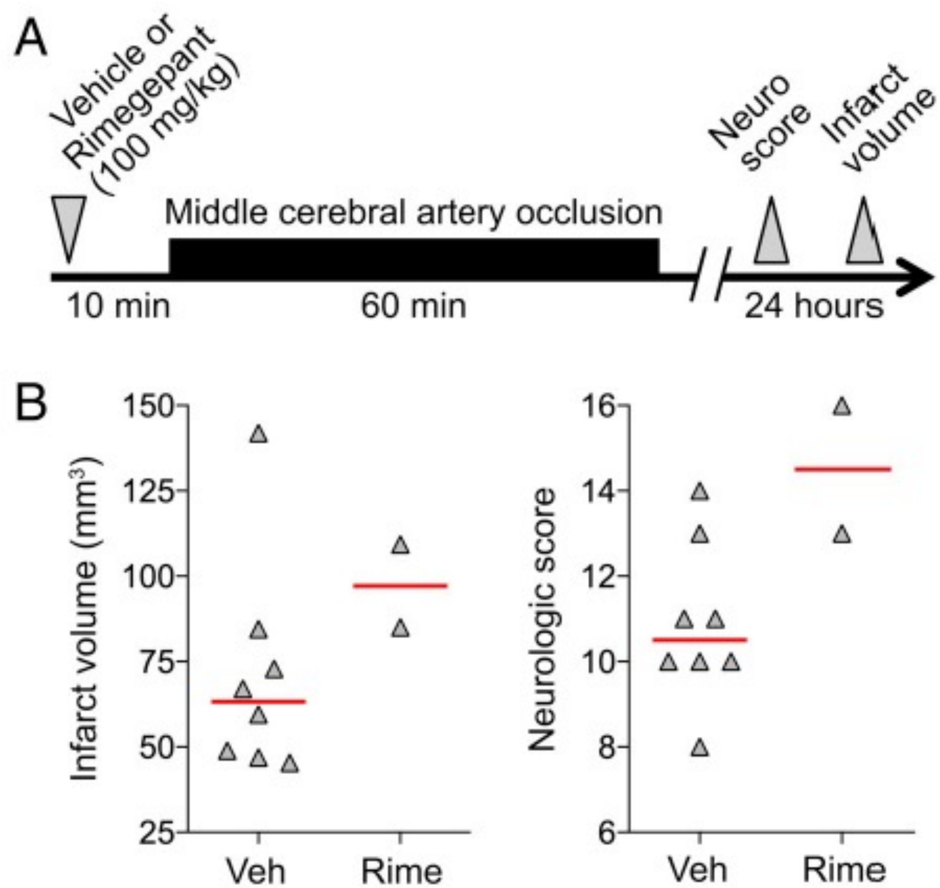


Dual action of ATO at both the CGRP and Amy1 receptors?



Anti-migraine Calcitonin Gene–Related Peptide Receptor Antagonists Worsen Cerebral Ischemic Outcome in Mice

Inge A. Mulder, MSc,[1] Mei Li, PhD,[1†] Tessa de Vries, MSc,[2†] Tao Qin,[1]
Takeshi Yanagisawa, MD, PhD,[1] Kazutaka Sugimoto, MD, PhD,[1]
Antoon van den Bogaerdt, PhD,[3] A. H. Jan Danser, MD, PhD,[2]
Marieke J. H. Wermer, MD, PhD,[4] Arn M. J. M. van den Maagdenberg, PhD,[4,5]
Antoinette MaassenVanDenBrink, PhD,[2] Michel D. Ferrari, MD, PhD,[4‡] and
Cenk Ayata, MD, PhD[1,6‡]



Une étude sur l'impact du olcegepant dans un modèle animal d'ischémie cérébrale a provoqué beaucoup de discussion

La prévention est la première étape

	Débutant	Avancé
Sommeil	Conseils de base sur hygiene de sommeil	TCC pour le sommeil +++
Nutrition	Repas réguliers Augmenter protéines Diminuer sucre et aliments modifiés Limiter / cesser alcool	Consultation nutrition Diète élimination Gluten-free diets, lactose-free diets Cétogène (evidence controversée)
Hydratation	Boire 1-2 l/jour Éviter avant le coucher	-
Caféine	Limiter à <200 mg/jour	Arrêt total pour 2 mois
Exercice	Régulier, modéré	Kinésiologie, physiothérapie Ajuster +++ Vélo stationnaire, Pilates, Essentrics
Relaxation	Cohérence cardiaque Apps, livres	CBT, ACT, PRT Progressive muscular relaxation / Jacobson Pleine Conscience
Gestion énergie	Livres, conseils de base	Ergothérapie, coach de vie

ACT, acceptance and commitment therapy; CBT, cognitive behavioural therapy.

Conclusions

- Les liens entre migraine et maladie vasculaire se clarifieront si on observe des sous-groupes bien définis
- Les triptans sont probablement plus sécuritaires que l'on ne le pense
- Les données sur les anticorps CGRP s'accumulent
  - La prudence s'impose, analyse cas-par-cas
- Les gépants s'ajoutent à nos options
  - La prudence s'impose
- La prévention est clé et la prise en charge des migraineux en jeune âge devrait réduire le fardeau vasculaire par la suite

Diapos additionnelles

Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study

Study in UK
7.89 million patients aged 25-84
Free of cardiovascular disease at baseline
Record MI, angina, TIA, ischemic stroke
NEW risk factors:
Migraine, Lupus, HIV, erectile dysfunction, severe mental illness, antipsychotics

** Did not distinguish MA and MO
** Prevalence of migraine was low: 6.4% women and 2.7% of men
Risk of CV events is increased by 36% (migraine)

Hippisley-Cox, BMJ Open 2017

ClinRisk

Welcome to the QRISK®3-2018 risk calculator https://qrisk.org/three

This calculator is only valid if you do not already have a diagnosis of coronary heart disease (including angina or heart attack) or stroke/transient ischaemic attack.

Reset | Information | Publications | About | Copyright | Contact Us | Algorithm | Software

About you

Age (25-84): 50

Sex: ○ Male ● Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Diabetes status: none

Angina or heart attack in a 1st degree relative < 60? ☐

Chronic kidney disease (stage 3, 4 or 5)? ☐

Atrial fibrillation? ☐

On blood pressure treatment? ☐

Do you have migraines? ☐

Rheumatoid arthritis? ☐

Systemic lupus erythematosis (SLE)? ☐

Severe mental illness? ☐
(this includes schizophrenia, bipolar disorder and moderate/severe depression)

On atypical antipsychotic medication? ☐

Are you on regular steroid tablets? ☐

A diagnosis of or treatment for erectile disfunction? ☐

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Standard deviation of at least two most recent systolic blood pressure readings (mmHg):

Body mass index

Height (cm):

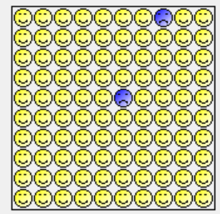
Weight (kg):

Your results

Your risk of having a heart attack or stroke within the next 10 years is:

2%

In other words, in a crowd of 100 people with the same risk factors as you, 2 are likely to have a heart attack or stroke within the next 10 years.



Risk of
a heart attack or stroke

Your score has been calculated using estimated data, as some information was left blank.

Your body mass index was estimated as 27 kg/m^2.

How does your 10-year score compare?

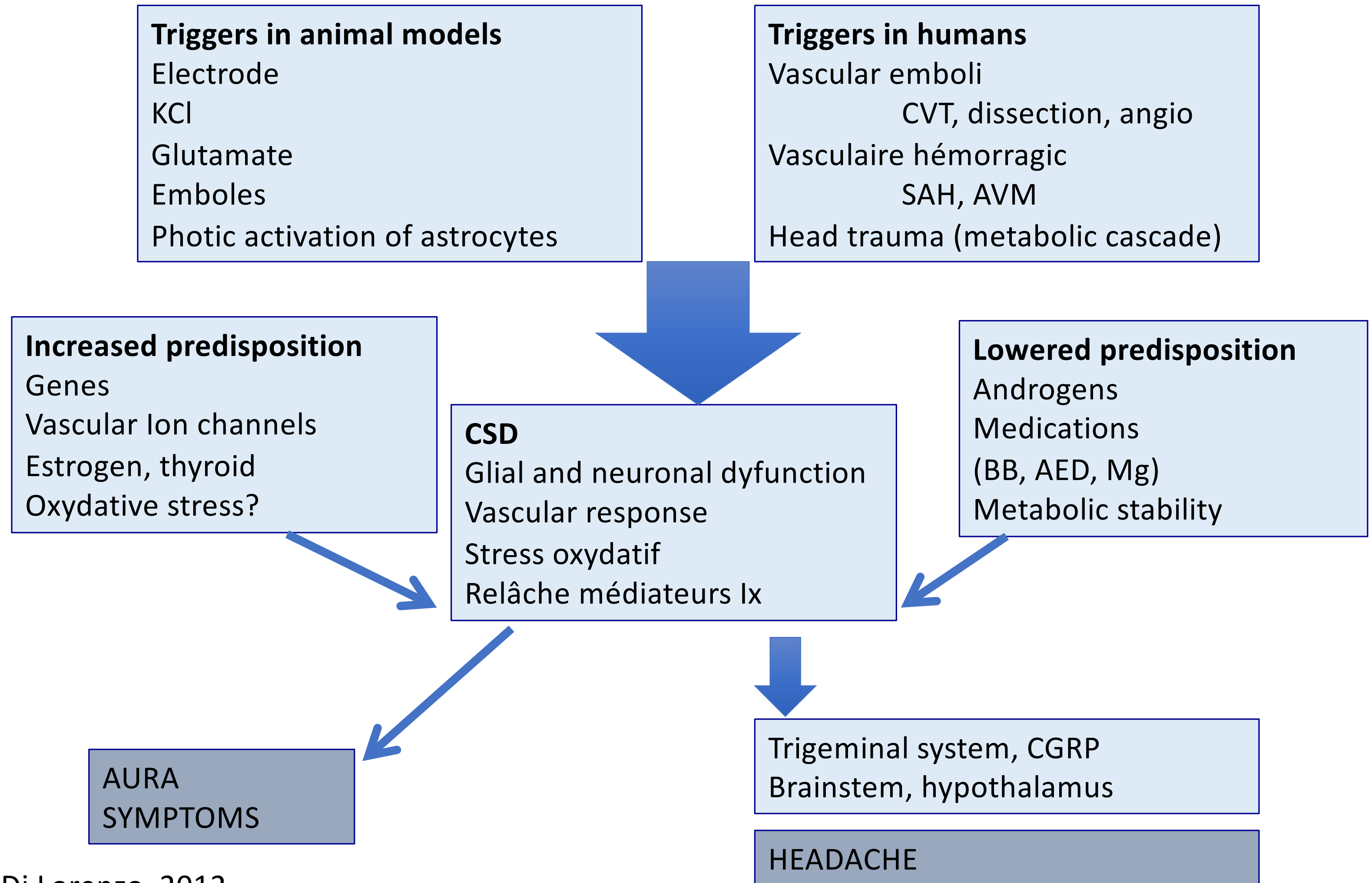
Your score

Your 10-year QRISK®3 score	2%
The score of a healthy person with the same age, sex, and ethnicity*	2.1%
Relative risk**	1
Your QRISK®3 Healthy Heart Age***	50

* This is the score of a healthy person of your age, sex and ethnic group, i.e. with no adverse clinical indicators and a cholesterol ratio of 4.0, a stable systolic blood pressure of 125, and BMI of 25.

** Your relative risk is your risk divided by the healthy person's risk.

*** Your QRISK®3 Healthy Heart Age is the age at which a healthy person of your sex and ethnicity has your 10-year QRISK®3 score.



Based on Di Lorenzo, 2012

Triptans and the healthy coronary arteries

- 5HT1b receptor is the key mediator
- Degree of VC is minimal in healthy coronary arteries
- Angiographic studies with high dose IV eletriptan show negligible constriction (-22% vs -16% for placebo)
- Angiographic study with suma = 12-17% of VC
- PET study with sumatriptan: no alteration of myocardial perfusion
- PET study with naratriptan: «minor effect»

Vincent, Am J Med 2005

Triptans and cardiovascular events in clinical trials: 4/384 781 = 1/100 000 treated attacks

40S The American Journal of Medicine, Vol 118, Suppl 1, March 2005

Table 1 Serious cardiovascular/cerebrovascular adverse events in prospective clinical trials*

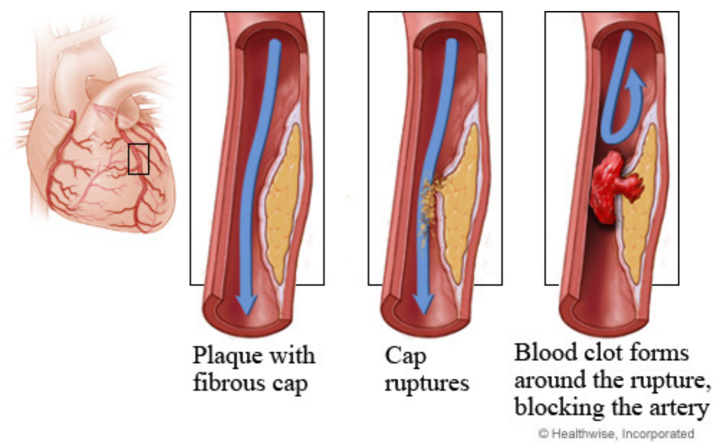
	Formulation	Subjects (N)	Treated attacks (n)	Serious cardiovascular/ cerebrovascular adverse events (n)
Almotriptan[55]	Tablet	2,500	15,000	1 unstable angina
Eletriptan[23]	Tablet	11,000	74,000	0
Frovatriptan[56]	Tablet	496 (long term) 1,554 (short term)	13,878 (long term) NR (short term)	0
Naratriptan[57]	Tablet	417	15,301	0
Rizatriptan[58]	Tablet	1,831	46,773	0
Sumatriptan[59]	Injection	12,339	185,579	2 CVA
Zolmitriptan[60]	Tablet	2,750	34,250	1 SVT
All studies	All	32,887	384,781	1 unstable angina, 2 CVA, 1 SVT

CVA = cerebrovascular accident; NR = not reported; SVT = supraventricular tachycardia.

*Only events that occurred within 24 hours after administration of a triptan are included in Table. The 1 case of presumed unstable angina had repolarization changes on electrocardiogram posteriolaterally 1 day after a dose of almotriptan and a subsequent catheterization revealed normal coronary arteries.

Triptan and the coronary arteries…
Data missing in high risk patients

- Data usually comes from healthy individuals, not vascular patients
- **Case reports** of MI, arythmia, ischemic colitis, unstable angina, cardiac arrest



Triptans: population studies on ischemic events

Velentgas, Headache 2004

- Retrospective study 130 000 migraine patients + 130 000 controls
- MI 1.4/1000 (no difference between migraine and non migraine)
- Current or recent use of triptan NOT associated with stroke or MI
- Ergotamine use almost significant (adjusted RR 1.49, 95% CI 0.93-2.41)

Hall, Neurology 2004

- 63 000 migraine patients, 13 000 with a triptan
- NO increased risk of stroke, MI, death, arythmia

One more database study from the Netherlands

- PHARMO database, 17 500 patients
- Triptan and ergotamine use, exposure quantified (past year)
  - >90 doses per year = overuse
- Analysis of cardiovascular medications

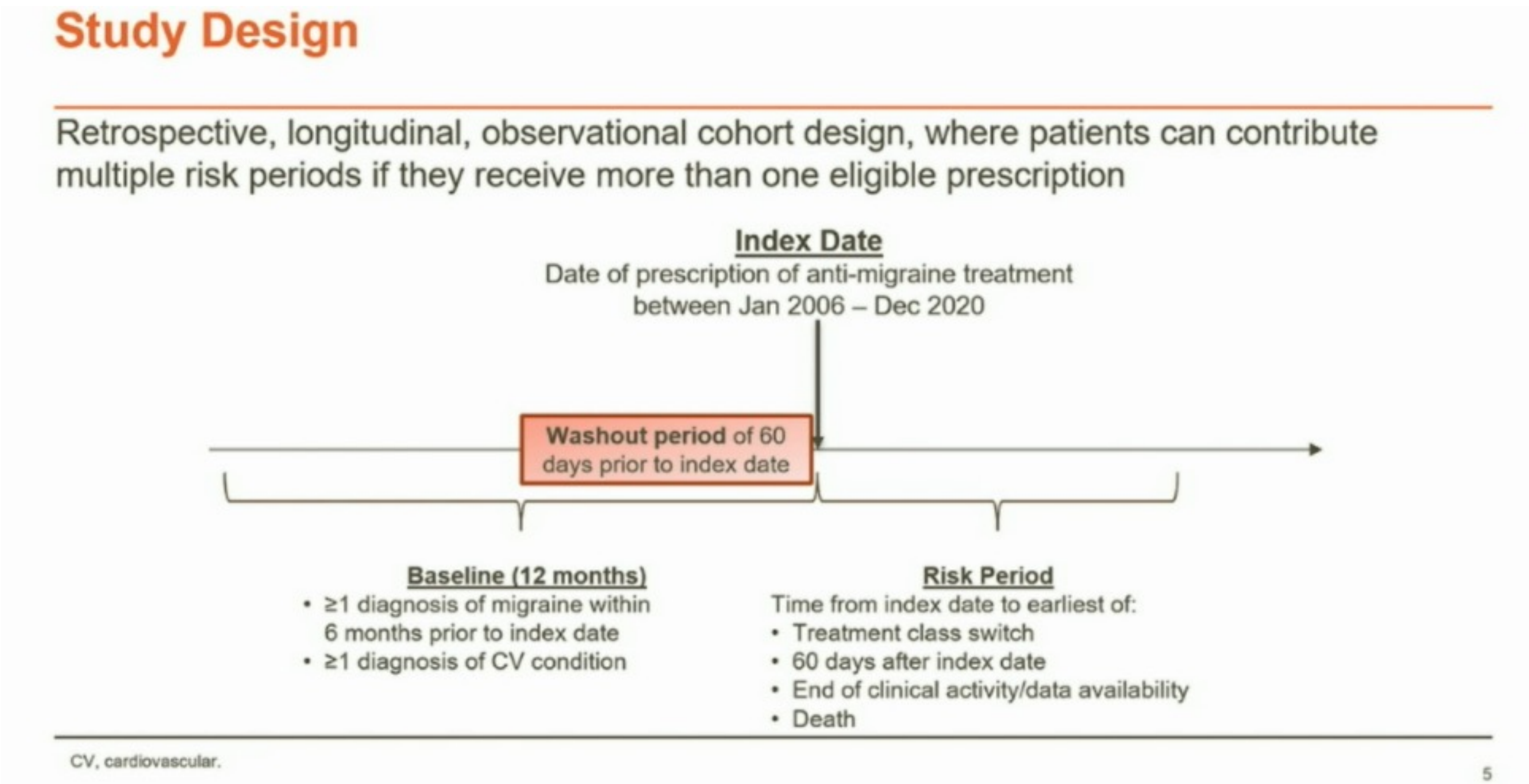
Triptan use or overuse does not increase the risk of ischemic complication (OR 0.96; 95% CI: 0.49 to 1.90)

Overuse of ergotamine was a risk (OR 2.55; 95% CI: 1.22 to 5.36)

- Even more so in pt using CV drugs (OR 8.52; 95% CI 2.57 to 28.2)

Wammes van der Heldjen, Neurology 2006

Triptans and cardiovascular risk



- Based on prescriptions not intake
- Migraine diagnosis code-based

Triptans and cardiovascular risk

YIKES

Sumatriptan, Butalbital, Oxycodone, and Ibuprofen Were the Most Frequently Prescribed Index Treatments

BUT WHY??

n (%)		
Triptans (N=4016)	**Opioids/butalbital (N=6084)**	**Non-aspirin NSAIDs (N=2021)**
Sumatriptan: 2368 (59.0)	**Butalbital: 2342 (38.5)**	**Ibuprofen: 1243 (61.5)**
Rizatriptan: 654 (16.3)	**Oxycodone: 1642 (27.0)**	Naproxen: 361 (17.9)
Zolmitriptan: 380 (9.5)	Tramadol: 288 (4.7)	Indomethacin: 138 (6.8)
Eletriptan: 241 (6.0)	Hydromorphone: 257 (4.2)	Diclofenac: 92 (4.6)
Naratriptan: 221 (5.5)	Hydrocodone: 232 (3.8)	Celecoxib: 74 (3.7)
Frovatriptan: 52 (1.3)	Codeine: 218 (3.6)	Ketorolac: 32 (1.6)
Almotriptan: 28 (0.7)	Morphine: 75 (1.2)	Other: 40 (2.0)
≥2 triptans: 72 (1.8)	Buprenorphine: 60 (1.0)	≥2 non-aspirin NSAIDs: 41 (2.0)
	Other: 64 (1.1)	
	≥2 opioids/butalbital: 906 (14.9)	

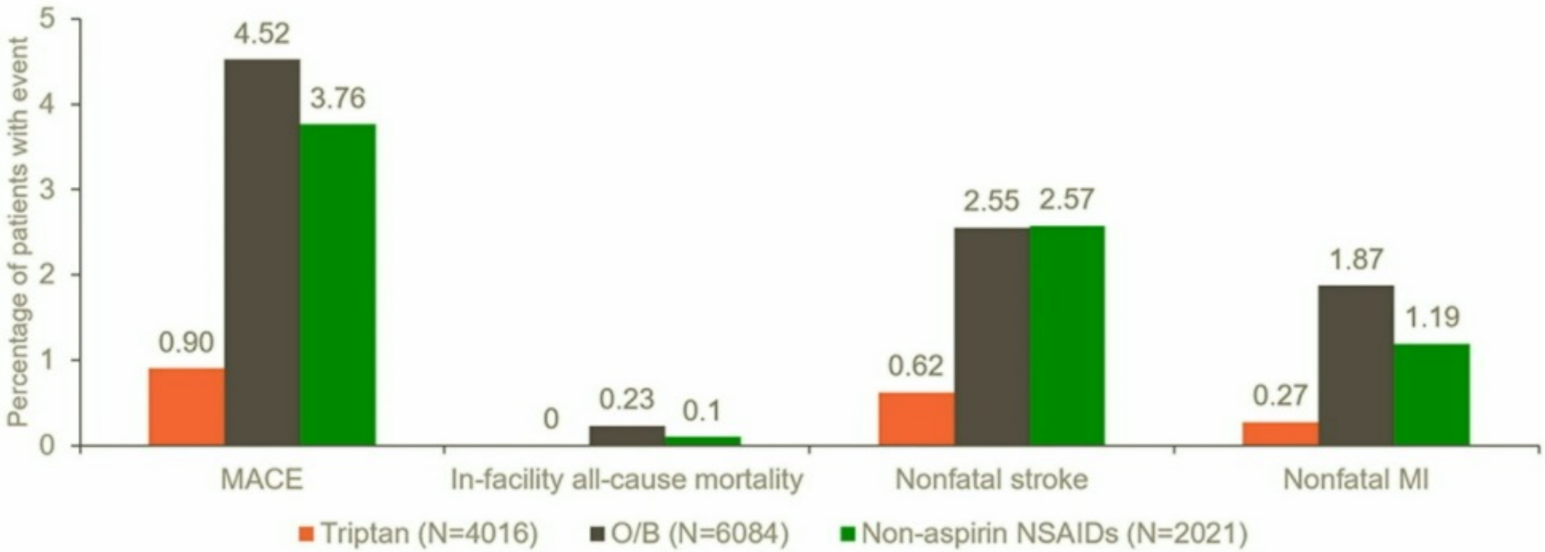
NSAID, nonsteroidal anti-inflammatory drug.

Triptans and cardiovascular risk

Triptans Were Associated With Fewer Events in Risk Period

Unadjusted Results

- Significantly fewer CV events with triptans compared with other commonly used anti-migraine treatments (*P*<0.001, all comparisons, except all-cause mortality due to absence of triptan events)



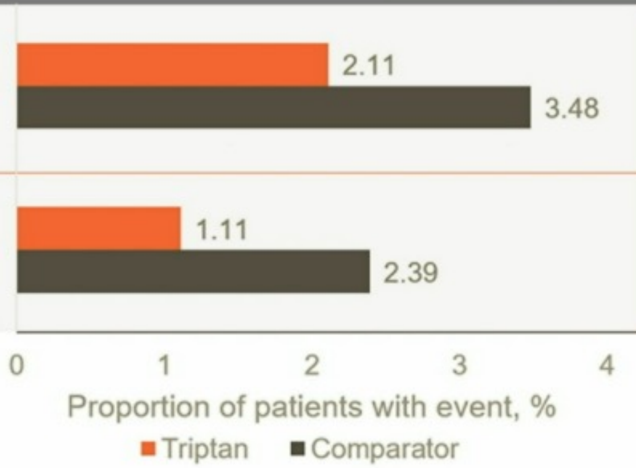
CV, cardiovascular; MACE, major adverse cardiovascular events (defined as first occurrence of any nonfatal MI, nonfatal stroke, or in-facility all-cause mortality); MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; O/B, opioid or butalbital.

Triptans and cardiovascular risk

Triptans Were Associated With Lower Risk of MACE Than Other Anti-Migraine Treatments

- Significantly lower rates of MACE vs opioids/butalbital and vs non-aspirin NSAIDs in the IPTW-adjusted analysis

		Hazard ratio (95% CI)	*P* value
Triptan vs O/B	Adjusted	0.38 (0.22, 0.67)	0.001
Triptan vs non-aspirin NSAIDs	Adjusted	0.46 (0.29, 0.71)	<0.001



CI, confidence interval; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events (defined as first occurrence of any nonfatal MI, nonfatal stroke, or in-facility all-cause mortality); MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; O/B, opioid or butalbital.

Similar results re: nonfatal stroke

In which patients do you currently perform a thrombophilia screen?

- Migraine (MO or MA) is not an indication for testing in my practice
- All migraine with aura patients are screened
- Migraine with aura according to their MRI
- Migraine with complex auras (sensory, speech, motor)
- This was not on my radar yet

Risk of events with thrombophilias

Thrombophilic defect	Annual risk of first DVT	Relative risk (compared to community controls)	Risk of recurrence
Antithrombin deficiency Protein C deficiency Protein S deficiency	1.52-1.90%	15-19x	At 5 yrs – 40% At 10 yrs – 55%
Factor V Leiden Prothrombin 20210A High FVIII	0.34-0.49%	3-5x	At 5 yrs – 11% At 10 yrs – 25%
High FIX High FXI High TAFI Hyperhomocysteinemia	Not independent risk factors for venous thrombosis. Risk associated with high FVIII		

Lijfering WM, Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood 2009;**113**:5314-5322.

HEADACHE CURRENTS

Hypercoagulability and Migraine

Gretchen E. Tietjen, MD; Stuart A. Collins, PhD

Association	Coagulation factor
Probable link	High estrogen states Thombocytosis vWF Tissue Plasminogen Activator Microparticles
Conflicting evidence	Anti-phospholipid Homocysteine Protein S MHTFR C677T
No link	Factor V Leyden Prothrombin Gene mutation

Table 1.—Diagnostic Evaluation of Migraine with Aura (MA)

Clinical Presentation	Possible Evaluation
MA, +/− history of other endotheliopathies	CBC, hs CRP, vWF antigen, fibrinogen, and fasting lipid profile, glucose level, glycosylated hemoglobin, homocysteine
MA, + personal or family history of thrombosis	CBC, hs CRP, vWF antigen, fibrinogen, and fasting lipid profile, glucose level, glycosylated hemoglobin, homocysteine Protein C, Protein S, Antithrombin deficiencies APC*, Prothrombin (Factor II)† Antiphospholipid antibodies: LA, aCL, β2GP1
MA, + subcortical white matter abnormalities on brain MRI	CBC, hs CRP, vWF antigen, fibrinogen, and fasting lipid profile, glucose level, glycosylated hemoglobin, homocysteine Antiphospholipid antibody profile: LA, aCL, β2GP1 CADASIL genetic testing if pattern is suggestive
MA, + stroke-like lesions on brain MRI	CBC, hs CRP, vWF antigen, fibrinogen, and fasting lipid profile, glucose level, glycosylated hemoglobin, homocysteine Protein C, Protein S, Antithrombin deficiencies, APC*, Prothrombin (Factor II)† Antiphospholipid antibody profile: LA, aCL, β2GP1 Evaluation for PFO: TCD/TTE with agitated saline/TEE

*If APC <2.3, check Factor V Leiden. †If Factor II is elevated, check prothrombin G20210A (Factor II mutation). CBC = complete blood count; hsCRP = high sensitivity c-reactive protein; vWF = von Willebrand factor; APC = activated protein C; LA = lupus anticoagulant; aCL = anticardiolipin antibodies; β2GP1 = Beta2 glycoprotein 1; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PFO = patent foramen ovale; TCD = transcranial Doppler; TTE = transthoracic echocardiogram; TEE = transesophageal echocardiogram.

Tietjen, Hypercoagulability and migraine, Headache 2018

Recommendations

- Patients in a high-risk group for cardiovascular events should not be prescribed a triptan.
- Those in an intermediate risk group should first be given nontriptan therapies.
- If they fail on these therapies, then triptans might be considered after a negative cardiac evaluation (e.g., coronary angiography or noninvasive cardiac testing).
- Those in a low-risk group can receive triptan therapy without prior cardiac evaluation.

Martin, Am J Med 2005

The risks we take everyday

Event	Risk
Dying in a plane crash	1/5 000 000
Dying over the next year by drowning or fire	1/50 000 (each)
Dying by getting murdered	1/11 000
Dying in a road accident	1/6 000 (1/10 000 in 2016 USA)
Dying **if** you get influenza	1/5 000
Dying while jogging	1/10 000
Diagnosis of cancer	1/3 600
Having a heart attack over 35	1/77
Having a stroke (woman <35)	1/10 000

Laudan L., The book of risks, fascinating facts about he chances we take every day, John Wiley & Sons 1994

Some familiar risks	**The chance they will happen**
Dying on the road over 50 years of driving	1 in 85
Annual risk of death from smoking 10 cigarettes per day	1 in 200
Needing emergency treatment in the next year after being injured by a can, bottle, or jar	1 in 100
Needing emergency treatment in the next year after being injured by a bed mattress or pillow	1 in 2000
Death by an accident at home	1 in 7100
Death by an accident at work	1 in 40 000
Death playing soccer	1 in 50 000
Death by murder	1 in 100 000
Being hit in your home by a crashing aeroplane	1 in 250 000
Death by rail accident	1 in 500 000
Being struck by lightning	1 in 10 000 000
Death from a nuclear power accident	1 in 10 000 000

Calman K, Royston G. Risk language and dialects. *BMJ* 1997;315:939-42.
Adams A, Smith A. Risk perception and communication: recent developments and implications for anaesthesia. *Anaesthesia* 2001;56:745-55.

Triptans, DHE and arteries (experiment)

Table 1. Therapeutic doses and C_{max} in patients.

Coronary arteries

	Dose and administration	C_{max}, nM	Predicted contraction Proximal	Predicted contraction Distal	Predicted contraction Meningeal	Predicted contraction Saphenous
			mean % 65–100 mM KCl maximum contraction (min–max)			
Dihydro-ergotamine	1 mg, SC (30)	3	0	0.7 (0–2.3)	13.6 (1.2–53.4)	7.7 (0–25.8)
	0.5 mg OI (30)	4	0 (0–0.1)	0.9 (0–2.7)	14.4 (1.4–55.2)	10.1 (0–32.5)
	1 mg, IV (30, 31)	65	1.2 (0–4.1)	3.2 (0–12.5)	18.4 (6.9–65.2)	$\boxed{38.3\ (2.4–92.9)}$
Sumatriptan	100 mg, PO (3, 7, 32, 33)	143	1.4 (0–3.3)	5.2 (0.1–25.9)	34.1 (2.3–97.0)	19.9 (1.4–35.9)
	6 mg, SC (3, 7, 32, 33)	211	1.8 (0–4.3)	2.7 (0.2–34.6)	37.6 (2.9–101.2)	22.9 (2.1–40.3)

Therapeutic doses and the subsequent acquired C_{max} (corrected for plasma protein binding) in patients are compared to the graphs in Figures 1 and 2 to predict contraction both in proximal and distal coronary arteries as well as middle meningeal arteries. Plasma concentrations obtained from the references mentioned in the table are averaged and corrected for plasma protein binding as described earlier (7).
PO: oral; SC: subcutaneous; IV: intravenous; OI: oral inhalation; min: minimum; max: maximum.

Labrujiere and Maassen van den Brink, Cephalalgia 2015

Migraine, triptan and blood vessels

- During an attack, MMA dilates more than MCA
  - Some studies even report NO dilation of the MCA
- The dilation seems to be associated with the side of the headache
- Sumatriptan reverts the dilation of the MMA, but has no effect on the MCA
- Relief seems to be associated with the effect on extra-cranial arteries, not the intracerebral ones
- A central effect of triptans is not excluded

Would this modify our risk evaluation for patients with AVMs, aneurysms, CADASIL, ischemic stroke?

Ashgar, Neurology 2010
Amin, Cephalalgia 2012
Amin, Lancet Neurol 2013
Amin, Cephalalgia 2013
Ashgar, Ann Neurol 2011
Petersen, Clin Pharm 2005