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Treatment with anti-CGRP (receptor) antibodies for migraine: can we predict effectiveness?

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Chapter 1

General introduction

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Adapted from:

Changing levels of sex hormones and calcitonin gene-related peptide (CGRP) during a woman's life: Implications for the efficacy and safety of novel antimigraine medications

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General introduction

Migraine

Migraine is a highly prevalent, primary headache disorder. It is estimated that 15% of the world population suffers from migraine, representing a large socioeconomic burden.¹ The diagnosis is based on the International Classification of Headache disorders (table 1).² It is characterized by recurrent headaches with unilateral pulsating pain of moderate to severe intensity, often aggravated by physical activity and accompanied by severe nausea or vomiting, or photophobia and phonophobia, or combination of these symptoms. When left untreated, typical attack duration is between 4 and 72 h.² A migraine attack is often divided in different phases: a premonitory phase, the aura phase, the headache phase and a postdromal phase. Premonitory symptoms are symptoms that precede and forward the aura or headache phase by 2-48 hours.² Several symptoms, such as mood changes, lethargy, difficulty with concentration and changes in appetite, have previously been reported as premonitory signals.³ About one third of patients experiences aura symptoms, which consists most frequently of transient visual disturbances that expand in the course of 5 to 60 minutes before the headache phase starts.² In the postdromal phase, following headache resolution, patients commonly report fatigue, difficulty with concentration and neck stiffness.²

Besides the separation into migraine with and without aura, migraine is also often divided into episodic and chronic migraine. Patients with chronic migraine have at least 15 headache days per month, of which at least 8 days have to fulfil the criteria for a migraine headache, for a duration of at least 3 months.² It is estimated that each year approximately 2.5% of patients with episodic migraine develop new-onset chronic migraine.⁴ Risk factors for migraine chronification that have been identified in the past are medication overuse of acute migraine/pain medication (such as triptans, analgesics, opioids, ergotamines), cutaneous allodynia and depression.⁵

Table 1 ICHD-3 criteria.

Migraine without aura	Migraine with aura
<p>A. At least five attacks fulfilling criteria B-D</p> <p>B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)</p> <p>C. Headache has at least two of the following four characteristics:</p> <ol style="list-style-type: none"> 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) <p>D. During headache at least one of the following:</p> <ol style="list-style-type: none"> 1. Nausea and/or vomiting 2. Photophobia and phonophobia <p>E. Not better accounted for by another ICHD-3 diagnosis.</p>	<p>A. At least two attacks fulfilling criteria B and C</p> <p>B. One or more of the following fully reversible aura symptoms:</p> <ol style="list-style-type: none"> 1. Visual 2. Sensory 3. Speech and/or language 4. Motor 5. Brainstem 6. Retinal <p>C. At least three of the following six characteristics:</p> <ol style="list-style-type: none"> 1. At least one aura symptom spreads gradually over ≥ 5 minutes 2. Two or more aura symptoms occur in succession 3. Each individual aura symptom lasts 5-60 minutes 4. At least one aura symptom is unilateral 5. At least one aura symptom is positive 6. The aura is accompanied, or followed within 60 minutes, by headache <p>D. Not better accounted for by another ICHD-3 diagnosis.</p>

Gender aspects of migraine

After the age of menarche, migraine prevalence in women increases to a three-to-one ratio when compared to men.⁶ The symptoms men and women report differ as well, as female patients are more likely to report additional symptomatology such as photophobia, phonophobia, nausea, vomiting and visual aura.⁶ Moreover, for many female patients, migraine occurrence often correlates to specific phases of the menstrual cycle, the highest incidence being reported just before and during the first days of menstruation.⁷ Conversely, during pregnancy, patients experience less migraine attacks. During perimenopause, patients report an increase in migraine frequency with, eventually, a postmenopausal decrease.^{8,9} The differences between men and women and the changes in migraine during different life stages in women clearly indicate a role for sex hormones in migraine.

Comorbidities of migraine

There are several known comorbidities of migraine and especially chronic migraine is associated with a higher prevalence of these comorbidities.¹⁰ Migraine patients are often diagnosed with additional chronic pain disorders, such as back or neck pain or fibromyalgia. In addition, other neurological disorders, such as epilepsy and stroke (specifically migraine with aura), have been associated with migraine.¹¹ Psychiatric disorders that have been associated with migraine include depression and anxiety.¹²

Trigeminovascular system and CGRP

A crucial role in the development of the headache phase of a migraine attack is attributed to the activation of the trigeminovascular system.¹³ The primary afferents of the trigeminal ganglion innervate the pial and dural meningeal vessels, while the efferent projections synapse with second-order neurons in the trigeminal nucleus caudalis (TNC) of the brainstem, which in turn project to the posterior thalamus. The thalamus integrates ascending input and projects to higher cortical areas.¹⁴ The most abundant neuropeptide found in the trigeminal nerve is calcitonin gene-related peptide (CGRP), which is expressed in 35-50% of neurons in the trigeminal ganglia.¹⁴ When the trigeminovascular system is activated, CGRP is released from the nerve endings surrounding the meningeal blood vessels causing vasodilation, further activation of the trigeminal nerve and nociceptive transmission.^{15,16} CGRP is a neuropeptide consisting of 37 amino acids, which can be found in both the peripheral and central nervous system. Two isoforms of this peptide exist: α -CGRP, which can be found in the central and peripheral nervous system and β -CGRP, which is mainly present in the enteric nervous system.^{16,17}

The CGRP family of peptides also includes adrenomedullin (AM), calcitonin (CT) and amylin (AMY) and their receptors are similar (Figure 1). The canonical CGRP receptor is a G protein-coupled receptor that activates a cyclic adenosine monophosphate (cAMP)-signalling pathway through which gene expression is modulated and receptor and ion channel activity regulated.¹⁸ It consists of calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1) and has been described in both neuronal and vascular tissue.¹⁹ The AM1 and AM2 receptors consist of CLR and RAMP2 or RAMP3, respectively. The calcitonin receptor (CTR) consists of only CTR, while the AMY1, AMY2 and AMY3 receptors, also reported to be present in neuronal and vascular tissue, consists of CTR and RAMP1, RAMP2 and RAMP3, respectively. Both Amylin and adrenomedullin receptors can be

found in the trigeminovascular system.¹⁴ CGRP is an agonist at the CGRP, the AMY1 receptor and to a lesser extent the AM receptors, while CGRP, AMY and AM can all bind the CGRP-receptor, though with different affinity.^{18,20}

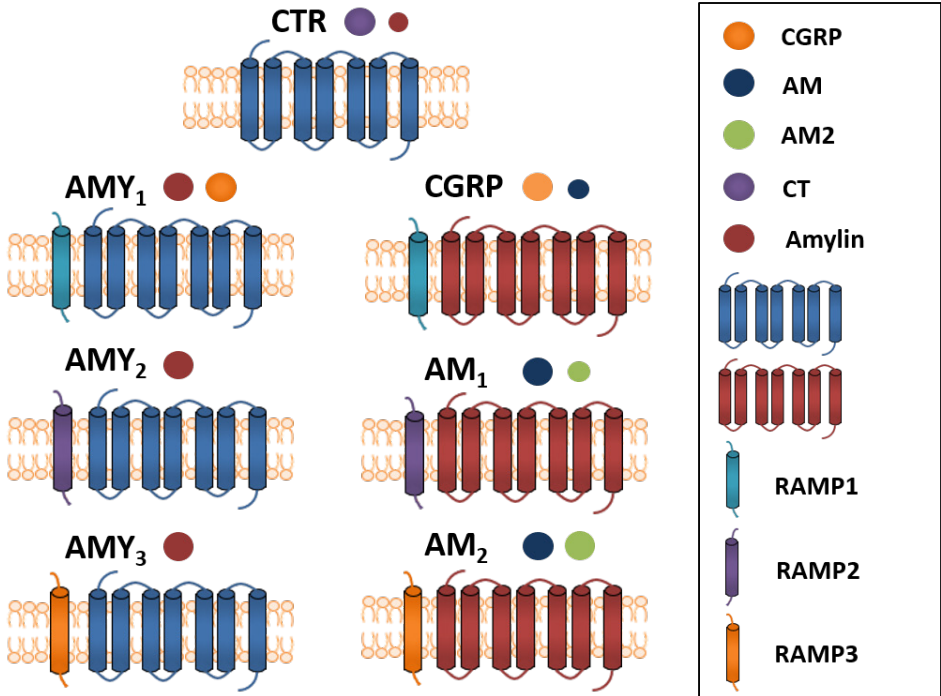


Figure 1 The receptors of the CGRP family of peptides. Ligands are indicated by spheres with relative sizes reflecting relative potency at each receptor, with the smaller sphere indicating lower potency of a given ligand.

Adapted from Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25, by D.L. Hay, 2018, British journal of pharmacology. 175(1), 3-17.

CGRP and migraine

Several studies showed the association of the trigeminovascular system and CGRP with migraine. During spontaneous migraine attacks levels of CGRP increase in the jugular vein²¹, while in chronic migraine patients the interictal CGRP levels (in the antecubital vein) were also found to be elevated.²² In addition, sumatriptan showed to normalize CGRP levels with headache relief in migraine patients and demonstrated to reduce capsaicin-induced trigeminovascular activity in healthy controls.^{13,23} Moreover, infusion of CGRP in migraine patients induces a delayed migraine-like headache, similar

to the subject's spontaneous attack, in approximately 60% of patients, while healthy controls only experience an initial non-migrainous headache.²⁴

During a migraine attack patients experience enhanced sensory processing, a debilitating feature which causes patients to avoid any type of sensory stimulation, e.g. light, sound, touch or smell. In mice studies, CGRP demonstrated to play a key role in light aversive behaviour.¹⁴ Mice spent less time in the light when CGRP was administered. Additionally, decreased movement was observed, possibly reflecting movement-aggravated pain which is often experienced during a migraine headache. Interestingly, treatment with a triptan or a monoclonal CGRP-blocking antibody attenuated the light aversive behaviour.^{25,26}

Migraine treatment

Migraine treatment consists of two components, namely the acute treatment of individual attacks and prophylactic treatment to reduce attack frequency, severity and duration. While migraine-specific acute treatment (e.g. triptans) has been available for approximately 30 years²⁷, until recently prophylactic treatment consisted only of medication originally developed for diseases other than migraine, such as hypertension, epilepsy and depression.²⁸ Commonly used are betablockers (metoprolol or propranolol), candesartan, valproate and amitriptyline (although the specificity of the effect of the latter drug is debated), and botulinum-toxin-A for chronic migraine. Although these drugs were proven to be effective in placebo-controlled trials²⁹, many patients discontinue treatment because of either inefficacy or debilitating side effects. Moreover, the site and mechanism of action of these drugs in migraine treatment remain unknown.

Migraine treatment targeting CGRP

Due to their role in migraine pathophysiology, the trigeminovascular system and CGRP were identified as possible targets in the treatment of migraine.¹³ Interestingly, triptans appear to inhibit calcitonin gene-related peptide release, most likely presynaptically through the 5-HT_{1D}(/1F) receptors.^{23,30} Initially, classical (small molecule) CGRP receptor antagonists were developed. These are known as 'gepants'. Ubrogepant has been approved by the FDA as abortive migraine treatment, atogepant as prophylactic treatment and rimegepant for both abortive and prophylactic treatment.³¹⁻³³ Simultaneously, IgG type monoclonal antibodies targeting CGRP and the CGRP receptor were developed. Due to their long plasma

half-life (about a month), these antibodies are only suitable for prophylactic treatment.³⁴ Three antibodies targeting CGRP (eptinezumab, fremanezumab and galcanezumab), and one targeting the CGRP receptor (erenumab) have been developed. They are administered monthly or once every three months. In recent years multiple phase-III trials have been performed, which have all shown an advantage compared to placebo.³⁵ About 40–60% of episodic migraine patients had at least 50% reduction in migraine days. Furthermore, a favourable tolerability profile was found when compared to the current prophylactics.³⁶ The low dosing frequency and the tolerability profile is assumed to lead to a higher compliance rate when compared to the available migraine prophylactics. Unfortunately, even though they were specifically developed for the treatment of migraine, not all patients benefit from these antibodies. Since this thesis mainly focuses on the monoclonal antibodies, results of the clinical trials on the monoclonal anti-CGRP antibodies are described hereafter in more detail.

Eptinezumab

Eptinezumab is a humanized IgG1 anti-CGRP antibody.³¹ It is dosed once every 12 weeks, and it is the only CGRP targeting antibody that is administered intravenously. In both episodic and chronic migraine the efficacy of both eptinezumab 100 mg and 300 mg was demonstrated in randomized placebo-controlled phase 3 trials.^{37,38} With a dosage of 100 mg, episodic migraine patients had an average reduction of 3.9 monthly migraine days (therapeutic gain compared to placebo 0.7 days), with 49.8% of patients reaching $\geq 50\%$ migraine reduction (in the placebo group 37.4%) after 12 weeks of treatment.³⁷ With 300 mg, episodic migraine patients had an average reduction in monthly migraine days of 4.3 (therapeutic gain compared to placebo 1.1 days), and 56.3% of patients reached at least 50% reduction in migraine days. In chronic migraine patients the 100 mg dose led to a mean reduction of 7.7 monthly migraine days (therapeutic gain compared to placebo 2.0 days), corresponding to a $\geq 50\%$ responder rate of 57.6% (39.3% in the placebo group). The 300 mg dose demonstrated a monthly migraine reduction of 8.2 (therapeutic gain compared to placebo 2.5 days), with 61.4% of patients being $\geq 50\%$ responders.

Erenumab

Erenumab is a human monoclonal IgG2 anti-CGRP-receptor antibody.³¹ It is dosed once every 4 weeks through subcutaneous injection, in either

70 mg or 140 mg. For episodic migraine multiple phase 3 trials have been performed.^{39,40} In the ARISE trial³⁹, patients were treated with either placebo or erenumab 70 mg and the clinical response was measured in the third month of treatment. Monthly migraine reduction was 2.9 days (in the placebo group 1.8 days), corresponding to 39.7% of patients reaching at least 50% reduction in monthly migraine days (29.5% in the placebo group). In the STRIVE trial⁴⁰, episodic migraine patients were treated with placebo, or erenumab 70 mg or 140 mg, and the clinical response was measured as change from baseline to month 4 through 6 in the mean number of migraine days per month. In the patient group treated with 70 mg the number of migraine days was reduced by 3.2, in the patient group treated with 140 mg by 3.7, and in the placebo group by 1.8. The $\geq 50\%$ responders rate was respectively 43.3% and 50% for the active treatment groups, and 26.6% in the placebo group.

The LIBERTY trial included patients with episodic migraine in whom 2-4 previous prophylactic treatments were unsuccessful.⁴¹ Patients were randomly assigned to either placebo or erenumab 140 mg, and the reduction in migraine days was measured in the third month of treatment. Of all patients treated with erenumab 30% had at least 50% reduction in migraine, compared with 14% in the placebo group. The average monthly migraine days reduced by 1.8 days (0.2 in the placebo group). For chronic migraine a phase 2 trial was performed, in which patients were randomly assigned to either placebo, erenumab 70 mg or erenumab 140 mg.⁴² Both 70 mg and 140 mg reduced monthly migraine days in the third month of treatment with 6.6 days, while placebo reduced monthly migraine by 4.0 days. The 50% responders rate was respectively 40% and 41% in the active treatment groups, and 23% in the placebo group.

Fremanezumab

Fremanezumab is a humanized monoclonal IgG2a anti-CGRP antibody.³¹ It is administered subcutaneously, either monthly 225 mg or quarterly 675 mg. In a placebo-controlled clinical trial episodic migraine patients had, after 3 months of treatment, a reduction in monthly migraine days of 3.7 (therapeutic gain 1.5) with a monthly 225 mg dosing, and a reduction of 3.4 with once 675 mg.⁴³ The trial demonstrated a 50% responders rate of respectively 47.7% and 44.4% for these dosing regimens (27.9% in the placebo group). The same dosing regimens were investigated in chronic

migraine patients.⁴⁴ Monthly 225 mg led to a migraine reduction of 4.6 days (therapeutic gain 2.1), with a $\geq 50\%$ responders rate of 41% (18% in the placebo group). Quarterly dosing demonstrated a monthly migraine reduction of 4.3 days, corresponding to a $\geq 50\%$ responders rate of 38%. A separate trial was conducted with episodic and chronic migraine patients who previously failed 2-4 prophylactic treatments.⁴⁵ With monthly dosing a monthly migraine reduction of 4.1 days (therapeutic gain 3.5) was observed, with $\geq 50\%$ responder rate of 34% (9% in the placebo group). With the quarterly dose monthly migraine days reduced by 3.7, with $\geq 50\%$ responder rate of 34%.

Galcanzumab

Galcanzumab is a humanized monoclonal IgG4 anti-CGRP antibody.³¹ Treatment starts with a loading dose of 240 mg after which monthly 120 mg is administered. This treatment regimen led to a decrease of 4.3 monthly migraine days in a placebo-controlled trial with episodic migraine patients (therapeutic gain compared to placebo 2.1).⁴⁶ The proportion of patients with $\geq 50\%$ reduction in migraine days was 59.3% (placebo group 36%). In the clinical trials with chronic migraine patients an average decrease in migraine days of 4.8 (therapeutic gain compared to placebo 2.1) was observed, with 27.6% of patients having $\geq 50\%$ reduction in migraine (compared to 15.4% in the placebo group).⁴⁷ In neither episodic nor chronic migraine did monthly galcanzumab 240 mg provide a greater effect over 120 mg. One trial included both episodic and chronic migraine patients who previously used 2-4 prophylactic treatments without success.⁴⁸ In episodic migraine there was an average migraine reduction of 2.9 days after 12 weeks of treatment (therapeutic gain 2.6), with 41.8% of patients reaching $\geq 50\%$ reduction in migraine days (17.1% in the placebo group). In the chronic migraine population monthly migraine days decreased by 6.0 (therapeutic gain 3.7), with 32% being a $\geq 50\%$ responder (compared to 8.9% in the placebo group).

Side notes clinical trials with anti-CGRP (receptor) antibodies

At first sight, all CGRP antibodies seem to have a similar efficacy as prophylactic treatment for migraine. However, caution is advised when making direct comparisons between these trials, as there are some differences in the definitions of both migraine days and primary outcome. Differences can be found in the outcome concerning migraine or headache days, in the definition of migraine days, in the definition of endpoint, i.e.

average change over longer period or change at a fixed timepoint, but also differences in population.⁴⁹ This makes the trials not directly comparable.

In addition, it should be noted that the results reported in these trials are reduction in monthly migraine days (MMD) during one month of treatment and do not include the consistency of response (what is the percentage of patients who reach the threshold of for instance 50% reduction of monthly migraine days (MMD) each month of these treatment periods). For clinical practice consistency of response is much more interesting, as patients want to reach a certain amount of reduction on each month of the treatment.

Potential risks of blocking CGRP

Due to their relatively large molecular weight, anti-CGRP (receptor) antibodies are not likely to pass the blood brain barrier and thus are not likely to cause central side effects. Nonetheless, CGRP is located in both the peripheral and enteric nervous system, and blocking CGRP could potentially lead to systemic side effects. The most common adverse events reported in clinical trials are mild, such as local injection-site reactions (such as erythema and pain), and upper respiratory tract infections, all similar between the different antibodies. Although the causal relation is still unclear, there have been a few cases of (fatal) cardio/cerebrovascular events.⁵⁰ Furthermore, the long-term effects of blocking CGRP in humans are not well known.^{50,51} Considering our knowledge of the presence and function of CGRP, a few potential risks that could accompany blocking CGRP will be discussed.

Potential risks in pregnancy

CGRP has been described to be involved in the regulation of the fetoplacental vascular tone.⁵² Indeed, in healthy pregnant women, CGRP levels are significantly increased throughout the pregnancy, while in the postpartum phase, serum concentrations of CGRP decrease significantly to levels similar to nonpregnant women.⁵³ Moreover, in pregnant patients with pre-eclampsia and intrauterine growth restriction, CGRP levels are lower compared to normotensive pregnancies.⁵⁴ In pregnant rats, blocking CGRP with a CGRP receptor antagonist led to an increased systolic blood pressure, foetal growth retardation and an increased foetal mortality.⁵⁵ In contrast, a study in which erenumab was administered during pregnancy in cynomolgus monkeys, showed a similar rate of infant and foetal loss in the erenumab and the control group, even though erenumab was found to

be transferred over the placenta.⁵⁶ A recent case report discussed a patient getting pregnant during treatment with erenumab.⁵⁷ By estimation she received the last erenumab injection around 2 weeks gestational age. During her pregnancy no blood pressure alterations or other complications were registered and the baby was born a term without any anomalies or health conditions. Noteworthy, the foetal exposure to antibodies directed against CGRP or its receptor is likely to happen in the second half of pregnancy. IgG antibodies are known to be able to cross the placenta through the neonatal Fc receptor (FcRn) in syncytiotrophoblast cells, which become present after 20–22 weeks of pregnancy.⁵⁸ Erenumab has a half-life of 28 days (4 weeks), making foetal exposure to erenumab in this case unlikely. Although these results seem reassuring, no sufficient evidence for safety in humans is available and physicians should take this potential risk into account and consider the long half-life when prescribing CGRP-targeting drugs.

Potential cerebro- and cardiovascular risks

Another potential concern of blocking CGRP is an increase in cerebro- and cardiovascular risks. As migraine itself has been reported to be a risk factor for ischemic stroke and cardiovascular events, especially in women, and even more when using combined oral contraceptives, it is important to study whether anti migraine treatment does not increase this risk.⁵⁹ The exact underlying mechanism for this is still unknown, which makes it difficult to assess whether adding anti-CGRP treatment would augment this risk. No safety concerns for cerebro- or cardiovascular events have been reported in the clinical trials with anti-CGRP (receptor) antibodies, although there have been a few reported cases of cardiovascular events during treatment with these antibodies⁶⁰⁻⁶², that were assumed not to be treatment-related by the investigators. Noteworthy, all trials excluded patients with a history of cardiovascular or cerebrovascular events. Even though the exact physiological function of CGRP has not been fully described, there is evidence that CGRP is involved in blood pressure regulation.^{16,63,64} Therefore, the use of these monoclonal antibodies may potentially lead to hypertension. In addition, it is clear that after an ischemic event, CGRP is released, which causes vasodilation.⁵⁹ This suggests that CGRP has a protective role. Moreover, during vascular inflammation, release of CGRP inhibits the proliferation of vascular smooth muscle cells, thus limiting the growth of atheromatous lesions.⁶⁵ This poses a concern as CGRP (receptor) blockade could lead to more extensive damage in an otherwise mild infarction. A small study performed in 2005, a study in health volunteers revealed no effect on cerebral blood flow or the

diameter of the middle cerebral artery in the 3 h after infusion of a CGRP receptor antagonist. Additionally, no effect on the extracranial arteries or systemic haemodynamic was recorded.⁶⁶

In a mouse model, the middle cerebral artery was occluded and infarct risk and volumes, collateral flow, and neurological deficits were compared after pre-treatment with olcegepant (single or 10 daily doses of 0.1-1mg/kg) or rimegepant (single doses of 10-100mg/kg) versus vehicle.⁶⁷ In this animal model, gepants worsened ischemic stroke via collateral dysfunction. CGRP pathway blockers might thus aggravate coincidental cerebral ischemic events. Therefore, the cerebrovascular safety of these agents must be better investigated, especially in patients at increased risk of ischemic events or in patients who are treated with prophylactic anti-CGRP medication. A different safety study explored the cardiovascular safety of CGRP receptor blockade with erenumab, in a randomized, double-blind, placebo-controlled study in patients with stable angina. Patients received a single infusion of erenumab (140 mg) and subsequently performed an exercise treadmill test. No difference was found between the erenumab and placebo group regarding time to exercise-induced angina, systolic and diastolic blood pressure or heart rate.⁶⁸ This may indicate that antibodies directed against CGRP or its receptor are safe in patients with a history of cardiovascular events. However, the treadmill test took place 30 min after infusion of erenumab, while no evidence was provided to show whether the CGRP receptor was already blocked at the time of the treadmill test.⁶⁹ This could potentially have taken several hours, given the large molecular size of erenumab and the location of the CGRP receptor in the smooth muscle wall of the blood vessel.

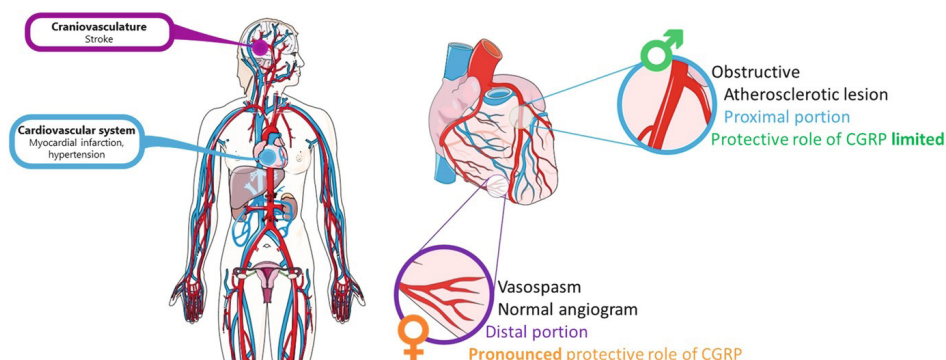


Figure 2 Schematic representation of the difference in pathophysiology of cardiovascular events in men and women and the potential protective role of CGRP.

Furthermore, although the majority of migraine patients are women, the majority of patients in this trial were men with stable angina. It is important to have in mind that myocardial infarction in men is usually caused by occlusion of the proximal coronary circulation, while in women vasospasm of the small intramyocardial parts of the coronary arteries, where CGRP leads to much larger vasodilatory responses to CGRP, is more common.^{59,70} This difference in pathophysiology could imply a different risk for men and women when blocking CGRP (Figure 2). Therefore, there is an urgency for cardiovascular safety studies with an adequate design, including the consideration of gender differences.

Noteworthy, as previously mentioned, CGRP not only activates the CGRP receptor, but also the type 1 amylin receptor. By blocking the CGRP receptor, CGRP can still act through the amylin 1 receptor and compensate some of the effects. On the other hand, in case of a CGRP blocking antibody, other peptides, like adrenomedullin, might act on the CGRP receptor (Figure 3).⁵⁹ It would be interesting to investigate whether safety studies of CGRP antibodies and CGRP receptor antibodies show similar results.

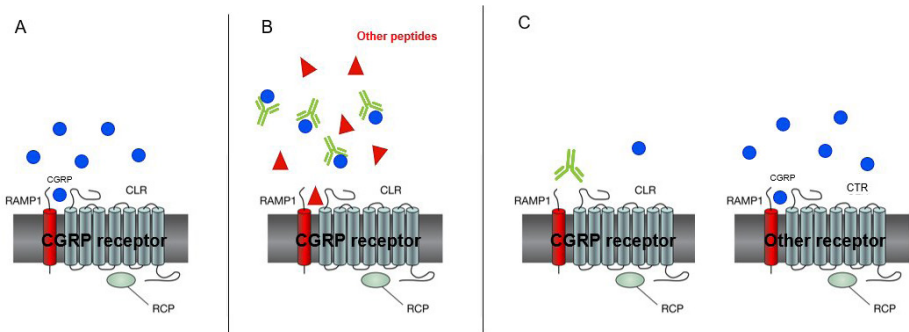


Figure 3 Schematic representation of potential compensation mechanisms in presence of anti-CGRP (receptor) antibodies. Adapted from *Wiping Out CGRP: Potential Cardiovascular Risks*, by A. Maassen van den Brink, 2016, *Trends in Pharmacological Sciences*, 37(9), 779-788.

A. In the absence of antibodies, CGRP can bind the CGRP receptor. **B.** In the presence of anti-CGRP receptor antibody, other peptides with affinity for the CGRP receptor may bind the receptor. **C.** In the presence of anti-CGRP-antibody, CGRP may bind to other receptors for which it has affinity.

Aims and outline of the Thesis

The aim of this thesis is to obtain a more comprehensive insight and understanding of the clinical response to treatment with anti-CGRP (receptor) antibodies in migraine patients. Different factors, clinical as well as pathophysiological, are being investigated in relation to the treatment response to these drugs.

Part I describes the effectiveness and safety of anti-CGRP (receptor) antibodies as prophylactic treatment in migraine patients with a high frequency of migraine attacks in a real life setting. We aimed to discover the consistency of the response to erenumab and to provide recommendations for clinical treatment guidelines for daily practice (**chapter 2**). In **chapter 3** the safety of erenumab and fremanezumab concerning blood pressure is assessed during a one-year follow-up period.

In part II we aimed to increase the understanding of the clinical response to erenumab and fremanezumab and uncover possible reasons for (non-) response. **Chapter 4** describes the trigeminovascular activity in response to capsaicin in migraine patients treated with erenumab. We evaluated whether erenumab inhibits forehead capsaicin-induced dermal blood flow (DBF) response and whether the degree of this response before starting treatment is of predictive value for the clinical response to erenumab. In **chapter 5**, we assessed whether visual hypersensitivity decreases with treatment with erenumab and fremanezumab, and evaluated whether increased visual sensitivity acts as a predictor for the clinical response. In **chapter 6**, serum CGRP levels of patients treated with erenumab are analysed. The association between CGRP before and shortly after starting treatment with erenumab and the degree of the clinical response is investigated.

Part III focuses on the relation of migraine and depression. In **chapter 7**, we evaluated whether treatment with erenumab or fremanezumab decreases symptoms of depression. In addition, we investigated whether the presence of depression before starting treatment is predictive for the response to prophylactic treatment with erenumab or fremanezumab. **Chapter 8** describes depressive symptoms during the different phases of a migraine attack. In a large cohort of episodic migraine patients, we investigated the temporal relationship between timing of

migraine attacks and depressive symptoms and evaluated if depressive symptoms increase in the days preceding the migraine headache as an early warning sign of an upcoming attack.

In **Chapters 9 and 10** a general discussion, future perspectives and a summary of this thesis are provided.

References

1. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiological reviews*. 2017;97(2):553-622.
2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
3. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia*. 2006;26(10):1209-1213.
4. Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. *Current pain and headache reports*. 2011;15(1):70-78.
5. Louter MA, Bosker JE, van Oosterhout WP, van Zwet EW, Zitman FG, Ferrari MD, et al. Cutaneous allodynia as a predictor of migraine chronification. *Brain*. 2013;136:3489-3496.
6. Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, Fanning KM, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2013;53(8):1278-1299.
7. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. *Neurology*. 2006;67:2154-2158.
8. Ibrahim K, Couturier EG, MaassenVanDenBrink A. Migraine and perimenopause. *Maturitas*. 2014;78(4):277-280.
9. Labastida-Ramirez A, Rubio-Beltran E, Villalon CM, MaassenVanDenBrink A. Gender aspects of CGRP in migraine. *Cephalalgia*. 2017;39(3):435-444.
10. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *Journal of neurology, neurosurgery, and psychiatry*. 2010;81(4):428-432.
11. Bauer PR, Carpay JA, Terwindt GM, Sander JW, Thijs RJ, Haan J, et al. Headache and epilepsy. *Current pain and headache reports*. 2013;17(8):351.
12. Louter MA, Pijpers JA, Wardenaar KJ, van Zwet EW, van Hemert AM, Zitman FG, et al. Symptom dimensions of affective disorders in migraine patients. *J Psychosom Res*. 2015;79:458-463.
13. Goadsby PJ, Edvinsson L. Trigeminovascular System and Migraine: studies Characterizing Cerebrovascular and Neuropeptide Changes Seen in Humans and Cat. *Annals of neurology*. 1993;33:48-56.
14. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. *Annual review of pharmacology and toxicology*. 2015;55:533-552.
15. de Vries T, Villalon CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. *Pharmacology & therapeutics*. 2020:107528.
16. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiological reviews*. 2014;94(4):1099-1142.
17. Deen M, Correnti E, Kamm K, Kelderman T, Papetti L, Rubio-Beltran E, et al. Blocking CGRP in migraine patients - a review of pros and cons. *The journal of headache and pain*. 2017;18(1):96.

18. Walker CS, Conner AC, Poyner DR, Hay DL. Regulation of signal transduction by calcitonin gene-related peptide receptors. *Trends Pharmacol Sci.* 2010;31(10):476-483.
19. Edvinsson L. The Trigeminovascular Pathway: Role of CGRP and CGRP Receptors in Migraine. *Headache.* 2017;57 Suppl 2:47-55.
20. Sonne N, Karsdal MA, Henriksen K. Mono and dual agonists of the amylin, calcitonin, and CGRP receptors and their potential in metabolic diseases. *Mol Metab.* 2021;46:101109.
21. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive Peptide Release in the Extracerebral Circulation of Humans During Migraine Headache. *Annals of neurology.* 1990;28:183-187.
22. Cernuda-Morollón E, Larrosa D, Ramón C, Vega J, Martínez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology.* 2013;81:1191-1196.
23. Ibrahim K, Danser A, Terwindt GM, van den Meiracker AH, MaassenVanDenBrink A. A human trigeminovascular biomarker for antimigraine drugs: A randomised, double-blind, placebo-controlled, crossover trial with sumatriptan. *Cephalalgia.* 2017;37(1):94-98.
24. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia.* 2010;30(10):1179-1186.
25. Mason BN, Kaiser EA, Kuburas A, Loomis MM, Latham JA, Garcia-Martinez LF, et al. Induction of Migraine-Like Photophobic Behavior in Mice by Both Peripheral and Central CGRP Mechanisms. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2017;37(1):204-216.
26. Kaiser EA, Kuburas A, Recober A, Russo AF. Modulation of CGRP-induced light aversion in wild-type mice by a 5-HT(1B/D) agonist. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2012;32(44):15439-15449.
27. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT 1B/1D agonists) in acute migraine treatment: a meta-analysis of 53 trials. *The Lancet.* 2001;358(9294):1668-1675.
28. Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneapolis, Minn).* 2015;21(4):973-989.
29. Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. *PLoS one.* 2015;10(7):e0130733.
30. Chan KY, Vermeersch S, de Hoon J, Villalon CM, Maassenvandenbrink A. Potential mechanisms of prospective antimigraine drugs: a focus on vascular (side) effects. *Pharmacology & therapeutics.* 2011;129(3):332-351.
31. Caronna E, Starling AJ. Update on Calcitonin Gene-Related Peptide Antagonism in the Treatment of Migraine. *Neurologic clinics.* 2021;39(1):1-19.
32. Deeks ED. Atogepant: First Approval. *Drugs.* 2021.
33. Pharmaceuticals B (2021) NURTEC ODT (rimegepant) orally disintegrating tablets Prescribing Information. FDA, New Haven, CT.
34. Paemeleire K, MaassenVanDenBrink A. Calcitonin-gene-related peptide pathway mAbs and migraine prevention. *Current opinion in neurology.* 2018;31(3):274-280.

35. Deng H, Li GG, Nie H, Feng YY, Guo GY, Guo WL, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis. *BMC Neurol.* 2020;20(1):57.
36. Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, Wen S, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia.* 2021;3331024211053571.
37. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia.* 2020;40(3):241-254.
38. Silberstein S, Diamond M, Hindiyyeh NA, Biondi DM, Cady R, Hirman J, et al. Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. *The journal of headache and pain.* 2020;21(1):120.
39. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia.* 2018;38(6):1026-1037.
40. Goadsby PJ, Reuter U, Hallstrom Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. *The New England journal of medicine.* 2017;377(22):2123-2132.
41. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *The Lancet.* 2018;392(10161):2280-2287.
42. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet Neurology.* 2017;16(6):425-434.
43. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. *JAMA.* 2018;319(19):1999-2008.
44. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. *The New England journal of medicine.* 2017;377(22):2113-2122.
45. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet.* 2019;394(10203):1030-1040.
46. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia.* 2018;38(8):1442-1454.
47. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology.* 2018;91(24):E2211-E2221.
48. Mulleners WM, Kim B-K, Láinez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet Neurology.* 2020;19(10):814-825.

49. McGinley JS, Houts CR, Nishida TK, Buse DC, Lipton RB, Goadsby PJ, et al. Systematic review of outcomes and endpoints in preventive migraine clinical trials. *Headache*. 2021;61(2):253-262.
50. Rivera-Mancilla E, Villalon CM, MaassenVanDenBrink A. CGRP inhibitors for migraine prophylaxis: a safety review. *Expert Opin Drug Saf*. 2020;19(10):1237-1250.
51. Rubio-Beltran E, Maassen Van Den Brink A. Understanding CGRP and Cardiovascular Risk. In: Brain S, Geppetti P, editors. *Calcitonin Gene-Related Peptide (CGRP) Mechanisms Handb Expl Pharmacol. Calcitonin Gene-Related Peptide (CGRP) Mechanisms*. 255: Springer, Cham,; 2019. p. 131-140.
52. Dong YL, Vegiraju S, Chauhan M, Gangula PR, Hankins GD, Goodrum L, et al. Involvement of calcitonin gene-related peptide in control of human fetoplacental vascular tone. *American journal of physiology Heart and circulatory physiology*. 2004;286(1):H230-239.
53. Saggese G, Bertelloni S, Baroncelli GI, Pelletti A, Benedetti U. Evaluation of a peptide family encoded by the calcitonin gene in selected healthy pregnant women. A longitudinal study. *Hormone research*. 1990;34(5-6):240-244.
54. Dong YL, Chauhan M, Green KE, Vegiraju S, Wang HQ, Hankins GD, et al. Circulating calcitonin gene-related peptide and its placental origins in normotensive and preeclamptic pregnancies. *American journal of obstetrics and gynecology*. 2006;195(6):1657-1667.
55. Gangula PR, Dong YL, Wimalawansa SJ, Yallampalli C. Infusion of pregnant rats with calcitonin gene-related peptide (CGRP)(8-37), a CGRP receptor antagonist, increases blood pressure and fetal mortality and decreases fetal growth. *Biology of reproduction*. 2002;67(2):624-629.
56. Bussiere JL, Davies R, Dean C, Xu C, Kim KH, Vargas HM, et al. Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine. *Regul Toxicol Pharmacol*. 2019;106:224-238.
57. Fofi L, Egeo G, Aurilia C, Barbanti P. Erenumab during pregnancy: a case report in a patient with chronic migraine. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2021;42(5):2145-2146.
58. Neil E. Simister CMS, Hua-Liu Chen and Joan S. Hunt. An IgG-transporting Fc receptor expressed in the syncytiotrophoblast of human placenta. *European journal of immunology*. 1996(26):1526-1531.
59. MaassenVanDenBrink A, Meijer J, Villalon CM, Ferrari MD. Wiping Out CGRP: Potential Cardiovascular Risks. *Trends Pharmacol Sci*. 2016;37(9):779-788.
60. Ashina M, Dodick D, Goadsby PJ, Reuter U, Silberstein S, Zhang F, et al. Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. *Neurology*. 2017;89(12):1237-1243.
61. Bigal ME, Walter S, Bronson M, Alibhoy A, Escandon R. Cardiovascular and hemodynamic parameters in women following prolonged CGRP inhibition using LBR-101, a monoclonal antibody against CGRP. *Cephalalgia*. 2014;34(12):968-976.
62. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, et al. 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. *The Lancet Neurology*. 2014;13(11):1100-1107.
63. Mai TH, Wu J, Diedrich A, Garland EM, Robertson D. Calcitonin gene-related peptide (CGRP) in autonomic cardiovascular regulation and vascular structure. *J Am Soc Hypertens*. 2014;8(5):286-296.

64. Danser AHJ, MaassenVanDenBrink A. Calcitonin Gene-Related Peptide Receptor Agonism: A Double-Edged Sword? *Circulation*. 2017;136(4):384-387.
65. Li Y, Fiscus RR, Wu J, Yang L, Wang X. The antiproliferative effects of calcitonin gene-related peptide in different passages of cultured vascular smooth muscle cells. *Neuropeptides*. 1997;31(5):503-509.
66. Petersen KA, Birk S, Lassen LH, Kruuse C, Jonassen O, Lesko L, et al. The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers. *Cephalalgia*. 2005;25(2):139-147.
67. Mulder IA, Li M, de Vries T, Qin T, Yanagisawa T, Sugimoto K, et al. Anti-migraine Calcitonin Gene-Related Peptide Receptor Antagonists Worsen Cerebral Ischemic Outcome in Mice. *Ann Neurol*. 2020;88(4):771-784.
68. Depre C, Antalik L, Starling A, Koren M, Eisele O, Lenz RA, et al. A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina. *Headache*. 2018;58(5):715-723.
69. Maassen van den Brink A, Rubio-Beltran E, Duncker D, Villalon CM. Is CGRP Receptor Blockade Cardiovascularly Safe? Appropriate Studies Are Needed. *Headache*. 2018;58(8):1257-1258.
70. Humphries KH, Pu A, Gao M, Carere RG, Pilote L. Angina with "normal" coronary arteries: sex differences in outcomes. *Am Heart J*. 2008;155(2):375-381.