Current Pain and Headache Reports (2019) 23: 85
https://doi.org/10.1007/s11916-019-0823-8

EPISODIC MIGRAINE (S NAHAS, SECTION EDITOR)

Efficacy of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the Preventative Treatment of Episodic Migraine in Adults

T. Dorosch[1] · C. A. Ganzer[2] · M. Lin[3] · A. Seifan[4]

Published online: 12 September 2019

Abstract

Purpose of Review Systematic review of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB) in the prophylactic treatment of adults with migraine. To identify gaps in research and provide guidance for future clinical trials.

Recent Findings A search was completed using PubMed, MEDLINE, Embase, and the Cochrane Library January 1, 1990 through December 31, 2017. The following are keywords used in the search: migraine, migraine prophylaxis/prevention, renin-angiotensin-aldosterone system, RAAS, ACE inhibitors, angiotensin-converting enzyme inhibitors: quinapril, perindopril, ramipril, captopril, enalapril, lisinopril, benazepril, fosinopril. Angiotensin receptor blockers, ARB, angiotensin II receptor antagonists: candesartan cilexetil, irbesartan, olmesartan, valsartan, losartan, azilsartan medoxomil, telmisartan, and eprosartan. The search included randomized controlled trials (RCT), systemic reviews and open-label studies of ACE inhibitors and ARB for the prevention of migraine attacks in adults 18–70 years old. Of 2461 retrieved articles, 18 included RCT, meta-analysis, systemic reviews, or guidelines published on ACE inhibitors or ARB in the prevention of migraine. Three RCT with telmisartan 80 mg, candesartan 16 mg, and enalapril 10 mg, and two open-label trials with lisinopril 5 mg and ramipril 5 mg found a high number of responders with greater than 50 % reduction in migraine attack frequency when compared to a 4-week baseline period. Candesartan was superior to placebo while telmisartan and enalapril were not.

Summary Lipophilic ACE inhibitors and ARBs can be effective prophylactic agents for reduction of migraine frequency in adults. Based on the limited number of published trials and small sample size, they are not recommended as first-line prophylactic agents. However, in populations with co-morbidities such as hypertension, they may be useful as first- or second-line prophylactics. Additional trials following the International Headache Society's guidelines on RCT are warranted.

Keywords Angiotensin-converting enzyme inhibitors · Angiotensin receptor blockers · Headache · Migraine

Introduction

Migraine attacks continue to be a common, disabling health problem in the United States (US) [1]. Annual US expenditure for migraine (treatments and services) was 9.2 billion dollars from 2004 to 2013 [2], which does not include lost productivity due to reduced quality of life and reduced job performance [3]. Head pain is the fifth leading cause of emergency department visits overall, and the third leading cause of emergency department visits for women. [1]

Treatment of episodic migraine is approached from an evidence-based practice guideline, and the current guidelines for prophylactic medication choice are established on published randomized controlled trials (RCT). However, these studies were carried out over 10 years ago [4], and only four

All authors contributed equally to this work.

This article is part of the Topical Collection on *Episodic Migraine*

✉ C. A. Ganzer
cganzer@hunter.cuny.edu

[1] Barry University, Miami, FL, USA

[2] Hunter-Bellevue School of Nursing, School of Health Professions, Hunter College, CUNY, 425 E. 25th St., Room 429W, New York, NY 10010-2590, USA

[3] Nova Southeastern, Ft. Lauderdale, FL, USA

[4] Neuro Well Free©, Oakland Park, FL, USA

drugs received US Food and Drug Administration (FDA) approval for the preventive treatment of episodic migraine in adults (propranolol, timolol, topiramate, and divalproex sodium, with one other approved for chronic migraine only (onabotulinumtoxina) [3].

The renin-angiotensin-aldosterone system has a widespread role within the cerebrovascular system, as well as the cardiovascular, pulmonary, and renal systems. In fact, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have shown remarkable promise as safe and effective alternatives to the four FDA-approved agents. A meta-analysis of 12,110 patients in 27 case series, open-label trials, and RCT compared ACE inhibitors and ARB to placebo [5]. Results showed the risk of migraine was one third lower in the treated group as compared to placebo, with minimal side effects [5]. Proposed mechanisms for these drugs in migraine prophylaxis includes improving neurovascular coupling, altering sympathetic tone, preventing vasoconstriction, promoting the breakdown of substance P, bradykinin, and enkephalin (proinflammatory markers), and possibly modulating pain and nociception [6, 7].

Current migraine treatment and prevention for most patient populations is not optimal. Patients who have used FDA-approved prophylaxis tend to respond in one of three ways: substantial relief (greater than 50 % reduction in migraine frequency), inability to tolerate side effects, or insufficient response [8]. The low side effect profile and lower cost of ACE inhibitors and ARB medications make them an attractive option for migraine patients. If shown to be effective, then all patients who are being treated for hypertension and also have migraine should be considered for monotherapy for both migraine and hypertension using an ACE or ARB.

Methods

Overview

The objective of this review is to update and re-evaluate recent data of ACE inhibitors and ARBs for the prevention of episodic migraine and most importantly based upon the analysis to inform whether clinicians should begin to consider changing practice. The review also identifies gaps in knowledge and may serve as a guide for future clinical trials.

Inclusion and Exclusion Criteria

The authors utilized the following criteria; English-language, randomized controlled, systemic reviews, or open-label trial design, and published in peer-reviewed journals. Study subjects ranging in age from 18 to 70 years of age, with a diagnosis of migraine with or without aura. The trials had to include prophylactic migraine treatment with either an ACE inhibitor, an ARB, or both. The prophylactic drug used had to have been targeting the frequency, severity, or duration of migraine. Trials were included whether they screened for comorbidities or not, such as hypertension, diabetes, or coronary artery disease. Inclusion of those studies was important in order to increase the number of trials reviewed for this study. Trials were excluded if they were over 20 years old, if they included participants under the age of 18 or over 70, if they had fewer than 20 participants, or if they included patients with diagnosis of cluster or tension attacks.

Search Strategy

A systematic review was conducted using four databases: PubMed, MEDLINE, EMBASE, and the Cochrane Library and Google Scholar. The search was developed with the assistance of a research librarian from Nova Southeastern University and Hunter College and detailed in Table 1. To ensure the capturing of every potentially relevant paper pertaining to the treatment of migraine in all databases, a broad search was conducted from January 1, 1990 through December 31, 2017. We chose this time-frame because it was during the 1990s when the clinical popularity of these medications emerged. Search terms were developed after formulating a Population, Intervention, Comparison, Outcome (PICO) hypothesis. The target population included adults with a diagnosis of episodic migraine. The interventions included ACE inhibitors and/or ARBs. Studies comparing the drug to placebo, those comparing the drug to another drug of different class, and open-label trials were included. The search terms included migraine, migraine prophylaxis, migraine prevention, renin-angiotensin-aldosterone system (RAAS), angiotensin-converting enzyme inhibitor: quinapril, perindopril, ramipril, captopril, enalapril, lisinopril, benazepril, fosinopril, angiotensin ii receptor blockers: candesartan cilexetil, irbesartan, olmesartan, valsartan, losartan, azilsartan medoxomil, telmisartan, and eprosartan. Search terms were used to identify titles, keywords, or abstracts. Abstracts were reviewed and studies selected based on PICO criteria.

Study Selection

This systematic review was conducted by two clinicians who reviewed all of the papers for the specified inclusion and exclusion criteria's separately. Papers which featured the keywords in any part of the manuscript were chosen for review. The papers were then independently reviewed with one investigator completing half of the reviews and the other investigator completed the other half. No review was done in duplicate. Once all abstracts were reviewed, and full publications were selected for inclusion, each trial was analyzed for the effectiveness of the drug as well as side effects and dropout rates due to adverse effects.

Table 1 Sample search strategy

OVID Medline search strategy that was used to identify citations that were included in this systematic review of efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the preventative treatment of episodic migraine in adults
1. Migraine.mp. or exp. migraine-type headache
2. Randomized controlled trial/or randomized.mp.
3. Migraine and/or angiotensin-converting enzyme inhibitor (ACE) and angiotensin receptor blocker/inhibitor (ARB),
4. Migraine and/or benazepril (Lotensin, Lotensin Hct), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil, Zestril), moexipril (Univasc) perindopril (Aceon), quinapril (Accupril)
5. Migraine and/or azilsartan (Edarbi), candesartan (Atacand), eprosartan, irbesartan (Avapro), losartan (Cozaar), olmesartan (Benicar), telmisartan (Micardis), valsartan (Diovan)
6. 3 or 4 or 5
7. 1 and 2 and 6 (duplicate citations were removed at this step)
Key: the forward-slash marks indicate the medical subject heading used or MeSH, mp. is keyword search that indicates a word in title, subject heading, or abstract. Exp was used to explode terms to include linked medical subject headings
As a part of this systematic review similar search strategies for databases including MEDLINE and EMBASE. Cochrane Library and Google Scholar (patents excluded) we used search strategy # 7.

Outcomes of Interest

Outcome measures included a greater than 50 % reduction in headache frequency or decrease in monthly migraine frequency, severity, or duration of attack.

Data Abstraction

Data for this systematic review were performed by two authors and all disagreements, including an impasse were resolved by a third author.

Assessment of Bias

Risk of bias was analyzed by the authors, according to the study type, including review of self-report method for reporting results, using the Cochrane risk of bias tool. It was also noted whether results were reported based on intent-to-treat population. Conflict of interest was assessed by evaluating the authors and sources of funding. Finally, the study was scrutinized using the International Headache Society published guidelines for controlled trials of prophylactic treatment of migraine in adults. The first edition was published in 1991, a second edition in 2000, and a third edition in 2008. The guidelines serve to "improve the quality of controlled clinical trials in migraine, because only quality trials can form the basis for international collaboration on drug therapy." [4] The criteria's from the guidelines that were assessed are listed in Table 2 below.

Results

Initially, a total of 2551 references were found. All abstracts and titles were screened for relevance and 71 were retrieved for full-text review. Ten RCTs and eight publications of open-label trials, meta-analysis, or guidelines were found. The meta-analysis and guidelines were reviewed for additional trials meeting search criteria but no additional studies were found. Five RCTs and six other study types were excluded due to publication date over 10 years ago, age less than 18, non-migraine population, and acute rather than preventative treatment. Thus, a total of five studies met inclusion criteria, including three RCT and two open-label studies.

None of the studies included in this review strictly followed the International Headache Society published guidelines for controlled trials of prophylactic treatment of migraine in adults. Only one trial included in this study (candesartan) reported on the intention to treat the population as well as those who completed the trial per protocol. The remaining trials' primary and secondary outcomes were reported using only the patients who completed the trial.

Regarding efficacy, four of five trials (three RCT's) reported a reduction in migraine frequency with ACEs or ARBs compared to placebo. Target populations included adults with episodic migraine, primarily women, between the ages of 20–70 with a mean age of 41. In most study populations, patients were able to control acute migraine with NSAIDS or previously prescribed abortive medications. For all studies, results were generated based on individual headache diaries. Four of the five clinical trials excluded patients with co-morbidities such as hypertension, congestive heart failure, and decreased renal/liver function. Only one study involved migraine patients who also had hypertension. Most trials were 3 months in duration (excluding baseline period), with one being just 2 months. The primary outcome measure was the most common frequency of monthly migraine. Secondary measures were responder rate (≥ 50 % reduction in migraine days), severity, and duration.

Table 2 International Headache Society Guidelines for controlled trials of prophylactic treatment of migraine in adults

Criteria	Stovner, L. 2013 [9]	Diener, HC. 2009 [10]	Sonbolestan, S. 2013 [11]	Schuh-Hofer, S. 2007 [12]	Park, HJ. 2013 [13]
Duration of disease > 6 months	X	X	X	X	X
Duration of observation of 3 months retrospective and 1 month prospective	X	X	X	X	X
Age at onset < 60 years	X	X	X	X	X
Age at entry > 18 years	X	X	X	X	X
Both female and male subjects	X	X	X	X	X
Screening and treatment of coexisting conditions	X	X	X	X	X
Monotherapy treatment with adequate wash-out periods	X	X	X	X	/
Double-blind technique	X	X	X	/	/
Placebo-controlled	X	X	X	/	/
Parallel-group comparison	/	X	X	/	/
Randomization in small blocks	X	X	X	/	/
Baseline period of > 1 month	X	X	X	X	X
Duration of treatment periods > 3 months	X	X	/	X	X
Control visits at screening, end of baseline, and every 4–6 weeks during treatment	X	X	X	X	X
Primary endpoint included # of headache days, # of migraine days, and/or # of migraine episodes	X	X	X	X	X

For diagnosis, all studies included in this review followed the International Headache Society's criteria for diagnosing migraine. To be included, subjects must have had between 2 and 8 migraines per month. This was confirmed by a 1-month baseline period prior to treatment during which participants recorded frequency, duration, and intensity of each episode.

Regarding validity, all five trials included in this review have low (level 1) level of evidence according to the US Preventative Task Force [9]. Confidence was limited by small sample sizes, lack of more high-quality RCT, and bias. The trials had relatively small cohorts between 21 and 94 patients. Only 2 of the 5 clinical trials followed the International Headache society's guidelines for controlled clinical trials on prophylaxis of migraine. The remainder followed some recommendations but not all. See Table 3 for a summary of results.

Three RCT's compared enalapril, telmisartan, and candesartan to placebos [10–12]. In all three trials, results showed reductions in migraine frequency from baseline. However, results were statistically significant in only one of the trials (candesartan) [12]. The proportion of responders with greater than 50 % reduction in migraine days was significantly higher in the treatment groups (mean 44 %) than placebo (mean 19 %). The strength of these studies came from well-controlled, randomized, double-, or triple-blind designs.

Candesartan 16 mg DAILY showed the most promising results in a well-conducted RCT [12]. Candesartan was superior to placebo in preventing migraine days and responder rate (43 % with candesartan and 23 % with placebo). The trial also found candesartan equal to propranolol in reducing migraine frequency compared to placebo. Thirteen participants responded to both candesartan and propranolol treatments, ten responded to candesartan only, and 8 responded to propranolol only. The most common side effect reported in the candesartan group was paresthesia, and in the propranolol group low heart rate during exercise and body pain. This candesartan RCT had the longest duration, largest sample size, and was done in a triple cross-over design in three 4-week blocks. The propranolol group reported significant adverse events compared to placebo with body pain and low heart rate at exercise ($P = < 0.05$). The candesartan group reported paresthesia more commonly than the placebo group ($P = < 0.05$) [13]. Both candesartan and propranolol groups reported more side effects than the placebo group. This trial has a risk of bias due to receiving funding and products from a pharmaceutical company.

The telmisartan trial did not produce statistically significant results compared to placebo. It had high risk of bias and several study limitations. Different treatment facilities were used to conduct this trial; results were different between treatment centers. Additionally, baseline values were substantially higher in the randomly assigned placebo group before the trial began. Self-reported values, specifically migraine hours per month, varied from 3 to 302.

The enalapril trial showed significant reduction in severity and duration, but not frequency, compared to placebo [12]. The authors used specific outcome measure tools such as the visual analog scale to rate severity. These tools are recommended by the International Headache Society to avoid

Table 3 Summary of evidence

Author/year	Study design/participants/inclusion criteria	Intervention (drug/dose) and control groups	Outcome measurement	Results
Stovner, L. 2013 [9]	Level I RCT, triple-blind, double cross-over. *N* = 72, 18 % male, 82 % female Candesartan group *n* = 59 Propranool group *n* = 61 Control group *n* = 61 *M* age = 37 Treatment duration: 3-, 12-week periods. Inclusion criteria: 18–65 years, migraine with or without aura or chronic; in retrospect, at least two migraine attacks per month over the last 3 months, and at least two or more attacks documented during a 4-week baseline period, first migraine over 1 year ago and before the age of 50. *Moderate risk of bias due to funding and drugs provided by AstraZeneca.	Candesartan 16 mg compared to propranolol slow-release 160 mg or placebo.	Primary: days with migraine per four-week period. Proportion of responders with > 50 % reduction in migraine days, days with headache, and hours with headache.	Candesartan and propranolol were both superior to placebo in reducing frequency 2.95, 2.91 and 3.53 respectively. ($P = 0.02$ for both). The proportion of responders with > 50 % reduction in migraine days were significantly higher for candesartan (43 %) and propranolol (40 %) than placebo (23 %). ($P = 0.025$ and < 0.050 respectively). Candesartan was not inferior to propranolol (and vice versa). (Stovner) Adverse events: candesartan ($n = 133$ %), propranolol ($n = 143$ %) and placebo ($n = 90$ %). These included tiredness, dizziness, nausea, constipation, sexual disturbances, and sleep disturbance. Ten participants dropped out (5 candesartan, 3 propranolol, 2 placebo).
Diener, HC. 2009 [10]	Level I RCT, placebo, double-blind. *N* = 94 (only 84 analyzed), 15.5% male, 84.5 % female. Interventional group *n* = 40 Control group *n* = 44 *M* age = 40.7 Treatment duration: 12 weeks with a 4-week baseline period. Inclusion criteria: age 18–65, history of migraine with or without aura for at least 1 year. Three to seven migraine attacks, with at least a 24-h pain-free interval between attacks during a four-week baseline period. *Note: High risk of bias. Authors received funding and honoraria from 13 pharmaceutical companies for this pilot.	Telmisartan 80 mg or placebo.	Primary: reduction in number of migraine days. Responder rate: greater than 50 % reduction in migraine days. A migraine day is a day with ≥ 1-h migraine symptoms recorded in a diary.	Reduction in migraine days was 1.65 with telmisartan and 1.14 with placebo ($P > 0.05$). Adjusting for baseline and center showed a 38 % reduction in migraine days with telmisartan vs. 15 % with placebo ($P = 0.03$). However, treatment centers had significant outcome differences ($P = 0.024$) indicating telmisartan did not consistently reduce migraine frequency across centers. Responder rate was 40 % in control and 25 % in placebo. Adverse events were similar between treatments. One patient from each group dropped out due to adverse effects (GI upset). Of the 95 enrolled, 90 completed the trial and only 84 were analyzed-no explanations were given.
Sonbolestan, S. 2013 [11]	Level I RCT, placebo, double-blind. *N* = 40, 15 % male, 85 % female Interventional group *n* = 21 Control group *n* = 19 *M* age = 34.4 Treatment duration: 8 weeks Inclusion criteria: patients attended the neurology clinics of Al-Zahar hospital, Isfahan, between July 2008–June 2009. Diagnosed with migraine without aura, without hypertension, diabetes mellitus, coronary artery disease, kidney disease, alcohol abuse, sinusitis, tension-type headaches > 5/month, body mass index > 35 kg/m^2, or tobacco user. Patients must also have at least 5 migraines per month.	Low-dose enalapril 5 mg BID or placebo.	Frequency (per month), severity (using a visual analog scale: severity from 1 to 10), and duration (hours per attack). Greater than 50 % reduction in migraine severity.	Significant reduction in migraine frequency in the enalapril group compared to baseline Enalapril: $M = 9.95$ h/month compared to baseline $M = 13.16$ h/month, ($P = 0.001$). In the control group, frequency increased significantly in the first month ($P = 0.027$) with no change in the second month. Significant reduction in migraine severity from 8.28 to 4.08 ($P = 0.00$). No difference in the placebo group. Duration in the enalapril group decreased dramatically ($M = 16$ h to 5.94), ($P = 0.001$). In the control group, the duration did not change. Reduction in headache severity is ≥ 50 % ($P = 0.016$). Enalapril: 48 % Placebo: 10.52 % No patients dropped out.

Table 3 (continued)

Author/year	Study design/participants/inclusion criteria	Intervention (drug/dose) and control groups	Outcome measurement	Results
Schuh-Hofer, S. 2007 [12]	Open-label study $N = 21$, 24 % male, 76 % female M age = 38 Treatment duration: 12 weeks Inclusion criteria: all patients had used at least one standard migraine prophylactic drug without relief. Attack frequency between two and eight per month, never used ACE-I or ARB before.	Lisinopril 2.5 mg for 7 days then increase to 5 mg per day.	Migraine attack frequency during the third month of treatment using a headache diary. Monthly migraine hours, severity, monthly doses of pain killers, and the responder rate (> 50 % reduction migraine attacks)	Compared to baseline, attack frequency was significantly reduced from a median of 44 h per month to 22 h per month ($P < 0.0005$). The median number of abortive tablets used decreased significantly by 37.5 % ($P = 0.002$). Responder rate was 52 %. Three patients dropped out due to cough.
Park, HJ. 2013 [13]	Open-label trial $N = 39$, 37 % male, 63 % female M age = 59.9 Treatment duration: 12-weeks Inclusion criteria: 20–70 years old, diagnosed with migraine without aura or chronic migraine and all had hypertension.	Ramipril 2.5 mg BID	Responders with 50 % or greater reduction in attack frequency compared to baseline headache days per month.	Responder rate of 41.9 %. The mean number of migraine at baseline was 19.9 days per month and 12 days per month at 12 weeks ($P < 0.001$ vs. baseline). The mean blood pressure was not altered. Four dropped out. Three reported no effect and one reported full improvement.

responder bias. Headache duration reduced from 16 h to less than 6 h per attack, with no dropouts and no significant adverse events reported. The small sample size $n = 40$ and short duration of 8 weeks, combined with the very low dose of enalapril used, represent key limitations.

Two open-label trials with a combined sample size of 50 showed significant reduction in attack frequency and abortive pain killers used per month. These trials tested low-dose ACE inhibitors lisinopril 2.5 mg daily and ramapril 2.5 mg twice daily and showed significant reduction in migraine frequency compared to baseline [14, 15]. Responder rates were between 42 and 52 % [15]. The most common side effect was dry cough; seven out of 100 participants dropped out because of this [14, 15]. One trial included patients with migraine plus hypertension, with a mean age of 60.

Discussion

In this study, we reviewed the strengths and weaknesses and results of three randomized trials and two open-label trials testing ACE inhibitors or ARBs for migraine prophylaxis. All trials showed a reduction in migraine days when compared to baseline testing but were inconsistent with respect to statistical significance compared to placebo. Only candesartan was shown to be statistically significantly effective in reducing migraine frequency compared to placebo. Candesartan was also shown to be non-inferior to propranolol, the most commonly used migraine prophylactic in the USA [14].

These results are consistent with the prior literature in several ways. Prior to 2007, several trials showed a low level of evidence for ACE inhibitors and ARB's having a role in episodic migraine prevention in adults. In a cross-over RCT performed in 2003, candesartan was effective in migraine prophylaxis as was shown [13]. The American Academy of Neurology released evidence-based guidelines on preventative treatment of migraine in 2012. These guidelines listed candesartan and lisinopril as third-line agents for migraine prevention and telmisartan as possibly ineffective [4]. The Canadian International Headache Society released guidelines the same year recommending either beta-blockers, candesartan or lisinopril as first-line choices in patients with hypertension [16]. In 2013, a large systematic review of 215 RCT was published examining 59 drugs from 14 different drug classes. The four FDA-approved drugs, as well as four off-label beta-blockers (metoprolol, atenolol, nadolol, and acebutolol), two ACE inhibitors (captopril and lisinopril), and one ARB (candesartan) outperformed placebo in reducing monthly migraine frequency [6]. Their results showed off-label ACE inhibitors and beta-blockers were the most effective with the least side effects [17].

The results of our review are also somewhat inconsistent with prior literature. Contrary to previous studies

Table 4 Key recommendations

Clinical recommendation	Evidence rating	Reference(s)	Comments
Candesartan was superior to placebo and baseline in reducing the frequency of migraine attacks. Propranolol was superior to placebo in reducing the frequency of migraine attacks.	A	[9]	RCT
Reduction in migraine days was 1.65 with telmisartan vs. 1.14 with placebo.	A	[10]	RCT
Significant reduction in migraine frequency in the enalapril group compared to baseline but not compared to placebo.	A	[11]	RCT
Compared to baseline, attack frequency was significantly reduced from a median of 44 h per month to 22 h per month.	C	[12]	Open-label
Mean number of migraine at baseline was 19.9 days per month and 12 days per month at 12 weeks	C	[13]	Open-label

demonstrating efficacy of telmisartan for migraine prophylaxis [18•], in the clinical trial included for this review, telmisartan 80 mg daily was not superior to placebo in one RCT [11]. This trial followed the strict International Headache Society's guidelines for conducting migraine studies, but the differences between treatment centers and high risk of bias diminished the quality [11]. Another important reason for failure of this trial to detect efficacy could have been the higher rate of migraine frequency in the placebo group at baseline. Certainly, our clinical experience and prior studies of telmisartan suggest that any drug in the same class as candesartan should be an effective prophylactic alternative.

Candesartan and telmisartan are the most lipophilic of the angiotensin receptor blockers, and therefore may deserve more attention by researchers and providers. Lipophilicity determines blood-brain barrier penetration. In patients with hypertension, simply switching to telmisartan or candesartan could reduce disability related to migraine. Both are once-a-day medications that are relatively cost-effective, especially if they could be treating two conditions at the same time. The open-label trial of ramipril suggested efficacy in patients with co-morbid hypertension and migraine. However, the age of the participants limits the generalizability of the findings to younger populations. Also, twice daily dosing limits scalability of this intervention.

Migraine is a serious public health issue with personal as well as economic costs. Up to 90 % of migraine patients report moderate to severe pain, 75 % report disability and 54 % are confined to bed during attacks [19]. This leads to loss of work, social life, family time, and overall quality of life. The decision to switch from abortive treatments to prophylactic treatments falls on the health provider's clinical judgment [8]. Studies suggest 35–40 % of adults with migraine should be offered prophylaxis based on frequency and disability, while only 10–15 % are prescribed prevention medication [20]. This may be due to the side effects of currently approved drugs, co-morbidities preventing patients from being candidates of the approved drugs, or high cost. Many patients never reach referral to a neurologist. Thus, family physicians have a great opportunity to impact quality of life for their patient. See Table 4 for summary of recommendations. Evidence ratings were based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework, with the following: (a) the authors have a lot of confidence that the true effect is similar to the estimated effect, (b) the authors believe that the true effect is probably close to the estimated effect, (c) the true effect might be markedly different from the estimated effect, and (d) the true effect is probably markedly different from the estimated effect [21].

Conclusion

Based on studies performed within the last 10 years, the evidence does not support using ACE inhibitors or ARB as first-line prophylactic agents in migraine for all patients. However, in populations with co-morbidities such as hypertension or high risk of side effects, these agents may be useful as first- or second-line preventatives. Telmisartan and candesartan, in particular, due to their lipophilicity, deserve more study. Most of the effective current drug options produce intolerable side effects [8].

Well-organized, high-quality trials of lipophilic ACEs or ARBs are needed, including better measurement of personalized responses to treatment, daily function, and quality of life [22]. Equally important is the need for increased awareness among primary care providers as to when a patient may benefit switching from separate treatment of hypertension and migraine using lipophilic ARBs such candesartan or telmisartan. More research and more provider awareness regarding lipophilic ARBs for migraine prophylaxis could help to reduce the massive health care expenditures and to improve quality of life for the sizable population of patients with episodic migraine [12–17, 18•, 19–22, 23•].

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache: The Journal of Head and Face Pain. 2013;53(3):427–36.
2. Raval AD, Shah A. National trends in direct health care expenditures among US adults with migraine: 2004 to 2013. J Pain. 2017;18(1):96–107.
3. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. Neurol Sci. 2008;29(1):110–22.
4. Silberstein S, Tfelt-Hansen P, Dodick DW, Limmroth V, Lipton R, Pascual J, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008;28(5):484–95.
5. Nandha R, Singh H. Renin angiotensin system: a novel target for migraine prophylaxis. Indian J Pharm. 2012;44(2):157.
6. Galletti F, Cupini LM, Corbelli I, Calabresi P, Sarchielli P. Pathophysiological basis of migraine prophylaxis. Prog Neurobiol. 2009;89(2):176–92.
7. Burnier M. Telmisartan: a different angiotensin II receptor blocker protecting a different population? J Int Med Res. 2009;37(6):1662–79.
8. Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. Cmaj. 2010;182(7):E269–E276. Epub 2010/02/18.
9. U.S. Preventive Services Task Force. Guildeline to clinical preventive services. Baltimore. p. 1989.
10. Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014;34(7):523–32.
11. Diener H, Gendolla A, Fruersenger A, Evers S, Straube A, Schumacher H, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia. 2009;29(9):921–7.
12. Sonbolestan SA, Heshmat K, Javanmard SH, Saadatnia M. Efficacy of enalapril in migraine prophylaxis: a randomized, double-blind, placebo-controlled trial. Int J Prev Med. 2013;4(1):72.
13. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA : J Am Med Assoc. 2003;289(1):65–9.
14. Park H-J, Lee S-T, Kim M. Inhibitory control of angiotensin-converting enzyme by ramipril in migraine. Neurology Asia. 2013;18(3):289–91.
15. Schuh-Hofer S, Flach U, Meisel A, Israel H, Reuter U, Arnold G. Efficacy of lisinopril in migraine prophylaxis–an open label study. Eur J Neurol. 2007;14(6):701–3.
16. Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012;39(2 Suppl 2):S1–59.
17. Shamliyan TA, Choi J-Y, Ramakrishnan R, Miller JB, Wang S-Y, Taylor FR, et al. Preventive pharmacologic treatments for episodic migraine in adults. J Gen Intern Med. 2013;28(9):1225–37.
18.• Ikeda K, Hanashiro S, Ishikawa Y, Sawada M, Kyuzen M, Morioka H, et al. Treatment with telmisartan, a long-acting angiotensin II receptor blocker, prevents migraine attacks in Japanese non-responders to lomerizine. Neurol Sci. 2017;38(5):827–31 **This manuscript demonstrates the efficacy of telmisartan for the treatment of migraines.**
19. Barbanti P, Aurilia C, Egeo G, Fofi L. Migraine prophylaxis: what is new and what we need? Neurol Sci. 2011;32(1):111.
20. Lipton RB, Manack Adams A, Buse DC, Fanning KM, Reed ML. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache-related disability. Headache: The Journal of Head and Face Pain. 2016;56(8):1280–9.
21. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ (Clinical research ed). 2008;336(7651):995–8.
22. Moschiano F, D'Amico D, Bussone G. Migraine prophylaxis: key points for the practising clinician. Neurol Sci. 2009;30(1):33–7.
23.• Halker RB, Starling AJ, Vargas BB, Schwedt TJ. ACE and ARB agents in the prophylactic therapy of migraine-how effective are they? Curr Treat Options Neurol. 2016;18(4):15 **This paper provides evidence based on clinical trials that ACE inhibitors and ARBs are effective and generally well tolerated when used for migraine prophylaxis.**