PROPOSAL FOR THE ADDITION OF BISOPROLOL TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES AS A THERAPEUTIC ALTERNATIVE TO PROPRANOLOL FOR PROPHYLAXIS OF MIGRAINE IN ADULTS

Proposed listing on the EML (proposed additions in red):

7. ANTIMIGRAINE TREATMENTS

7.2 Migraine prophylaxis

Beta-blockers

- propranolol tablets 20 and 40 mg
- bisoprolol tablet 1.25 mg; 5 mg

Applicant:
The applicants are, jointly, two international scientific societies (the International Headache Society [https://ihs-headache.org/en/] and the European Headache Federation [https://www.ehf-headache.com/]), and two charities (*Lifting The Burden* [https://www.l-t-b.org/], which is in Official Relations with WHO), and Disease Relief by Excellent and Advanced Means (DREAM [https://www.dream-health.org/a-new-public-health-model/?lang=en]).

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Section 1: Summary statement of the proposal

The global migraine prevalence is 14–15%, with minor variations across regions.*(1)* Reliable estimates show that migraine accounts for 4.9% of global population ill health quantified in years lived with disability (YLDs).*(2, 3)* Migraine manifests with recurrent and unpredictable attacks of head pain, often severe, accompanied by other disabling symptoms such as nausea, vomiting, intolerance to sensory stimuli (photophobia and phonophobia), all of which impair function*(4)*. Inadequately treated, it may increase in frequency and evolve into chronic migraine, with headache on more days than not, with commensurate increases in ill-health and disability burdens, and in direct and indirect costs.*(5)*

This submission calls for the inclusion of bisoprolol (tables 1.25 and 5 mg) as a therapeutic alternative to propranolol on the EML for the prevention of migraine attacks in adult subjects. Migraine preventive treatment is recommended in the presence of at least 4 migraine days per month and/or when migraine substantially impacts quality of life *(6)*. Effective migraine prevention can improve health, function, participation in daily activities and quality of life, and avert both acute medication overuse and progression into chronic migraine.*(7)*

Beta-blockers are recommended among the first-line treatment options for migraine prevention in several guidelines.*(8, 9)*

The EML includes propranolol 20 mg and 40 mg tablets as the sole option for migraine prevention. Propranolol is typically administered in dosages ranging from 40 to 320 mg per day. Its elimination half-life is 4-5 hours; unless it is administered in the more costly and less widely available long-acting formulation, this necessitates multiple doses daily if effective cover is to be maintained.

Bisoprolol, another beta-blocker indicated for migraine prevention, offers advantages over propranolol. It has a more selective receptor affinity, potentially reducing adverse effects. Moreover, bisoprolol requires only once-daily administration, which may enhance treatment adherence and thereby improve its effectiveness in migraine prevention.*(10)*

Section 2: Consultation with WHO technical departments

During the preparation of this application there have been multiple meetings with Drs Tarun Dua, Nicoline Schiess and Rodrigo Cataldi of the Brain Health Unit, Department of Mental Health, Brain health & Substance Use, World Health Organization (WHO).

They have provided guidance and suggestions, and critically assessed drafts of this application.

Section 3: Other organization(s) consulted and/or supporting the submission

In addition to the four joint applicants (IHS, EHF, LTB and DREAM), we have also consulted the European Migraine and Headache Association (Mrs Elena Ruiz de la Torre), https://www.emhalliance.org/, who is in full support of this applicaton (see page 35).

Section 4: Key information summary for the proposed medicine(s)

□ Beta-blockers

INN	bisoprolol
ATC code	C07AB07
Indication	Migraine - prophylaxis

ICD-11 code **8A80 1-3** Migraine, migraine with aura, chronic migraine

Dosage form	Strength	EML	EMLc
Tablets	1.25 mg; 5 mg	Yes (for other indications)	No

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

In the 23rd (2023) edition of the EML, section 7 Antimigraine medicines lists only propranolol for the prophylaxis of migraine. The submission proposes individual square box listing of bisoprolol as an alternative to propranolol.

Justification of choices of the representative medicines

Bisoprolol is listed in the EML for other indications than migraine such as antianginal medicine, antiarrhythmic medicine, antihypertensive medicine, and as medicine used in heart failure.

Bisoprolol has a number of perceived advantages over propranolol.

Bisoprolol has a longer half-life (10-12 hours), allowing for once-daily dosing, which is expected to improve patient adherence *(10, 11)*. Propranolol has a half-life of 4-5 hours, necessitating multiple doses daily if effective cover is to be maintained *(12-14)*.

Bisoprolol is a cardioselective beta-blocker, primarily targeting β1-adrenergic receptors in the heart. This reduces the likelihood of adverse effects related to β2-receptor blockade. Due to its β1-selectivity, bisoprolol poses a lower risk of bronchoconstriction, making it a safer option for patients with respiratory conditions such as asthma or chronic obstructive pulmonary disease (COPD). Its selective action on β1-receptors also minimizes peripheral vasoconstriction, a side effect that can occur with non-selective beta-blockers such as propranolol.*(15, 16)*

Bisoprolol is non-lipophilic, and therefore associated with reduced risk of CNS-related side effects such as fatigue, depression, and sleep disturbances compared to propranolol.*(17)*

All of these characteristics are expected to result in better overall tolerability and fewer side effects, which can improve patient comfort and compliance with long-term treatment.

Section 6: Information supporting the public health relevance

Indication

We propose the addition of bisoprolol for the prophylaxis of migraine with and without aura.

Epidemiology and burden of migraine

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, and photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours).*(4)* All of these symptoms are disabling and impair participation in life activities. In about one quarter of those affected, episodes may be preceded by transient focal neurological symptoms (most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits). The global prevalence of migraine is estimated at 14-15% (more than one billion people worldwide), 2-3 times higher in women than men*(2, 3)*. The disorder is ubiquitous, despite regional variations.*(1)*

Migraine contributes significantly to the global disease burden.*(1-3)* In the Global Burden of Disease (GBD) study 2021*(3)*, migraine was the fourth highest cause of years lived with disability (YLDs) at level 4. In the detailed analysis of GBD2016, migraine accounted for 45.1 million disability-adjusted life years (DALYs).

There is evidence that, every year, 2-3% of people with episodic migraine (headache on fewer than 15 days/month transition to the much more disabling chronic migraine (headache on ≥15 days/month of which a majority are with symptoms of migraine).*(18)*

Therefore, the impact of migraine on population health is very substantial, and associated with major impairments in participation, quality of life and productivity.*(19)* However, all of these can be reduced by appropriate treatments to abort ongoing episodes (acute treatment) or to prevent new ones (prophylaxis).

Multiple drugs belonging to different pharmacological classes are used for migraine prophylaxis.*(4)* They can be subdivided into two general categories depending on their mechanisms of action: non-migraine specific and migraine-specific. Beta blockers belong to the non-migraine specific group. Drugs for migraine prophylaxis reduce monthly migraine days by a percentage that varies from 30 to 75%. So far, it is not possible to predict which subject will respond to a drug, nor the extent of the response.

Alternative medicines currently included on the Model Lists for the proposed indication

PROPRANOLOL

The WHO Model List of Essential Medicines includes only propranolol for migraine prophylaxis.

Propranolol is a non-selective beta-blocker that has been widely used for migraine prevention. Its mechanism of action in migraine prophylaxis is not fully understood, but it is believed to

involve several pathways. Propranolol blocks both β1- and β2-adrenergic receptors, leading to reduced sympathetic nervous system activity. This results in the stabilization of vascular tone, preventing the vasodilation and subsequent vasoconstriction believed to contribute to migraine headaches. Additionally, propranolol may inhibit cortical spreading depression, a wave of neuronal and glial depolarization associated with migraine aura. It may also reduce the sensitivity of the trigeminal nerve to pain stimuli, further decreasing the likelihood of migraine attacks. The cumulative effect of these actions makes propranolol an effective option for reducing the frequency and severity of migraines in many patients.*(20)*

Section 7: Treatment details

Section 7: Treatment Details for Bisoprolol in Migraine Prevention

Dosage Regimen and Duration of Treatment

Medicine Delivery(6, 21, 22):

- Route of Administration: Oral administration.

- Dosage Range: The typical starting dose of bisoprolol for migraine prevention is 5 mg once daily. The dose may be titrated up based on patient response and tolerability, with a maximum dose of 10 mg once daily generally recommended. In some cases, lower starting doses (e.g., 2.5 mg) may be appropriate, particularly in patients who are sensitive to beta-blockers.

- Titration: Dosage adjustments should be made gradually, usually every 1-2 weeks, depending on the clinical response and any side effects experienced by the patient.

- Duration of Treatment: Migraine prophylaxis with bisoprolol is typically long-term. Patients should be reassessed periodically (e.g., every 3 to 6 months) to evaluate the effectiveness of the therapy and determine whether to continue, adjust, or discontinue treatment. In cases where migraines have been well-controlled for 6 to 12 months, a trial of tapering off the medication may be considered under medical supervision.

Requirements to Ensure Appropriate Use of Bisoprolol

Patient Eligibility Criteria:

- Age: Bisoprolol is generally recommended for adult patients. It is not typically used in children for migraine prevention due to limited evidence on safety and efficacy in this population.

- Comorbid Conditions: Patients with certain cardiovascular conditions such as hypertension, ischemic heart disease, or arrhythmias may particularly benefit from bisoprolol as it can address both migraine and cardiovascular concerns. However, patients with severe bradycardia, atrioventricular block, or significant cardiac failure should not use bisoprolol.

- Contraindications: Patients with a history of severe bronchospastic diseases (e.g., asthma), uncontrolled congestive heart failure, recent myocardial infarction, severe hepatic impairment, depression should not use bisoprolol.

Diagnostic and Monitoring Test Requirements

- Baseline Tests: Prior to initiating bisoprolol, baseline assessments should include blood pressure and heart rate measurements. An electrocardiogram (ECG) may be recommended to rule out significant bradycardia or heart block.

- Ongoing Monitoring: Patients should have their blood pressure and heart rate monitored during treatment, particularly during dose adjustments. In patients with comorbid conditions,

additional monitoring of liver function or renal function may be required, depending on their medical history.

Treatment Administration Requirements and Setting

- Administration: Bisoprolol is taken orally, once daily, preferably in the morning. It can be taken with or without food.
- Setting: Bisoprolol administration for migraine prevention is typically managed in an outpatient setting, such as neurology clinics, primary care and, potentially, also via community pharmacy facilities.
- Preparation: No special compounding or preparation is required. Bisoprolol is available in tablet form and is easy to administer.

Required Skill Levels of Healthcare Providers and Availability

- Provider Expertise: Healthcare providers prescribing bisoprolol for migraine prevention should have basic expertise in managing migraine and be familiar with beta-blocker use, including potential side effects and contraindications.
- Provider Availability: Bisoprolol is a commonly prescribed medication and there are no special requirements. Follow-up can be managed through primary care or, potentially, community pharmacy facilities.

Section 8: Review of evidence for benefits and harms

Evidence of efficacy for propranolol and bisoprolol vs comparators

We conducted a systematic search of the literature dealing with trial assessing the efficacy of beta-blockers in the prevention of migraine together with a large group of headache experts from several countries, including some contributors to this application, and strictly based on the use of the GRADE methodology.

Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions and overviews of reviews (Appendices 1 and 2). Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic.

A literature search for systematic reviews and meta-analyses and the RCTs published after the reviews and the meta-analyses was performed in 2022. As the process of literature search and analysis took more than 12 months, search strings were re-launched in May 2023 and November 2023 to update the search to the RCTs published from February 2022.

Search of available evidence was performed according to the Cochrane guidelines for systematic reviews of interventions *(23)* and overviews of reviews *(24)*. Cochrane guidelines were also followed for study selection, data extraction and synthesis. Reporting was performed according to relevant items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement *(25)*.

The literature search was performed for each pharmacological class of migraine prophylactic treatments. Three scientific databases were searched, namely PubMed, Scopus, and Cochrane Database, since the beginning of indexing, utilizing the PICOM (Patients – Intervention – Comparison – Outcome – Methods) methodology. To ensure a broad coverage of available literature, when building search strings, only Participants (i.e., migraine patients) and Interventions (i.e., drugs) were considered for each topic. The same search strings were launched in two separate searches. In search 1, we looked for systematic reviews and meta-analyses, while in search 2 we looked for RCTs published after the reviews and the meta-analyses retrieved in search 1. If Search 1 did not allow to retrieve any systematic review or meta-analysis, Search 2 was considered for RCT inclusion since the beginning of indexing of each database. Search 1 was performed at the beginning of search, while Search 2 was performed at the beginning and repeated in May 2023 and November 2023. Only published literature was considered for searches. Reference management and duplicate removal were performed with EndNote X6®.

Study selection

The selection process was performed in two stages. In stage 1, systematic reviews and meta-analysis covering the topic of interest were screened to identify eligible studies. In stage 2,

additional RCTs, published after the selected systematic review and meta-analyses were considered for inclusion. In case no systematic reviews and meta-analyses were available, only RCTs were selected.

Stage 1. Each module working subgroup initially received from the coordination supporting group an .xlsx file containing authors, publication year, title, abstract, and DOI of references retrieved during Search 1 (systematic reviews and meta-analyses) after duplicates were removed. Any further duplicates identified during the study selection process were accounted for in the study selection flow-chart. Module subgroups performed the study selection process in two phases, first evaluating titles and abstracts for eligibility, and then evaluating the full text of eligible references for inclusion. Inclusion and exclusion criteria for both phases are reported in Appendix 1. The evaluation process was performed by one rater, with a second rater consulted in case of uncertainty.

Stage 2. Module working subgroups received from the coordination supporting group an .xlsx file that contained the authors, publication year, title, abstract, and DOI of references retrieved during Search 2 (RCTs) after removing duplicates. To review all the literature that was not included in the selected systematic reviews and meta-analyses, the module working subgroups identified the most recent and comprehensive systematic review or meta-analysis on each pharmacological class and extracted the temporal limit (i.e., the 'until date') of the search. They then evaluated only the studies published after the identified 'until date' following the same evaluation procedure described in stage 1. The inclusion and exclusion criteria for eligibility and inclusion in phase 2 are presented in Appendix 2.

If duplicates were identified during study selection, they were considered and accounted for in the study selection flow-chart. Full texts of all RCTs identified in all systematic reviews and meta-analyses included in stage 1 were evaluated according to the same criteria. Therefore, module subgroups selected the final number of RCTs included in the review. This final number was revised if needed after the literature search updates performed in May 2023 and November 2023.

Main evidence: Our review includes results from RCTs with measurable outcomes of interest and reporting a sample size calculation and a study hypothesis for superiority or non-inferiority in the case of comparison between two active principles or an active principle and placebo. For each comparison, data included in this section were meta-analyzed separately for each outcome, introducing, when needed, subgroup analyses to describe the effect of different dosages. Analyses referring to outcomes of interest were considered among main evidence also if those outcomes were secondary outcomes in the included studies, provided that they were pre-specified. To describe all data retrieved in a homogenous way, meta-analyses were conducted also when only one study was available for a comparison and outcome.

Additional evidence: We also assessed data from RCTs lacking a clear study hypothesis for superiority or non-inferiority or a sample size calculation related to the comparison that is being considered (or, if performed, minimum sample size was not achieved). Data were meta-analyzed with the same procedure adopted for the previous section. This section also includes summaries of data from studies reporting considered outcomes and expressed through indexes not allowing to perform meta-analyses (e.g., medians or mean without SD).

Meta-analyses were performed using RevMan®, version 5.3. Computed effect sizes were Standardized Mean Difference (SMD) for continuous outcomes and Relative Risk (RR) for categorical outcomes. Pooled effect sizes were computed using the random effect model and expressed with a 95% Confidence Interval (95% CI).

The search strings used for retrieving systematic review/meta-analysis and for additional RCTs are reported in Appendix 1.

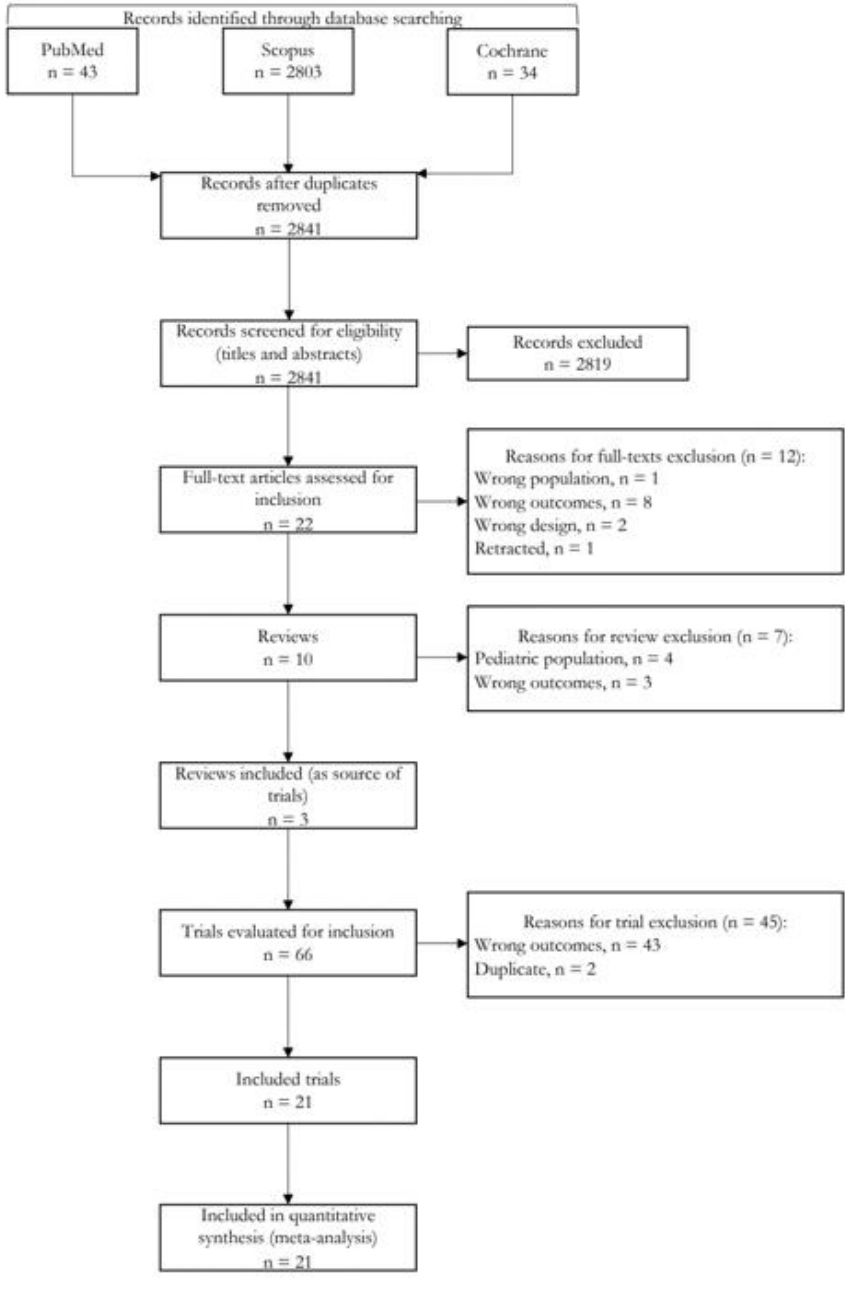

Figure 1. Flow-chart of the literature search for beta-blockers.

Overall, we retrieved 2386 references from searching for RCTs and after removing duplicates we had 2211 references to analyze (Figure 2). However, considering the most recent included meta-analysis on the topic*(22)*, the analysis of additional RCTs was performed for papers published since 21 August 2018 (623 references). No additional RCT was included in meta-analyses. The literature update performed in May 2023 and November 2023 led to the inclusion of one further RCT.*(26)*

Overall, 22 RCTs were included in the literature synthesis on beta-blockers overall.

For the analysis of the efficacy of drugs for the prevention of migraine, the outcomes considered were:

- persisting monthly headache/migraine days, defined as the residual days reported by patients at the end of the treatment (as reported in headache diaries);
- change in monthly headache/migraine days, defined as the variation in days reported by patients from baseline to the end of follow-up (as reported in headache diaries);
- ≥50% responder rate, defined as the proportions of patients reporting a ≥50% reduction in monthly headache/migraine days compared with baseline. The ≥50% reduction of monthly attacks was also considered for ≥50% responder rate whenever the reduction in monthly headache/migraine days was not available.

For beta-blockers, we also considered the outcomes of change in monthly migraine attacks and of persisting monthly migraine attacks. This choice was made to include even the oldest RCTs of beta-blockers. As the additional outcomes were not initially considered for the guidelines, the resulting quality of evidence was considered by definition as very low.

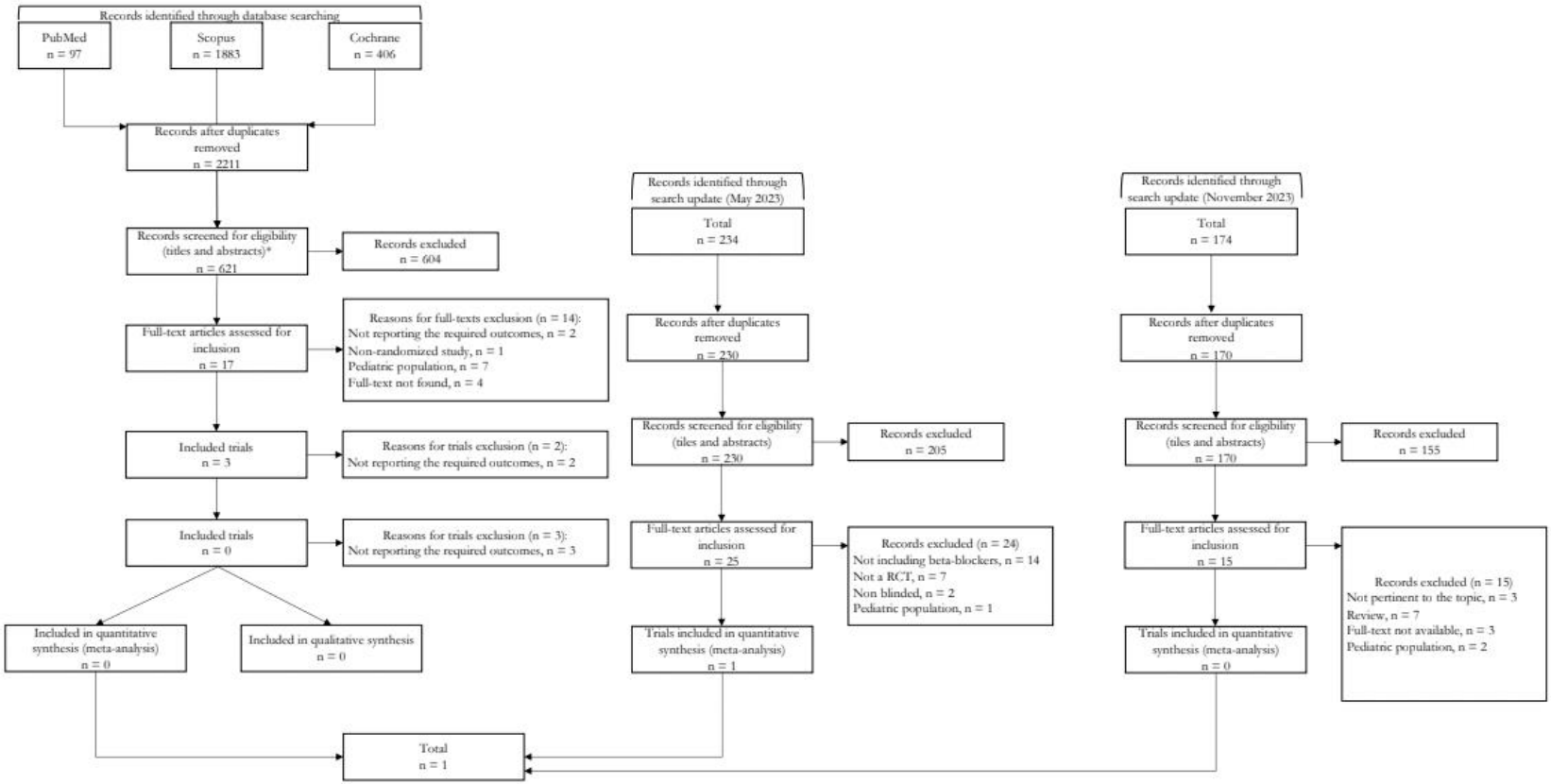

Figure 2. RCTs flow chart selection criteria.

Propranolol

We assessed the literature on the efficacy of propranolol in migraine prevention because propranolol in 2024 represents the only migraine preventive drug listed in the EML although the evidence of efficacy is very limited and to verify whether there was a stronger evidence of efficacy for other beta-blockers.
According to the systematic search of the evidence, there is one RCT comparing propranolol to placebo in patients with episodic migraine.*(27)* The risk of bias was considered serious (Figures 3 and 4). The RCT showed benefit of oral propranolol 160 mg daily over placebo considering the outcomes of change in monthly migraine days (Figure 3) and ≥50% responder rate (Figure 3). The quality of evidence was considered low (Table 1).

Additional evidence was derived from one RCT comparing propranolol to placebo *(28)* in participants with migraine without distinction between episodic and chronic. The risk of bias was considered not serious (Figures 5 and 6). The RCT showed no benefits of oral propranolol 160 mg daily over placebo considering the outcomes of persisting monthly migraine days (Figure 5) and ≥50% responder rate (Figure 6). The quality of evidence was considered moderate (Table 2).

There were 8 additional RCTs comparing propranolol to placebo.*(29-36)* Those RCTs did not report the predefined outcomes established to evaluate efficacy of migraine preventive drugs. The overall risk of bias from those RCTs was considered serious (Figures 7 and 8). The RCTs showed benefits of oral propranolol 80 mg and 160 mg daily over placebo considering the outcome of ≥50% responder rate (Figure 7) and of oral propranolol 160 mg daily over placebo considering the outcome of persisting monthly migraine attacks (Figure 8). The quality of evidence was considered very low.

There was no evidence of efficacy of lower doses than 160 mg daily. There was no evidence of efficacy specific for chronic migraine.

Bisoprolol

The systematic search of the literature revealed one RCT*(37)* comparing oral bisoprolol 5 mg or 10 mg to placebo over a treatment period of 12 weeks in participants with migraine (no distinction between episodic and chronic). The study had a very serious risk of bias, and the quality of evidence was overall considered very low (Figures 9 and 10). The study showed benefits of oral bisoprolol 5 mg and 10 mg over placebo considering the outcomes persisting monthly migraine days (Figure 9) and change in monthly migraine days (Figure 10).

It is important to note that many of the oral medications used for migraine prevention were evaluated in older trials that do not meet current standards for high-quality evidence. Despite this, these drugs, including beta-blockers, have long been the cornerstone of migraine prevention and have been widely used around the world.

Bisoprolol was not specifically studied in special groups of subjects with migraine such as pregnant women or in the elderly.

Bisoprolol is not routinely recommended in pregnancy due to limited safety data. Beta-blockers, in general, can cross the placenta and have been associated with potential fetal risks, including growth restriction and neonatal bradycardia. Although bisoprolol's selective beta-1 adrenergic blocking properties may reduce adverse effects compared to non-selective beta-blockers, its use should be carefully weighed against potential risks.
Bisoprolol is frequently prescribed to elderly patients for indications other than migraine. In the elderly, bisoprolol is generally well-tolerated, but careful dosing and gradual titration are advised due to age-related changes in drug metabolism and elimination. Potential side effects, such as fatigue, bradycardia, hypotension, and dizziness, may be more pronounced in this population, increasing the risk of falls. Monitoring and adjusting for renal function is essential, as impaired clearance can lead to drug accumulation.

Propranolol versus Bisoprolol

There were no studies comparing propranolol and bisoprolol in terms of efficacy or safety in migraine populations.

Safety and tolerability of beta-blockers

Tolerability: beta-blockers present some adverse events that might limit their use in the general population. These effects, typical of non-cardioselective beta-blockers such as propranolol, are mostly associated with the antagonism of beta-2 receptors located in smooth muscle cells in the lungs, pancreas, bladder, uterus, blood vessels, and gastrointestinal system, thus affecting affect smooth muscle relaxation in bronchioles, blood vessels, and the uterus, as well as alter metabolic processes such as glycogenolysis and insulin release from pancreatic beta cells*(38)*. Moreover, lipophilic beta-blockers such as propranolol can cross the blood–brain barrier, leading to depression, fatigue, and disorders of sleep.*(22, 28, 38, 39)* Also, beta-blockers can cause impaired glucose metabolism, with new-onset diabetes.*(28, 39)* Gastrointestinal complaints, with nausea, abdominal cramps and diarrhea, weight gain, paresthesias, and Raynaud's phenomenon, dizziness and vertigo have also been reported.*(22, 28, 38-42)*

Warnings and Contraindications: beta-blockers are contraindicated in patients with asthma, congestive heart failure, cardiac dysrhythmia, depression.*(22, 38, 39)* Indeed, due to the risk of bradyarrhythmia, they should not be used in recent myocardial infarction, coronary artery disease, congestive heart failure.*(39)* Extreme caution is recommended in patients with a history of asthma due to concerns of decreasing pulmonary function and inducing bronchospasm.*(39, 40)* Data from literature indicates that depression is commonly reported after the use of beta-blockers.*(22, 28, 38)* Additional caution is required in subjects taking triptans, as beta-blockers increase plasma concentrations of triptans.*(39)* Considering the risk of myasthenic crisis exacerbation, attention is needed in patients with myasthenia gravis.*(43)* Finally, beta-blockers should not be used in hemiplegic migraine, as safety was not investigated

and the evidence of efficacy is lacking in this clinical population.*(39)* Bradycardia and hypotension may limit their use in cardiopathic patients.

Serious safety concerns: RCTs and real world-evidence highlighted some serious safety concerns. Real world evidence demonstrated a potentially fatal outcome in patients with asthma.*(39, 44)* Caution is necessary in older cardiopathic subjects. These patients may benefit from the use of low dose of cardioselective beta-blockers.*(22, 39)*

Bisoprolol showed a good profile of safety and tolerability, according to the limited data available from one RCT*(37)* on patient with migraine. The RCT counted a comparable number of adverse effects between bisoprolol and placebo, mostly represented by fatigue and dizziness. Only dizziness was more common in the active treatment group compared to placebo. A reduction in heart rate and systolic and diastolic pressure was observed only in the active treatment group. No serious adverse events were reported.

Some serious adverse effects were reported in trials on beta-blockers for migraine prevention, including one case of hepatitis.*(34)* Only one fatal adverse event was reported in a case report of timolol eye-drop treatment for glaucoma.*(44)*

Conclusions from the systematic analysis of evidence
The evidence of efficacy in the prophylaxis of migraine is limited for both propranolol and bisoprolol. Propranolol is presently the only drug for the prophylaxis of migraine in the EML. Altogether, this reinforces our request to accept bisoprolol as an additional option to propranolol because of a better usability (once a day) and a more favourable cardiac safety profile.

Certainty assessment					№ of patients		Effect		Quality	Importance
Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute (95% CI)		
Change in monthly migraine days – Propranolol 160 mg oral vs Placebo										
Serious	Not applicable[1]	Not serious	Not serious	None	143	143	-	SMD **0.3** (0.5-0.0) **lower**	⨁⨁⨀⨀ **Low**	Critical
≥50% responder rate – Propranolol 160 mg oral vs Placebo										
Serious	Not applicable[1]	Not serious	Not serious	None	61/143 (42.7%)	31/143 (21.7%)	**RR 1.97** (1.37-2.83)	**210** (80-397) **more per 1.000**	⨁⨁⨀⨀ **Low**	Critical
[1]Only one trial										

Table 1. GRADE evidence profile from the single relevant RCT for oral propranolol 160 mg versus placebo for episodic migraine.

Certainty assessment					№ of patients		Effect		Quality	Importance
Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute (95% CI)		
Persisting monthly migraine days – Propranolol 160 mg oral vs Placebo										
Not serious	Not applicable[1]	Not serious	Not serious	None	60	60	-	SMD **0.3 lower** (0.7 lower to 0.0 higher)	⨁⨁⨁⨀ **Moderate**	Critical
≥50% responder rate – Propranolol 160 mg oral vs Placebo										
Not serious	Not applicable[1]	Not serious	Not serious	None	24/60 (40.0%)	14/60 (23.3%)	**RR 1.71** (0.99 to 2.98)	**166 more per 1.000** (from 2 fewer to 462 more)	⨁⨁⨁⨀ **Moderate**	Critical
[1]Only one trial										

Table 2. GRADE evidence profile for oral propranolol 160 mg versus placebo in people with migraine (no distinction between episodic and chronic).

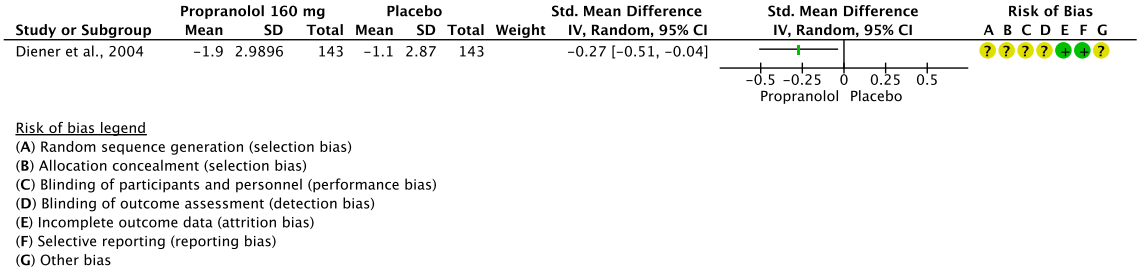

Figure 3. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome change in monthly migraine days in people with episodic migraine.

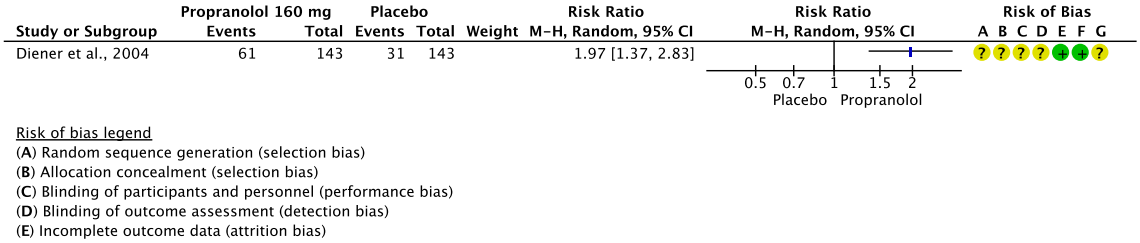

Figure 4. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome ≥50% responder rate in people with episodic migraine.

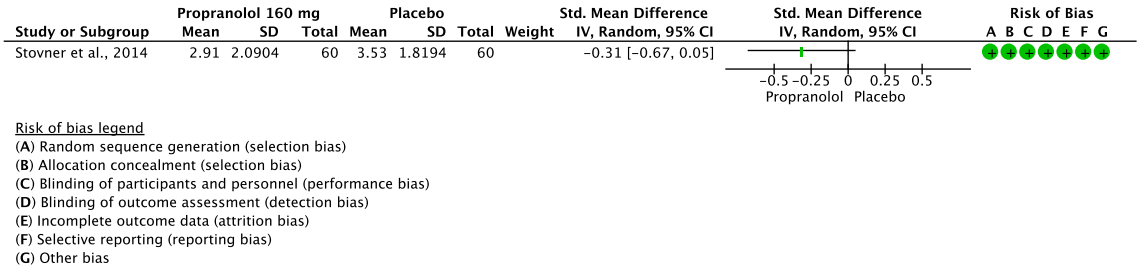

Figure 5. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome persisting monthly migraine days in people with migraine (no distinction between episodic and chronic).

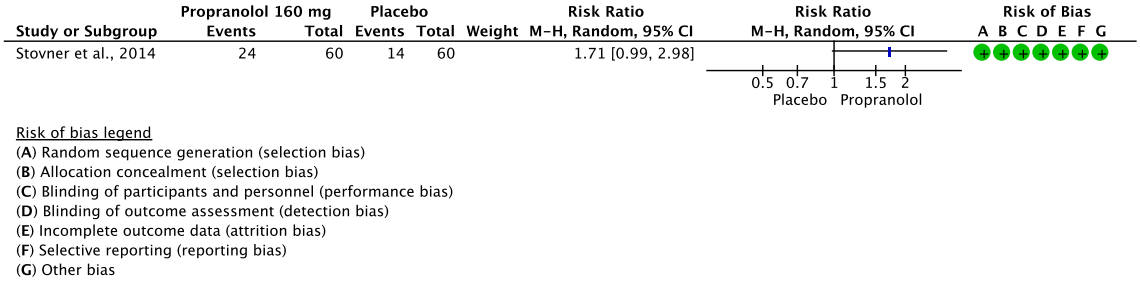

Figure 6. Forest plot showing the comparison between oral propranolol 160 mg daily and placebo for the outcome ≥50% responder rate in people with migraine (no distinction between episodic and chronic).

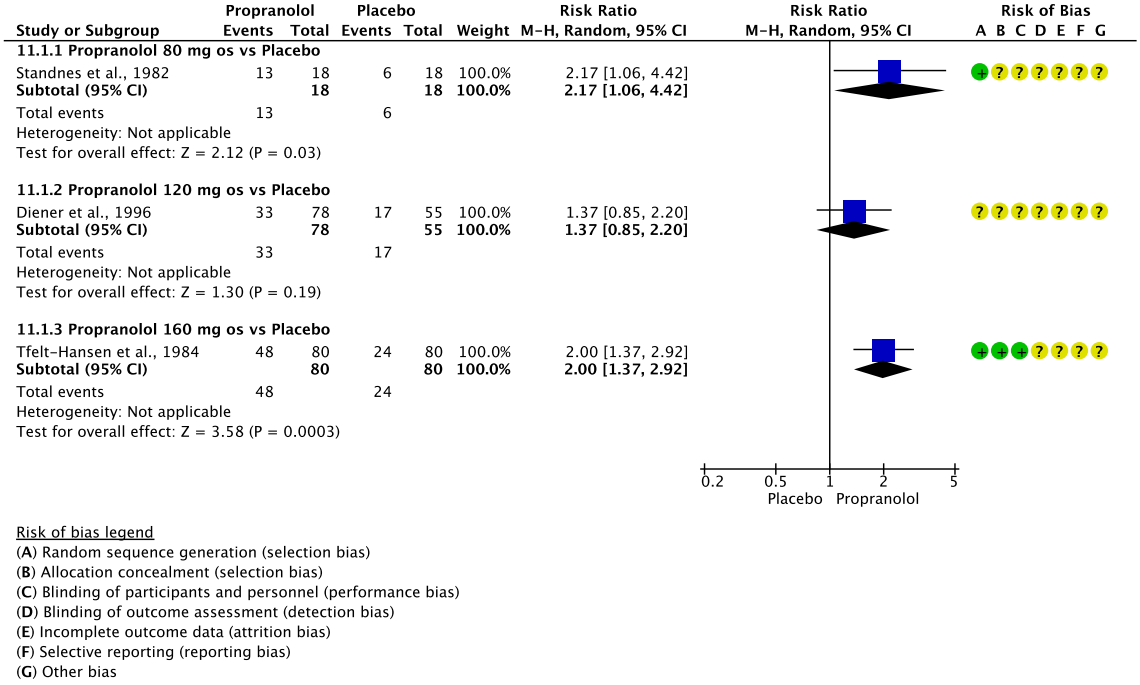

Figure 7. Forest plot showing the comparison between oral propranolol and placebo for the outcome ≥50% responder rate in people with migraine (no distinction between episodic and chronic).

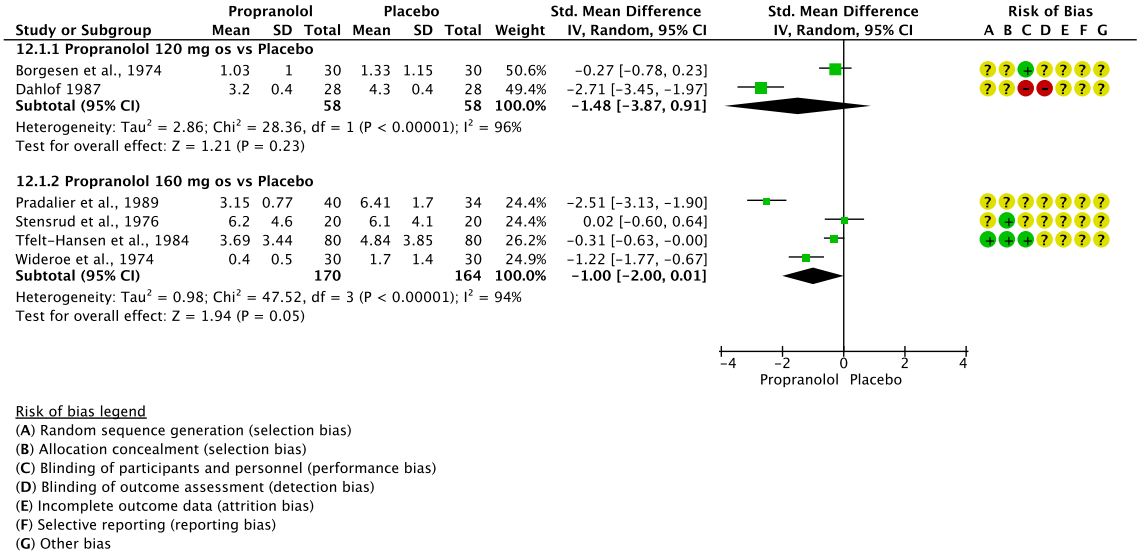

Figure 8. Forest plot showing the comparison between oral propranolol and placebo for the outcome persisting monthly migraine attacks in people with migraine (no distinction between episodic and chronic).

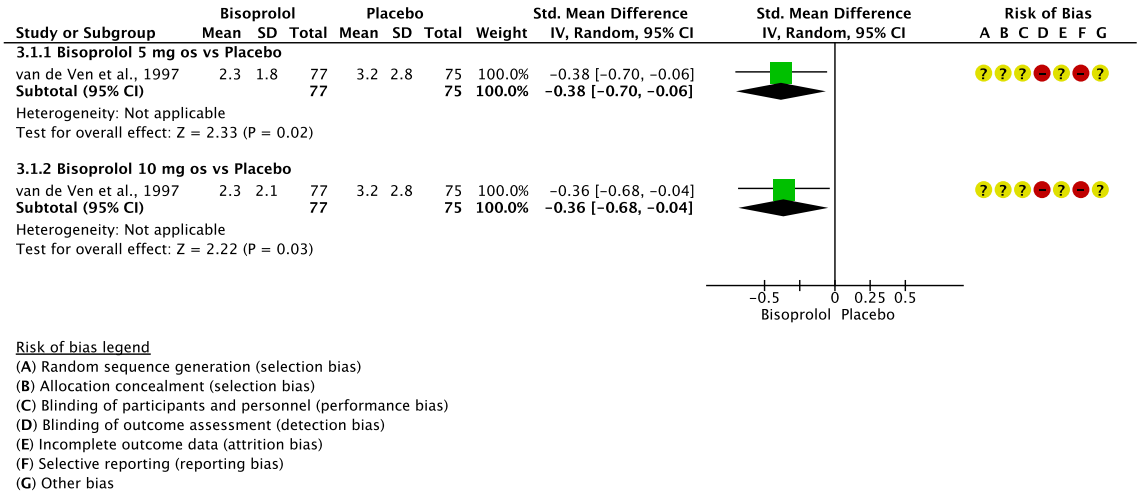

Figure 9. Forest plot showing the comparison between oral bisoprolol 5 or 10 mg and placebo for the outcome persisting monthly migraine days in people with migraine (no distinction between episodic and chronic).

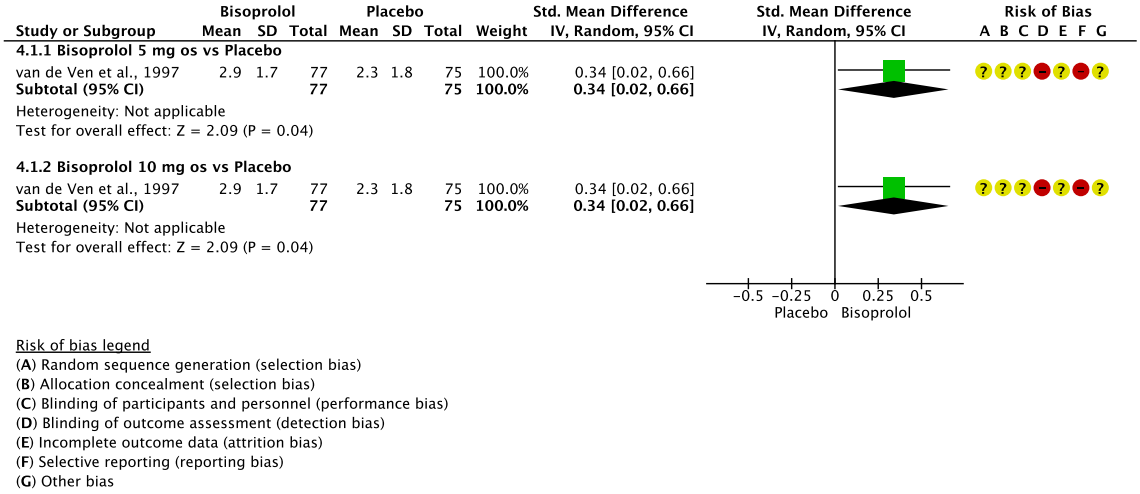

Figure 10. Forest plot showing the comparison between oral bisoprolol 5 or 10 mg and placebo for the outcome change in monthly migraine days in people with migraine (no distinction between episodic and chronic).

Section 9: Summary of recommendations in current clinical guidelines

Recommendations in existing WHO guidelines

N.A.

Recommendations in other current clinical guidelines

Table: Summary of recent guidelines and recommendations including propranolol and bisoprolol for the preventive treatment of migraine.

Guideline	Year	Recommendation
WHO - Lifting the Burden/ European Headache Federation (EHF) Guidelines *(45)*	2007	• Beta-blockers, including bisoprolol 5-10 mg or and propranolol long-acting 80 mg od-160 mg bd, are indicated as preventive drugs with good evidence of efficacy for migraine
European Federation of Neurological Societies (EFNS) Guidelines *(46)*	2009	• Beta-blockers are clearly effective in migraine prophylaxis. • The best evidence has been obtained for metoprolol and propranolol. Also, bisoprolol […] might be effective.
Danish Headache Society Guidelines *(47)*	2021	• Beta-blockers should normally be chosen as the first of first-line drugs. There is best evidence for propranolol […].40 mg × 2 increased at a weekly interval to a maximum of 120mg × 2. There is often an effect at 120–160mg daily. • There is some evidence for the effect of bisoprolol
German Headache Society Guidelines *(48)*	2022	• The beta blocker propranolol is effective in migraine prevention • The evidence for the preventive treatment effect of other beta-blockers is less well established • Bisoprolol was significantly superior to placebo in one trial and equally effective to metoprolol in another.

Section 10: Summary of available data on comparative cost and cost-effectiveness

There are no published studies on the cost-effectiveness of propranolol or bisoprolol for migraine prevention.

In this modelling, we compared bisoprolol (5 mg daily) with propranolol (160 mg daily), the latter being already on the EML for this indication. The study by Linde, Steiner and Chisholm *(49)*, using WHO-CHOICE, provided a valuable cost-effectiveness modelling framework for migraine in four low- and middle-income countries. We assessed effectiveness in terms of HLYs gained per treated individual. We estimated HLYs gained as the product of the reduction in mean time in the ictal state (rTIS) and the disability weight (DW) of 0.441 for the ictal state from the Global Burden of Disease (GBD) 2013 study. We used a treatment timeframe of 6 months, the typical duration of treatment in clinical practice.

To derive rTIS, we used reported reductions in monthly migraine days (rrMMD) in RCTs (see section 8): for propranolol 1.5; for bisoprolol 2.9. We assumed that effective treatment reduced the frequency of attacks without affecting their duration.

We assumed conservatively that rrMMD was achieved by linear reduction over the first 3 months then maintained over months 4-6. Thus, actual reduction over a 6-month treatment period (arMMD) was given by the formula:

arMMD (per 6 months) = ([rrMMD/2*3]+[rrMMD*3]) = rrMMD*4.5.

To establish mean duration (D) of headache occurring on 1 MMD, we used data from population-based studies conducted by *Lifting The Burden* among N=8,363 in 14 countries (China, Mongolia, Nepal, India, Pakistan, Saudi Arabia, Morocco, Benin, Cameroon, Ethiopia, Zambia, Peru, Lithuania and Russian Federation, which represented a range of low- to high-income settings), considering only those reporting 4-14 days/month (the candidate population for beta-blockers). From these, D=21.5 hours. Therefore:

rTIS (per 6 months) = {(arMMD*[21.5/24])/365} years

and

HLYs gained per treated patient (per 6 months) = rTIS*0.441.

In terms of costs, we included only medication acquisition costs, assuming other healthcare costs to remain constant across different treatment options. We assumed treatment was continued initially for 3 months, but from months 4 to 6 only in the proportion (Pr) who had responded (ie, those reporting a reduction in MMDs after 3 months of at least 50%). We established unit costs in US$ of bisoprolol 5 mg tablets and propranolol 160 mg (4*40 mg tablets) as the medians of those reported for each by experts in nine countries (Moldova, Georgia, Egypt, Nepal, India, Indonesia, Mongolia, Argentina and Brazil) along with those provided by the UK NHS drug tariff, and multiplied these by 30 to derive monthly medication costs (Table 3: bisprolol US$ 2.24/month; propranolol US$ 3.55/month).

Table 3. Medication acquisition costs reported from nine countries and in the UK NHS drug tariff

			Propranolol 160 mg (4*40 mg)						Bisoprolol 5 mg				
Country	**Exchange**		**Cost 40 mg local**	**Quantity**	**Cost 160 mg local**	**Monthly cost local**	**Monthly cost $**		**Cost local**	**Quantity**	**Unit cost local**	**Monthly cost loca**	**Monthly cost $**
Egypt	0.02064		55.00	50	4.400	132.00	2.72		51.00	30	1.700	51.00	1.05
Moldova	0.05643		19.00	50	1.520	45.60	2.57		25.00	30	0.833	25.00	1.41
Nepal	0.00737		40.50	10	16.200	486.00	3.58		126.00	10	12.600	378.00	2.79
India	0.01198		10.00	40	1.000	30.00	0.36		39.00	10	3.900	117.00	1.40
Georgia	0.3663		3.62	20	0.724	21,72	7.96		1.70	10	0.170	5.10	1.87
Indonesia	0.00006		488.00	1	1952.000	58560.00	3.51		1452.00	1	1452.000	43560.00	2.61
Mongolia	0.000296		7600.00	20	1520.000	45600.00	13.50		18000.00	30	600.000	18000.00	5.32
Argentina	0.00104		280.45	1	1121.800	33654.00	35.00		293.55	1	293.550	8806.50	9.16
Brazil	0.17961		0.11	1	0.440	13.20	2.37		0.93	1	0.930	27.90	5.01
UK (NHS drug tariff)	1.31205		0.71	28	0.101	3.04	3.99		0.73	28	0.026	0.78	1.02
Median							**3.55**						**2.24**

To derive costs for 6 months (180 days), we used the formula:

6-month cost = monthly medication cost * [(6*Pr)+(3*{1–Pr})]

reflecting that treatment was discontinued after 3 months (with no further costs) in non-responders.

We used data from three RCTs (section 8, Figures 4, 6 and 7) to calculate Pr = 133/283 (47.0%) for propranolol. No RCTs reported Pr for bisoprolol, so, for this analysis, we assumed the same (conservatively, since bisoprolol performed better on the measure rrMMD).

Table 4 summarises the input data.

Table 4: Summary of input data

	Monthly medication cost (from Table 3: US$ 2024 values)	Mean frequency (F) (monthly migraine days) from N=8,363 in 14 countries (F 4-14)	Mean attack duration (D) (hours) from N=8,363 in 14 countries (F 4-14)	Proportion of those treated who report response (Pr) (reduction in F by ≥50% at 3 months)	Change in monthly migraine days (treated)
Bisoprolol (5 mg daily)	2.24	6.5	21.5 hours	47%	-2.9
Propranolol (160 mg daily)	3.55	6.5	21.5 hours	133/283 (47.0%)	-1.49

Cost/HLY gained

Accordingly, cost/HLY gained was given by:

cost over 6 months/{[(rrMMD*4.5)*(21.5/24)]/365}*0.441}

for propranolol:

cost/HLY gained = 3.55*[(6*0.47)+(3*0.53)]/{[(1.5*4.5)*(21.5/24)]/365}*0.441 = US$ 417

for bisoprolol:

cost/HLY gained = 2.24*[(6*0.47)+(3*0.53)]/{[(2.9*4.5)*(21.5/24)]/365}*0.441 = US$ 136.

On this evidence, both treatments are highly cost-effective, but bisoprolol dominates (less expensive, more effective).

It should be noted that this analysis did not include likely additional gains with bisoprolol associated with better tolerability and better adherence (less wastage), since no empirical evidence was available to quantify these. Neither did it include additional healthcare provider costs that might be associated with prescriptions and monitoring, which would apply equally to both medications.

Incremental cost-effectiveness (ICER)

In this modelling, again comparing bisoprolol (5 mg daily) with propranolol (160 mg daily), we applied the same assumptions and took data from the same sources. Among non-responders, MMDs were considered to remain unchanged during the treatment period. In contrast, responders were assumed to experience a linear decline in MMDs during the first 3 months to their new value, maintaining this reduction for the remainder of the 6 months. The key findings are in Table 5.

Table 5: ICER analysis

	Six-month treatment cost per person (US$ 2024 values)	**HLY gained per person**	**Diff 6-month costs per person**	**Diff HLYs gained per person**	**ICER (extra US$ to be invested per HLY gained)**	**Comments**
Bisoprolol (5 mg daily	9.88	1.41E-02	-5.78	6.81E-03	lower cost, more effective	**preferred option**
Propranolol (160 mg daily)	15.66	7.31E-03	comparator			**dominated**

Bisoprolol 5 mg daily is the preferred option, dominating propranolol 160 mg daily (less expensive, more effectiveness) (Table 5).

It should be noted that this analysis, and the preceding one, was sensitive to comparative costs. While median cost of bisoprolol was lower than median cost of propranolol, in some countries bisoprolol was more expensive (Table 3).

It should further be noted that there are wide uncertainties in both analyses in view of the poor quality of the input data from RCTs conducted many years ago (see section 8).

Section 11: Regulatory status, market availability and pharmacopoeial standards

Bisoprolol: Regulatory Status, Market Availability, and Pharmacopoeial Standards

1. Regulatory Status

Regulatory Approval:
- United States: Bisoprolol is approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypertension, heart failure, and chronic stable angina.
- European Union: Bisoprolol is approved by the European Medicines Agency (EMA) for the management of hypertension, chronic heart failure, and angina pectoris.
- Other Regions: In many other countries, bisoprolol is approved for similar indications, including hypertension and heart failure.

Off-Label Use:
- Bisoprolol is used off-label for conditions such as migraine, atrial fibrillation and anxiety.

Bisoprolol in EML
Bisoprolol is listed in the EML for the following conditions: antianginal medicine, antiarrhythmic medicine, antihypertensive medicine, and as medicine used in heart failure. Its use in the treatment of other diseases may support not only its availability in countries but also its regulatory status. Bisoloprolol is currently included in WHO EML and in the national EMLs of 48 countries.

2. Market Availability

- Brand Availability: Bisoprolol is available globally under several brand names (e.g. Zebeta, Concor).
- Generics: Bisoprolol is available in generic form in many countries, contributing to its widespread availability and lower cost compared to branded versions.
- Patent Status: Bisoprolol's original patents have expired, leading to a broad availability of generic versions. There are numerous generic manufacturers producing bisoprolol.

3. Supply Chain and Shortages
- Bisoprolol is generally well-supplied. There are typically few supply chain issues for bisoprolol, but regional distribution problems could impact availability.

4. Pharmacopoeial Standards

Propranolol: https://pheur.edqm.eu/app/11-5/content/11-5/0568E.htm?highlight=on&terms=propranolol

Bisoprolol: https://pheur.edqm.eu/app/11-5/content/11-5/1710E.htm?highlight=on&terms=bisoprolol

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To whom it may concern

Re: Support and Endorsement for the application for the inclusion of additional drugs for the treatment of migraine in the WHO Essential Medicines List

On behalf of EHMA, the leading non-profit umbrella organization of 34 patient associations for Migraine, Cluster Headache, Trigeminal Neuralgia and other headache diseases, dedicated to supporting individuals with migraine and other headache, I am writing to express our wholehearted support and endorsement for the joint application made by the International Headache Society, Lifting the Burden and European Headache Federation to include addition drugs for the acute and preventive treatment of migraine in the World Health Organization Essential Medicines List.

Migraine, characterized by their severe and debilitating nature, pose a significant challenge to those affected, impacting their quality of life and daily functioning. As a patient organization, we witness firsthand the profound suffering experienced by individuals with this condition. Despite the availability of effective treatments, many patients still face barriers to accessing these critical therapies, particularly in regions with limited healthcare resources.

The inclusion of additional treatment options, such as naproxen, eletriptan, amitriptyline, bisoprolol and fremanezumab in the WHO Essential Medicines List is a crucial step towards improving global access to these essential medications. It would ensure that effective and life-changing treatments are available to individuals regardless of their geographic or economic circumstances. This inclusion not only aligns with the WHO's mission to improve global health equity but also represents a significant advancement in the fight against a condition that affects millions worldwide.

Our organisation is committed to supporting this initiative and are available to provide any further information or assistance. We look forward to the positive impact this development will have on the global health landscape.

Sincerely,
EMHA – European Migraine and headache Alliance