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# Research Submission

## Warfarin for Refractory Chronic Cluster Headache: A Randomized Pilot Study

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**Objective.—To investigate the effect of low-intensity anticoagulation with warfarin on chronic cluster headache refractory to pharmacological management.**

**Background.—Isolated case reports on induction of remission in patients with intractable chronic cluster headache upon institution of oral anticoagulant therapy do exist. Nonetheless, evidence from randomized controlled trials on the role of oral anticoagulants in cluster headache is lacking.**

**Methods.—Thirty-four patients with refractory chronic cluster headache were randomized to receive warfarin or placebo for 12 weeks. Warfarin was administered to achieve an international normalized ratio between 1.5 and 1.9. After a washout period of 2 weeks, patients were crossed over from 1 treatment to the other. Status of cluster headache was assessed during both treatment periods. The primary outcome measure was the occurrence of remission lasting ≥4 weeks.**

**Results.—Seventeen (50%) patients underwent remission for ≥4 weeks during the warfarin period vs 4 (11.8%) patients during the placebo period ($P = .004$). This was associated with absolute risk reduction of 0.38 (95% CI = 0.18-0.58), and number needed to treat of 2.6 (95% CI = 1.7-5.5). The Kaplan–Meier curves for occurrence of remission had a hazard ratio of 5.26 (95% CI = 2.13-13.03, $P = .0003$). Frequency, duration, and intensity of cluster attacks were all significantly lower during treatment with warfarin ($P < .01$).**

**Conclusion.—In patients with refractory chronic cluster headache, low-intensity anticoagulation with warfarin was associated with significantly higher incidence of remission and less impact of headache on patients' lives compared with placebo.**

**Key words: cluster headache, chronic, refractory, warfarin, low-intensity anticoagulation**

**Abbreviations: CCH chronic cluster headache, CH cluster headache, HIT-6 Headache Impact Test-6, INR international normalized ratio, VKA vitamin K antagonists**

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The prevalence of cluster headache (CH) has been variably reported as ranging from 56 to 326 per 100,000 in the general population,[1,2] and from 229 to 2500 per 100,000 in selected populations.[3,4] Nonetheless, a lifetime prevalence rate on the order of 279 per 100,000 seems to be the most likely figure in those aged over 14 years.[5] In contrast to time-honored notions, a progressively increasing prevalence is being reported among women.[6]

Cluster headache is perhaps the most painful of primary headache disorders, and in its chronic form, it may run a relentless course that is refractory to pharmacological treatment.[7] Intractable chronic cluster headache (CCH) could be quite incapacitating requiring interventional[8] or surgical[9,10] options be applied to management. However, such interventions may not be feasible in all patients for evident reasons.[11]

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*Conflict of Interest:* None.

There have been isolated case reports on induction of remission in patients with CCH refractory to pharmacological treatment upon institution of oral anticoagulant therapy.[12,13] Similar reports on the efficacy of oral anticoagulants in migraineurs do exist.[14-17] Nonetheless, evidence from randomized controlled trials on the role of oral anticoagulant therapy in CH is lacking.

The aim of the present trial was to study the effect of low-intensity anticoagulation with warfarin on the occurrence of remission lasting 4 weeks or longer in patients with CCH refractory to pharmacological treatment.

## METHODS

This randomized, double-blind, placebo-controlled, crossover study was conducted during the period from November 2006 to October 2009. After approval of the institutional review board (Research Ethics Committee, Faculty of Medicine, Ain Shams University, Cairo, Egypt) and obtaining an informed consent, 27 patients who suffered from refractory CCH, and who were referred to the pain clinic of Ain Shams University Hospital, were included. Details of the trial protocol could be obtained from the Department of Anesthesiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

**Patient Selection.—**Patients with CCH were eligible if they were severely disabled by the headache as evidenced by a score of 60 or more on the Arabic version of the Headache Impact Test-6 Questionnaire (HIT-6™ v.1.1, Quality Metric, Inc., Lincoln, RI, USA and GlaxoSmithKline, Brentford, Middlesex, UK), which is an authentic translation of the English version of the Questionnaire, despite having tried 4 prophylactic medications including verapamil, lithium, topiramate, and gabapentin. The prophylactic medications should have been administered, singly or in combination, in the maximal tolerated doses for at least 6 months with failure to bring about a tangible improvement in the quality of life as evidenced by an HIT-6™ score of 55 or less, corresponding to the "some impact" or "little or no impact" categories of the Questionnaire. The diagnosis of CCH was based on experiencing at least 5 cluster bouts fulfilling the International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria for CH that kept recurring for >1 year without remission or with remission lasting <1 month.[18] Patients were ineligible if they had migrainous features or suffered from other recurrent headache disorders.

All patients were assessed for the risk of oral anticoagulant-related bleeding using the Outpatient Bleeding Risk Index.[19] Patients were excluded if they scored 1 or more, which corresponded to an intermediate-to-high risk. This was signified by the presence of 1 or more of the following: age ≥65 years, history of stroke or gastrointestinal bleeding, recent myocardial infarction, diabetes mellitus, hematocrit <30%, or serum creatinine >1.5 mg/dL. Patients were also excluded if they had to receive heparin (fractionated or unfractionated), antiplatelet agents, or non-steroidal anti-inflammatory drugs, or if oral anticoagulants had to be administered for reasons other than that of the study. Other exclusion criteria were history of bleeding diatheses, thrombocytopenia (platelet count <150,000/$\mu$L), hypertension, peptic ulcer disease, pregnancy, or lactation.

**Study Flow and Patient Randomization.—**Patients were provided with a diary and were asked to record daily the frequency, duration, and intensity (on a scale from 0 to 10) of cluster attacks experienced. After a washout period of 2 weeks during which ineffective prophylactic medications were discontinued, a run-in period of 4 weeks was allowed to determine the baseline status of CH. During both the washout and the run-in periods, abortive medications were permitted as needed for the cluster attacks. These consisted in oxygen inhalation, if available, subcutaneous sumatriptan, and intranasal lidocaine.

At the end of the run-in period, baseline prothrombin time and international normalized ratio (INR) were obtained, and the baseline status of CH was estimated by averaging the frequency, duration, and intensity of cluster attacks as recorded in the headache diary. In addition, the impact of headache on patients' lives was assessed using the Arabic version of the HIT-6™ Questionnaire. Thereafter, recruited subjects were randomly allocated to receive warfarin (WP sequence) or placebo (PW sequence) for 12 weeks. After a washout period of 2 weeks, patients were crossed over to receive the

other treatment for another 12 weeks. Randomization was carried out by a clinician not involved in the trial using a computer-generated random number list. The list was created with the GraphPad StatMate™ v.1.01i software (GraphPad Software Inc., San Diego, CA, USA) using blocks of 4 patients each, and was accessible to clinicians attending to patients at the anticoagulation clinic through the computer database immediately prior to implementation of randomization.

During the warfarin treatment period, patients were provided with 2-mg tablets of warfarin, and low-intensity anticoagulation was instituted to achieve a target INR between 1.5 and 1.9. During the placebo period, a placebo was substituted for warfarin. The placebo tablets were prepared by the hospital's pharmacy and were identical to those of warfarin as regards appearance and taste. The test drugs were dispensed in similar bottles numbered for each patient according to the computer-generated random number list.

Abortive medications were allowed during both treatment periods, as well as during the washout period. These included oxygen inhalation, oral zolmitriptan, and intranasal lidocaine. However, no prophylactic medication was administered during any of these periods.

**Management of Anticoagulant Therapy.—**Anticoagulant therapy was managed at the anticoagulation clinic by clinicians who were not blinded to the treatment received. A dosing nomogram for low-intensity anticoagulation[20] was used to keep the INR in the desired range. Warfarin was initiated at 2 mg/day, and the INR was assayed on days 3, 4, 5, and 6 from the initiation of warfarin,[21] then every 2 weeks thereafter.

For patient blinding, the INR was assayed during the placebo period as described for warfarin. However, a sham INR was serially selected from a randomly prepared list of values in the desired range to relay to the pain clinic, and the placebo dose was adjusted by the anticoagulation services staff accordingly using the same nomogram as for warfarin.

**Outcome Measures and Assessment of Headache.—**The primary outcome measure was the occurrence of remission lasting 4 weeks or longer. Secondary outcome measures were the status of CH and its impact on the patients' quality of life.

During each treatment period, patients were seen at the pain clinic every 4 weeks by physicians blinded as to the treatment received. At each visit, the impact of headache on the patients' lives was scored using the Arabic version of the HIT-6™ Questionnaire. The Questionnaire returned a total score ranging from 36 to 78, and the impact of headache was stratified according to the attained score into 4 categories: "very severe impact = score $\geq$60," "substantial impact = score of 56-59," "some impact = score of 50-55," and "little or no impact = score $\leq$49."

**Statistical Analysis.—**The required sample size was estimated using the Power Analysis and Sample Size software v. 08.0.9 (PASS©, NCSS LLC, Kaysville, UT, USA). The primary outcome measure was the proportion of patients who underwent remission lasting $\geq$4 weeks. Using a design with 2 repeated measurements, it was estimated that a sample of 25 patients would achieve a power of 0.91 to detect a difference of 40% between the 2 treatments, when the 2-sided $\alpha$-error was 0.05 and the correlation (rho) between observations on the same subject was 0.9.

Statistical analysis was carried out on a personal computer using the Statistical Package for Social Sciences© v. 17 (SPSS©, SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov's goodness-of-fit test was performed initially to test the hypothesis that numerical data were normally distributed. Numerical data were presented as mean (standard deviation), if normally distributed, or as median (interquartile range), if non-normally distributed. Categorical data were presented as ratio or as number (%).

To compare normally distributed numerical data, the paired-samples Student's *t*-test or the independent-samples *t*-test was used to compare paired or unpaired data, respectively. For non-normally distributed numerical data, the Wilcoxon signed-ranks test was used to compare paired data, and the Mann–Whitney *U*-test was applied for unpaired data.

The McNemar test was used to compare categorical data, if paired, and the Pearson chi-square test

was used for unpaired data. The Fisher's exact test was applied in place of the Pearson chi-square test when appropriate.

Kaplan–Meier curves for occurrence of remission lasting 4 weeks or longer were constructed using GraphPad Prism© v. 5 (GraphPad Software Inc., San Diego, CA, USA), and the difference between curves was compared using the log rank test. The beginning of remission was the time point for entry in the Kaplan–Meier analysis.

An interim analysis was conducted using the O'Brien–Fleming method after 50% of the required sample size had been recruited, in order to decide whether to continue or to stop patient recruitment.

$P < .05$ was regarded as statistically significant.

## RESULTS

Between November 2006 and October 2009, 45 patients were referred to the pain clinic with refractory CCH. Five (11.1%) patients did not fulfill eligibility criteria, while 6 (13.3%) declined to participate in the study. Thirty-four (75.6%) patients were enrolled and were randomized to receive warfarin followed by placebo (WP sequence, n = 18) or to receive placebo followed by warfarin (PW sequence, n = 16). In the WP sequence, 1 (5.6%) patient requested to withdraw from the study in the 8th week, and 3 (16.7%) patients were lost to follow-up (2 [11.1%] in the 10th week, and 1 [5.6%] in the 12th week). On the other hand, 3 (18.8%) patients in the PW sequence were lost to follow-up (1 [6.3%] in the 6th week and 2 [12.5%] in the 10th week). Twenty-seven (79.4%) patients completed the study (14 in the WP sequence, and 13 in the PW sequence). Patients who requested to withdraw from the study and those lost to follow-up were excluded from the per-protocol (PP) analysis but were included in the intention-to-treat (ITT) and Kaplan–Meier analyses as censored data (Fig. 1).

An interim analysis using the O'Brien–Fleming method was planned after 50% of the required sample size had been recruited. The analysis used a final 1-sided $\alpha$-error of 0.025, which was associated with a Z statistic of 1.98, and an interim $\alpha$-error of 0.003 which was associated with a Z statistic of 2.8. The interim analysis showed a trend toward a difference in the incidence of remission and in the HIT-6 scores between the 2 groups with no difference in untoward side effects. So, recruitment of patients continued till the required sample size was attained.

Table 1 shows the demographic data and baseline characteristics of CH. There were no statistically significant differences between the 2 study sequences as regards any of these parameters ($P > .05$). Figure 2 shows the INR during each treatment period. Starting from the 3rd day on, the INR was significantly higher during the warfarin period as compared with the placebo period ($P < .001$).

Table 2 shows the characteristics of cluster attacks during both treatment periods. The average frequency, duration, and intensity of cluster attacks were all significantly lower during treatment with warfarin as compared with placebo ($P < .01$). Likewise, the HIT-6™ scores were significantly lower during the warfarin period ($P < .01$). The median (interquartile range) duration of remission during the warfarin period was 5.1 (0-6.5) weeks compared with 0 (0-0) weeks during the placebo period ($P = .001$).

There was no statistically significant difference between the washout periods of warfarin and placebo as regards the average frequency of cluster attacks ($P = .05$). However, both the average duration and average intensity of attacks were significantly lower during the warfarin washout period ($P = .004$ and $P = .005$ respectively). The median (interquartile range) duration of remission during warfarin washout was 6.5 (0-9) days vs 0 (0-0) days during placebo washout ($P = .004$). The average frequency, duration, and intensity of cluster attacks during warfarin washout were all significantly lower compared with their corresponding run-in values. However, no such differences were observed between the placebo washout and run-in periods (Table 3).

Table 4 shows both PP and ITT analyses for the occurrence of remission and impact of CH. As regards PP analysis, 27 patients complied with the study protocol, 17 (63%) of whom underwent remission for ≥4 weeks during the warfarin period compared with 4 (14.8%) during the placebo period ($P < .001$). This was associated with a relative risk of

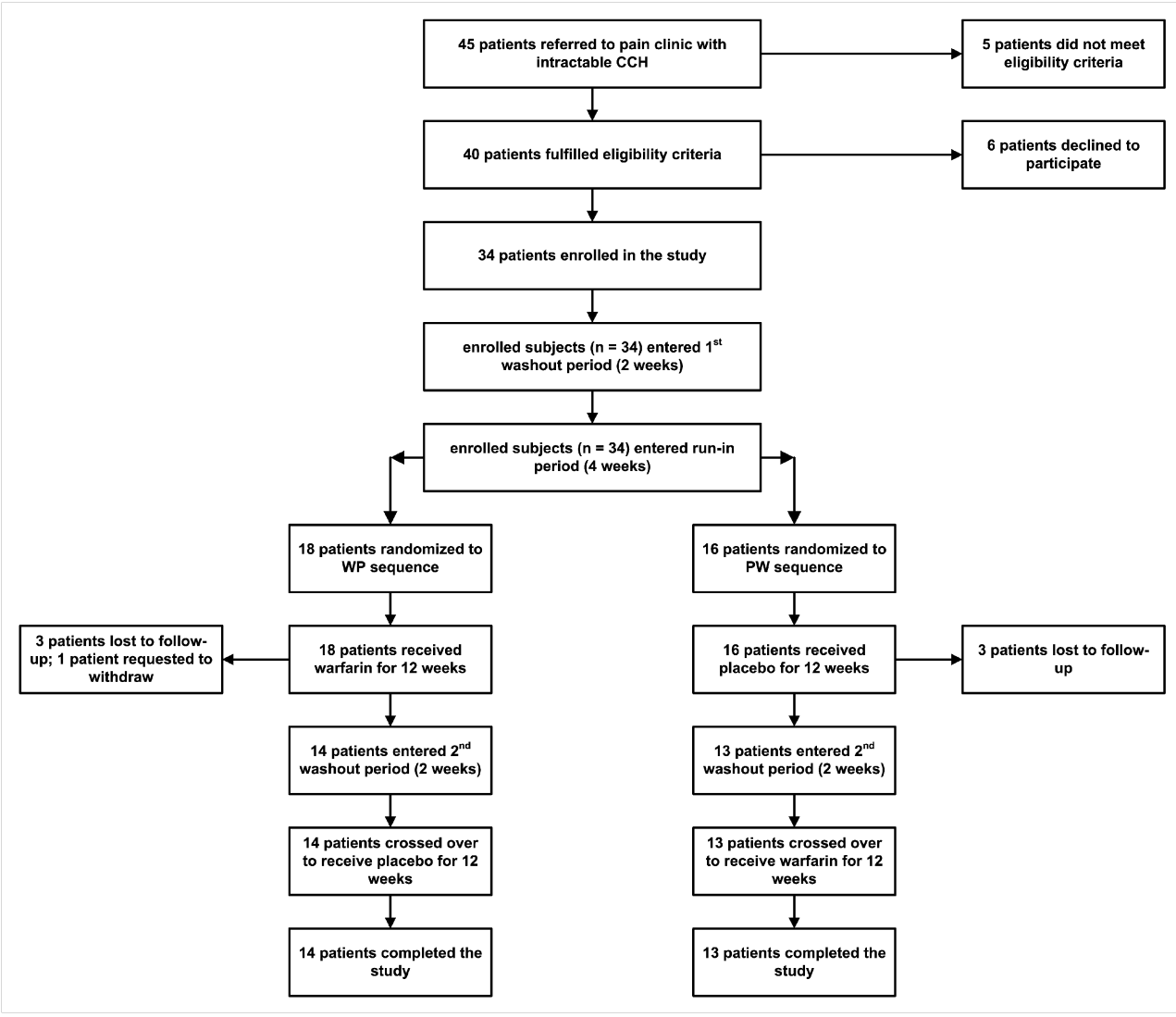


**Fig 1.—Flow chart showing patient selection and randomization, crossover from 1 treatment to the other, number of patients lost to follow-up, and number of patients completing the study. CCH = chronic cluster headache; PW = placebo–warfarin; WP = warfarin–placebo.**

0.43, absolute risk reduction of 0.48 (95% CI = 0.26-0.71), and number needed to treat of 2.1 (95% CI = 1.4-3.9; Table 5).

As regards ITT analysis, 34 patients were intended to be treated according to the study protocol, 17 (50%) of whom underwent remission for ≥4 weeks during the warfarin period compared with 4 (11.8%) patients during the placebo period ($P = .004$; Table 4). This was associated with a relative risk of 0.57, absolute risk reduction of 0.38 (95% CI = 0.18-0.58), and number needed to treat of 2.6 (95% CI = 1.7-5.5; Table 5).

Both PP and ITT analyses showed that significantly more patients were in the "some, little or no impact" categories of the HIT-6 Questionnaire while on warfarin treatment as compared with placebo ($P < .01$; Table 4).

Figure 3 shows the characteristics of the Kaplan–Meier curves for occurrence of remission lasting ≥4 weeks. The curves had a hazard ratio of 5.26 (95% CI = 2.13 to 13.03, $P = .0003$). During the warfarin period, the median time to remission was 4 weeks. However, as >50% of the patients did not go into remission by the end of the placebo period, the

**Table 1.—Demographic Data and Baseline Characteristics of Cluster Headache**

| Variable | All Studied Population (n = 34) | WP Sequence (n = 18) | PW Sequence (n = 16) | *P* value (WP Sequence vs PW Sequence) |
|---|---|---|---|---|
| Age (year) | 44.6 (4.8) | 44.1 (5.1) | 45.2 (4.5) | .502 |
| Gender (male/female) | 26/8 | 15/3 | 11/5 | .429 |
| Duration of CH (year) | 7 (4.75-11) | 7 (4-9.75) | 7 (5.25-11) | .591 |
| Duration of chronic phase of CH (year) | 6.5 (4-8.25) | 7 (4-8.25) | 6 (5 –9.5) | .768 |
| Laterality of CH (right/left/alternating) | 13/15/6 | 5/10/3 | 8/5/3 | .325 |
| Average frequency of attacks (attacks/day) | 3 (3-4) | 3.5 (3-4.25) | 3 (2.25-4) | .656 |
| Average duration of attacks (minute) | 48.8 (18.2) | 45.8 (16.2) | 53.0 (20.2) | .317 |
| Average intensity of attacks | 9 (8-10) | 9 (8-10) | 8.5 (7.25-9) | .434 |
| HIT-6™ score | 64 (62-66) | 64 (61.75-66.5) | 63 (62-66) | .903 |
| Impact of CH (very severe or substantial impact/some, little or no impact) | 34/0 | 18/0 | 16/0 | NA |

Data are mean (standard deviation), ratio, or median (interquartile range).
CH = cluster headache; CCH = chronic cluster headache; HIT-6™ = Headache Impact Test-6™; NA = not applicable; PW = placebo–warfarin; WP = warfarin–placebo.

median time to remission could not be defined for this period.

None of the 34 patients enrolled had major hemorrhagic complications. However, 2 (5.9%) patients developed mild nasal bleeds, and 2 (5.9%) had mild skin bruises related to trauma while on warfarin therapy. All 4 patients had INR values in the desired range and were managed conservatively. None of the patients developed bleeding diatheses during the placebo period. These minor hemorrhagic complications, however, did not attain statistical significance ($P = .113$).

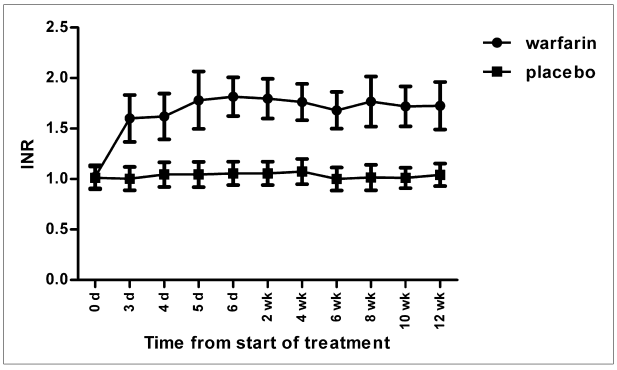


**Fig 2.—International normalized ratio during treatment with warfarin and placebo. INR = international normalized ratio.**

## DISCUSSION

The present study showed that administration of warfarin to achieve low-intensity anticoagulation (INR 1.5 to 1.9) in patients with CCH refractory to pharmacological treatment was associated with a significantly higher incidence of remission lasting 4 weeks or longer compared with placebo. There was in addition a significant improvement in the impact of CH on the patients' quality of life as evidenced by the significantly lower HIT-6™ scores during treatment with warfarin.

Few case reports have described the induction of remission in patients with refractory CCH upon institution of warfarin therapy.[12,13] Similar case reports on the efficacy of warfarin[14,15] or acenocoumarol[16] in patients with migraine do exist. Besides, an observational study[17] involving patients with chronic headaches who received acenocoumarol for non-neurological indications reported a reduction in the frequency of headaches in significantly more patients with migraine as compared with those with non-migrainous headaches.

In contrast to these reports, 1 randomized crossover study,[22] showed that low-intensity anticoagulation with acenocoumarol (INR 1.5 to 2.0) was not associated with significant reduction in the frequency

**Table 2.—Characteristics of Cluster Headache during Both Treatment Periods**

| Variable | Warfarin Period (n = 27) | Placebo Period (n = 27) | *P* value |
|---|---|---|---|
| Average frequency of cluster attacks (attacks/day) | | | |
| Baseline | 3 (3-4) | 3 (3-4) | .840 |
| Week 4 | 2 (1-3) | 3 (3-4) | .001 |
| Week 8 | 0 (0.5-3) | 3 (2-3.5) | .001 |
| Week 12 | 0 (0.5-3) | 2 (2-3) | .007 |
| Average duration of cluster attacks (minute) | | | |
| Baseline | 45 (40-60) | 45 (38.75-63.75) | .858 |
| Week 4 | 35 (20-40) | 45 (40-60) | .001 |
| Week 8 | 25 (0-40) | 45 (40-57.5) | <.001 |
| Week 12 | 15 (0-40) | 45 (40-50) | <.001 |
| Average intensity of cluster attacks | | | |
| Baseline | 9 (8-9) | 9 (8-9) | .853 |
| Week 4 | 7 (5-8) | 9 (8-9) | .001 |
| Week 8 | 5 (0-8) | 8 (8-9) | .001 |
| Week 12 | 3 (0-8) | 8 (7-9) | <.001 |
| HIT-6™ score | | | |
| Baseline | 64 (62-66) | 63 (62-66) | .057 |
| Week 4 | 57 (50-62) | 62.5 (60.75-68.25) | <.001 |
| Week 8 | 40 (36-62) | 62 (58-65.5) | <.001 |
| Week 12 | 38 (36-66) | 60 (56-63) | .006 |
| Duration of remission (weeks) | 5.1 (0-6.5) | 0 (0-0) | .001 |

Data are median (interquartile range) or ratio.
HIT-6™ = Headache Impact Test-6™.

of migrainous attacks. However, that study may have been underpowered owing to the small number of patients who completed the study (12 subjects with an estimated power of 0.65). This, and the fact that the authors used an open-label design, makes their results difficult to interpret.

On the other hand, 1 case report[23] described a patient who experienced symptoms compatible with CH upon administration of warfarin after aortic valve replacement surgery. The headache disappeared after substituting acenocoumarol for warfarin and the authors believed a causal relation

**Table 3.—Cluster Headache Status During the Washout Periods of Warfarin and Placebo Compared With Each Other and With Their Corresponding Run-In Periods**

| Variable | Warfarin Washout Period (n = 14) | Placebo Washout Period (n = 13) | *P* value† | Warfarin Run-in Period (n = 14) | *P* value‡ | Placebo Run-in Period (n = 13) | *P* value§ |
|---|---|---|---|---|---|---|---|
| Average frequency of attacks (attacks/day) | 0 (0-3) | 3 (2-4) | .05 | 3.5 (3-4) | .007 | 3 (2.5-4) | .096 |
| Average duration of attacks (minute) | 30 (23-40) | 48 (37.25-60.75) | .004 | 45 (30-60) | .007 | 45 (35-75) | .373 |
| Average intensity of attacks | 5 (4-7) | 8 (7.75-9) | .005 | 9 (8-10) | .004 | 8.5 (7.5-9) | .518 |
| Duration of remission (days) | 6.5 (0-9) | 0 (0-0) | .004 | 0 (0-0) | .008 | 0 (0-0) | .317 |

Data are median (interquartile range).
†For warfarin washout period vs placebo washout period.
‡For warfarin washout period vs warfarin run-in period.
§For placebo washout period vs placebo run-in period.

**Table 4.—Per-Protocol and Intention-to-Treat Analyses for the Occurrence of Remission and Impact of Cluster Headache**

| | Per-Protocol Analysis | | | Intention-to-Treat Analysis | | |
|---|---|---|---|---|---|---|
| Variable | Warfarin | Placebo | *P* value | Warfarin | Placebo | *P* value |
| Number studied | 27 | 27 | — | 34 | 34 | — |
| Number (%) undergoing remission | 17 (63) | 4 (14.8) | <.001 | 17 (50) | 4 (11.8) | .004 |
| Number (%) in "some, little, or no impact" categories of the HIT-6™ Questionnaire | | | | | | |
| Week 4 | 13 (48.1) | 1 (3.7) | .001 | 13 (38.2) | 1 (2.9) | .007 |
| Week 8 | 18 (66.7) | 3 (11.1) | <.001 | 18 (52.9) | 3 (8.8) | .002 |
| Week 12 | 18 (66.7) | 6 (22.2) | .001 | 18 (52.9) | 6 (17.6) | .007 |

Data are number (%).
HIT-6™ = Headache Impact Test-6™; — = inconclusive results.

existed between administration of warfarin and occurrence of the headache. The authors based their assumption solely upon the temporal association between the 2 incidents, and hypothesized that an excipient incorporated in the pharmaceutical preparation of the drug might have been the culprit. Notably, 1 patient in the series of Kowacs and colleagues[13] underwent temporary exacerbation of his CH before going into remission. This phenomenon, which is difficult to explain, was not encountered in any of the patients in the present study.

Although interventional[8] and surgical[9,10] remedies remain an option for refractory CCH, this may not be feasible in all patients.[11] Besides, the procedures are not without hazards, some of which may be grave,[24] and pain relief is seldom lasting.[25] In this regard, oral anticoagulant therapy may have a potential role in intractable CCH.[12,13] However, evidence from randomized controlled trials on the use of oral anticoagulants in this context is lacking.

Enrolling patients in randomized controlled studies that involve administration of anticoagulant therapy for CCH may pose ethical and methodologi-

**Table 5.—Per-Protocol and Intention-to-Treat Risk Analyses**

| | Per-Protocol Analysis | Intention-to-Treat Analysis |
|---|---|---|
| Number of patients studied | 27 | 34 |
| Number of patients without remission during warfarin period | 10 | 17 |
| Number of patients without remission during placebo period | 23 | 30 |
| Risk for CH during warfarin period | 0.37 | 0.5 |
| Risk for CH during placebo period | 0.85 | 0.88 |
| Relative risk | 0.43 | 0.57 |
| Relative risk reduction | 0.57 | 0.43 |
| Absolute risk reduction (95% CI) | 0.48 (0.26-0.71) | 0.38 (0.18-0.58) |
| Number needed to treat (95% CI) | 2.1 (1.4-3.9) | 2.6 (1.7-5.5) |

CH = cluster headache, 95% CI = 95% confidence interval.

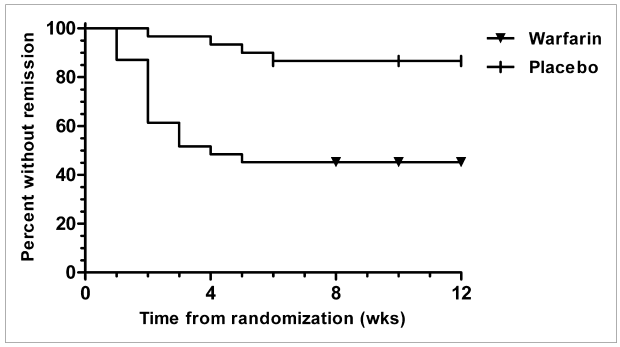


**Fig 3.—Kaplan–Meier curves for occurrence of remission lasting ≥4 weeks during treatment with warfarin and placebo. Marks along the curves indicate the time at which observations were censored. Hazard ratio = 5.26 (95% CI = 2.13-13.03, *P* = .0003).**

cal issues for researchers. First, the institution of anticoagulation in absence of thromboembolism, or the risk thereof, may be questioned in view of the attendant hazards associated with this therapy. Second, a double-blind model in which both patients and investigators are blinded may not be appropriate. In the present trial, the studied population was desperately disabled by their headaches as evidenced by the persistently high HIT-6™ scores despite trying various prophylactic agents for fairly prolonged periods at the maximum tolerated doses. Thus, based on limited reports purporting induction of remission following anticoagulation with warfarin in patients suffering from refractory CCH,[12,13] low-intensity anticoagulation was instituted after explaining risks and benefits to the patients.

A major bleed is by far the most feared of the complications related to oral anticoagulant therapy. Nevertheless, a strong correlation has been demonstrated between the risk of vitamin K antagonist (VKA)-related hemorrhage and the intensity of anticoagulation, regardless of the indication for use.[26] In fact, the intensity of anticoagulation is perhaps the single most important risk factor for intracranial bleeds in patients taking warfarin.[27] In view of the paucity of data on the use of VKA in refractory CCH,[12,13] and in absence of randomized controlled trials on the optimal intensity of anticoagulation, any dosage recommendation in this context would be arbitrary. However, as intense levels of anticoagulation would be hardly warranted in absence of the risk for thromboembolism, the present study opted for low-intensity anticoagulation with a targeted INR ranging from 1.5 to 1.9. In fact, low-intensity anticoagulation on this order has been previously tried by other authors[22] for intractable migraine with no ill effects. Besides, 1 study[28] showed that in patients with stage IV breast cancer, low-intensity anticoagulation targeting an INR of 1.3 to 1.9 was not associated with an increased incidence of hemorrhage.

In the present study, recruited subjects were at low risk for hemorrhagic complications of VKA as evidenced by an Outpatient Bleeding Risk Index of zero,[19] and the INR was closely monitored throughout the study. In fact, a multi-component approach to anticoagulation including, among other interventions, risk stratification and INR monitoring was shown to reduce major bleeds by as much as 50%.[29] In this context, the Outpatient Bleeding Risk Index[19] might be of value for risk stratification and deciding upon institution of oral anticoagulant therapy in patients with intractable CCH, as this index was prospectively validated in outpatients receiving oral anticoagulants,[30,31] and was found to discriminate between low- and moderate-risk,[30] as well as between high- and intermediate-risk patients.[31]

Conceivably, the model adopted by the present study to blind for the drugs administered may be regarded as rather intricate. However, owing to evident limitations related to blinding for the administration of an anticoagulant, such an elaborate model was resorted to. A similar model was previously employed by other investigators[32] in order to ensure blinding of both patient and investigator without compromising patient safety.

The mechanism by which warfarin and related drugs could benefit CH or other headaches of trigeminovascular origin is not clear. Although warfarin was shown to exert potent anti-inflammatory effects in experimental inflammatory models,[33] this seems to be an unlikely mechanism in view of the remarkably much higher doses required to demonstrate it. Thus, an apparently more plausible hypothesis may be related to vitamin K, which seems to exert biologically relevant actions on dendritic and neuronal metabolism.[34] In fact, both vitamin K1 and K2 were shown to enhance neural outgrowth by activating processes catalyzed by protein kinases.[35] Besides, there is growing evidence that protein kinases may play some role in controlling the circadian pacemaker of the hypothalamus,[36] which is believed to be implicated in the circadian and circannual phenomena of CH.[37,38] Another potential mechanism for warfarin may be related to the action of nitric oxide on vascular smooth muscle, as vitamin K2 has been shown to increase the inducible form of nitric oxide synthase in vascular smooth muscle.[39] Thus, by antagonizing the actions of vitamin K, warfarin may suppress nitric oxide-mediated neurogenic inflammation, which is a leading mechanism in the trigeminovascular hypothesis of CH.[40]

The definition of what constitutes refractory or intractable CH poses a problem for both clinicians and researchers.[41] In the present study, the concept of functional and social disability in addition to pharmacological refractoriness[41,42] was adopted as a criterion for refractoriness or intractability. Thus, to quantify CH-related disability, the HIT-6™ Questionnaire was employed. The HIT-6™ Questionnaire has been shown to be an easy-to-use, convenient tool that could provide pertinent information on the impact of headache.[43] In fact, 1 study[44] has demonstrated a strong correlation between scores obtained with the HIT-6™ Questionnaire and the duration of disability as recorded in headache diaries.

The HIT-6™ Questionnaire, as originally developed,[43] was proposed to measure the impact of headache on a patient's life. Although the HIT-6™ Questionnaire has been most commonly linked to migraine,[44-47] the tool was utilized to evaluate other headache disorders as well. In a large study,[48] patients consulting general practitioners for various headache disorders were surveyed using the HIT-6™ Questionnaire. The authors categorized the population they studied into 3 groups: migraine, migrainous disorder, and other episodic headaches, and reported that the HIT-6™ scores were significantly higher in the migraine group than the others. Another descriptive study from France[49] employed the French version of the Questionnaire to evaluate the functional impact of CCH. The investigators reported that 74% of the patients they evaluated were in the "severe impact" category of the Questionnaire.

Data on the natural history of CCH may be regarded as uncertain or, at best, incomplete owing to the paucity of studies, inconsistency of definitions, the need to follow up patients for fairly prolonged periods, and the inherent difficulty in distinguishing changes brought about by medications from that caused by the natural history of the disease.[50-53] In 1 study,[50] 52.4% of those who had suffered from CCH for over 10 years continued to have the chronic form. The pattern of CH transformed to the episodic form in 32.6% of patients, and to an intermediated form in another 14.3%. Another study[51] that followed up a few number of patients with CCH for periods ranging from 10 to 25 years reported that 57.1% of the patients continued to suffer from CCH with no remission, 28.6% transformed to the episodic form, 28.6% developed transitory remission, while 14.3% had prolonged remission lasting >4 years. A third study[52] investigating dropout patients with CH reported that 60% of those having CCH of <21-year duration underwent no change in the pattern of headache, while 20% transformed to the episodic form, and 5% underwent prolonged remission. Based on data from 3 studies,[50,52,53] Torelli and Mazoni[54] inferred that 48% to 53% of patients with CCH would run an unremitting course, 12% would undergo prolonged remission, 20% to 32.6% would transform to episodic CH, and 14.3% would evolve into a combined form. A tendency to undergo longer remission has also been claimed as sufferers from CH get older.[55]

In this context, accounts of spontaneous remission of refractory CCH have been described among patients awaiting interventional procedures. In 1 series,[24] 9 (75%) out of 12 patients awaiting approval for insertion of a hypothalamic implant underwent spontaneous remission and were excluded from the study. The relevance of this phenomenon to the current study may warrant discussion. Although it may be assumed that the higher remission rate observed in the present study in association with warfarin administration could be attributed to a similar or related phenomenon, the assumption is probably unlikely. It may be contended that by using of a double-blind placebo-controlled design and crossing patients from 1 treatment to the other, the chance to observe a difference attributed to such a phenomenon would be presumably equal for either treatment. The observation of a consistently significant difference between the 2 treatments may, thus, be claimed to be related to the use of the relevant drug.

Owing to the low prevalence of CH, the present study used a crossover rather than a parallel-arm design. By using patients as their own controls, the number of patients needed to attain a given power would be almost halved.[56] Another potential benefit inherent in this design is elimination of between-patient variability that could confound the results

obtained.[57] Although a carry-over effect of 1 treatment into a 2nd or subsequent treatment period has been a concern confounding the results obtained in crossover models,[58,59] the impact of such a carry-over effect has been questioned by some authors[60] as theoretical. In the current study, a carry-over effect was unlikely, as a washout period of 2 weeks was allowed between the 2 treatment periods which is quite longer than the known duration of pharmacological actions of warfarin.[61]

## CONCLUSION

In patients with refractory CCH who are at low risk for anticoagulant-related hemorrhagic complications, low-intensity anticoagulation with warfarin to achieve an INR on the order of 1.5-1.9 has been associated with a significantly higher incidence of remission lasting ≥4 weeks, as well as significantly less impact of headache on the patients' quality of life as compared to placebo. Larger randomized controlled studies, however, are required to identify the optimal level and duration of anticoagulation, and the potential risks of such an intervention.

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