INTRODUCTION

Most migraine patients require drug therapy for the treatment of their acute headaches. Analgesics such as acetylsalicylic acid (aspirin), paracetamol (acetaminophen), metamizole, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, gepants and ditans showed efficacy in the treatment of migraine attacks in placebo-controlled studies. For over-the-counter (OTC) preparations, either mono-substances, two-drug combinations, such as aspirin plus paracetamol or analgesics plus caffeine, or a three-drug combination of aspirin, paracetamol and caffeine (APC) may be considered. The effectiveness of acetylsalicylic acid and paracetamol as mono-substances has been shown by numerous randomized studies. A Cochrane review of six studies with 900 or 1000 mg acetylsalicylic acid found a significant superiority versus placebo for the endpoint of being pain-free after 2 h in the treatment of migraine attacks with a rate ratio (RR) of 2.08 (95% confidence interval [CI] 1.7–2.6) [1]. For paracetamol (acetaminophen),
Caffeine is used as an adjuvant in the treatment of both pain and headaches [5]. Caffeine alone shows analgesic properties in some clinical pain conditions (e.g., postdural puncture headache [6]). A Cochrane review from 2014 [5] analysed studies comparing analgesics (e.g., aspirin, ibuprofen, or paracetamol), without and with 100 to 130 mg caffeine in acute pain conditions and found a significantly higher response rate of analgesics with caffeine. In a head-to-head study, APC was superior to aspirin and paracetamol in the treatment of acute tension-type headache and migraine [7].

The three-drug combination APC was the first OTC medication registered for the treatment of migraine in the United States in 1998 [8], and is recommended as first-line migraine treatment by the US, German, Swiss, and Austrian headache societies [9,10]. This combination is available today in many countries (e.g., Russia, Canada, China, Germany, Belgium, Austria, Netherlands, Spain, Italy, Poland, Czech Republic, Ireland, France, Slovak Republic, Norway, United Kingdom). In European countries (including Russia) alone, more than 800 million packs were sold between 2011 and 2015 (unpublished analysis provided to the German Health Authority). In the United States, approximately 37 million people experience migraine [11], and more than 13 million packs of a single APC product branded for migraine were sold in 2019 [12]; thus, on average, every third North American migraine patient purchased one pack of this single APC product in this year.

Despite this long and widespread use, a systematic review and meta-analysis investigating the efficacy and tolerability of APC for the treatment of acute migraine attacks has not yet been performed. This study aims to fill this gap.

**METHODS**

Randomized, blinded, placebo-controlled studies investigating patients experiencing episodic migraines, and using APC or placebo to treat a migraine attack, were identified. Studies using one dose of APC in a migraine attack with at least moderate headache intensity were included.

The main outcomes were pain-free response at 2 h and pain relief (from severe or moderate to mild or no pain) at 2 h. The following definitions were used: pain-free: pain reduced from “severe” or “moderate” to “no pain” (four-point Likert item or pain reduced by 90% from baseline (100-mm visual analogue scale [VAS])); pain relief: pain reduced from “severe” or “moderate” to “mild” or “no pain”, or pain reduced by 50% from baseline (100-mm VAS). Additional outcomes were responses at other time points (0.5–6 h), reduction of nausea, photophobia, phonophobia, restoration of usual activities, and adverse events (AEs).

**Search methods for identification of studies**

An electronic search in the Embase database with the search terms “((paracetamol/exp OR ‘paracetamol’ OR ‘acetaminophen’/exp OR ‘acetaminophen’)) AND (‘aspirin’/exp OR ‘aspirin’) AND (‘caffeine’/exp OR ‘caffeine’) AND (‘migraine’/exp OR ‘migraine’)) AND (‘clinical trial’/de OR ‘controlled clinical trial’/de OR ‘randomized controlled trial’/de) AND (‘article’/it OR ‘conference abstract’/it OR ‘conference paper’/it)” was conducted on 25 August 2020.

In addition, electronic searches with the search terms aspirin AND paracetamol AND caffeine AND migraine were performed using the following data sources:

(i) US clinical trial registry (https://clinicaltrials.gov/)
(ii) European Union clinical trial registry (https://eudraCT.ema.europa.eu)
(iii) Chinese clinical trial registry (http://www.chictr.org.cn)
(iv) Indian clinical trial registry (http://ctri.nic.in/Clinicaltrials/login.php)
(v) Pan African clinical trial registry (https://pactr.samrc.ac.za)

**Data extraction and management**

Two review authors (W.L. and T.W.) extracted the data; percentages were transformed into absolute numbers. We resolved discrepancies and confirmed calculations by discussions; no third review author was involved. W.L. entered data into REVIEW MANAGER, and T.W. checked for accuracy. For all studies, the risk of bias was assessed as outlined in the Cochrane Handbook [13].

**Measures of treatment effects**

All investigated outcome variables are rates. RRs (benefit ratios or risk ratios) were used to establish statistical difference. Absolute rates and rate differences (RDs) were calculated from the median placebo group rate and the RR.

**Data synthesis**

Effect sizes and combined data for meta-analyses were only calculated for outcomes where there were at least two studies. The RRs of benefit or harm, with 95% CIs, were computed using Mantel–Haenszel statistics.

Random-effect meta-analysis models were used because heterogeneity was expected due to the known variation in pain assessments used in different patient and study settings.

Corresponding absolute APC rates, RDs and numbers needed to treat (NNTs) with their 95% CIs were calculated from the median placebo group rates as anticipated placebo rates, and the RRs were calculated from the random-effects meta-analyses.
For sensitivity analyses, absolute differences of rates with 95% CIs using a Mantel–Haenszel random-effect model were additionally calculated.

Heterogeneity of response rates was assessed via \( I^2 \) statistics. The meta-analysis was performed using Cochrane software RevMan 5.3.

Certainty of evidence levels were assessed according to the Cochrane Handbook, Chapter 14 [14], by W.L. and T.W., and then discussed with all authors.

RESULTS

Description of the studies

Seven randomized controlled studies were identified for this meta-analysis [7,15–18] (Figure 1). Study characteristics and assessments of bias are presented in the online Supporting Information. The Novartis study (NCT01248468 [15]) reported its results on Clinicaltrials.gov, but has not been published in a scientific journal. One study [7] investigated tension-type headache as well as migraine. Only data on treated migraine attacks were used for the meta-analysis (data were provided by the study sponsor). All seven studies, with a total of 3306 patients, could be used for pooled comparisons.

The studies investigated two tablets of usual APC combinations, corresponding to 500/400/100 mg aspirin/paracetamol/caffeine [7], or 500/500/130 mg [15–18]. In all studies, medications were taken when the pain of the treated migraine attack was moderate or severe.

Risk of bias in included studies

All studies provided information concerning the randomization process and the method used for blinding investigators and patients. Deviations from the intended treatments were not possible due to the masked treatment: rescue medication use was more often reported in the placebo groups and a potential bias could only be an underestimation of the true APC effect. The percentage of missing data was negligible, probably because of the short duration of the observation intervals. Assessment of outcomes was carried out in blinded conditions. Not all investigated variables were included in all individual studies and therefore not all studies could be integrated in all meta-analyses; but all studies reported their specific primary endpoints, which were generally measuring very similar effects to our efficacy endpoints, so that we can exclude a reporting bias.

We judged the risk of bias assessments unanimously as low; for more details see the Supporting Information.

Main outcomes

Analysis outcomes are shown in Table 1.

Pain free at 2 h

Six studies (2934 participants) provided data for pain-free response at 2 h [7,15–17]. The relative frequencies of the individual studies are shown in Figure 2.

The relative benefit of treatment with APC compared with placebo was RR 2.2 (95% CI 1.5 - 3.1). The median placebo rate was 9%, the corresponding APC rate was 19.6% (95% CI 12.9– 29.9), the corresponding absolute RD was 10.6% (95% CI 3.9– 20.9), and the NNT was 9.4 (95% CI 4.8–25.6).

Heterogeneity of the placebo rates in the individual studies was large. Heterogeneity among the individual RRs was substantial: \( I^2 = 82\% \). All studies, however, showed effects in the same direction (i.e., no qualitative interaction), and four of six studies were significant. Therefore, the random-effects model results are considered appropriate and no downgrading of the certainty of evidence seemed necessary. A model for absolute differences shows a similar result, with an RD = 14% (95% CI 8–20), but also heterogeneity, with an \( I^2 \) value = 77%.

Pain relief at 2 h

Five studies (1771 participants) provided data for pain relief at 2 h [7,17,18]. The relative frequencies of the individual studies are shown in Figure 3.

The relative benefit of treatment compared with placebo was: RR 1.7 (95% CI 1.5 - 1.9). The median placebo rate was 31.2%, the corresponding APC rate was 54.3% (95% CI 48.7–60.2), the
| Outcomes                  | Patients ($Studies) | Events/Patients | Relative effect | Anticipated absolute rates % | Evidence (GRADE) |
|---------------------------|---------------------|-----------------|----------------|-----------------------------|-----------------|
|                           |                     | Placebo         | APC            | RR (95% CI)                 |                 |
| Pain-free at              |                     |                 |                |                             |                 |
| 30 min                    | 2565 (5)            | 11/934          | 26/1631        | 1.04 (0.43–2.52)            | 1.05            |
|                           |                     | 1.09 (0.5–2.7)  | 0.04 (−0.6–1.6) | moderate<sup>b</sup>        |                 |
| 1 h                       | 2565 (5)            | 36/934          | 159/1631       | 1.80 (1.25–2.58)            | 4.1             |
|                           |                     | 7.4 (5.1–10.6)  | 3.3 (1.0–6.5)  | high                        |                 |
| 2 h                       | 2934 (6)            | 141/1055        | 567/1879       | 2.18 (1.43–3.32)            | 9.0             |
|                           |                     | 19.6 (12.9–29.9)| 10.6 (3.9–20.9)| high                        |                 |
| 3 h                       | 2565 (5)            | 166/934         | 731/1631       | 2.43 (1.67–3.55)            | 15.2            |
|                           |                     | 36.9 (25.4–54.0)| 21.7 (10.2–39.8)| high                        |                 |
| 4 h                       | 2565 (5)            | 235/934         | 863/1631       | 1.99 (1.48–2.67)            | 22.0            |
|                           |                     | 43.8 (32.6–58.7)| 21.8 (10.6–36.7)| high                        |                 |
| 6 h                       | 1220 (3)            | 142/618         | 305/602        | 2.20 (1.87–2.60)            | 20.8            |
|                           |                     | 45.8 (38.9–54.1)| 25.0 (18.1–33.3)| high                        |                 |
| Pain relief at            |                     |                 |                |                             |                 |
| 30 min                    | 1771 (5)            | 61/746          | 141/1025       | 1.46 (0.97–2.20)            | 7.8             |
|                           |                     | 11.4 (7.6–17.2)| 3.6 (−0.2–9.4) | moderate<sup>b</sup>        |                 |
| 1 h                       | 1771 (5)            | 142/746         | 420/1025       | 2.04 (1.72–2.42)            | 17.8            |
|                           |                     | 36.3 (30.6–43.1)| 18.5 (12.8–25.3)| high                        |                 |
| 2 h                       | 1771 (5)            | 265/746         | 679/1025       | 1.74 (1.56–1.93)            | 31.2            |
|                           |                     | 54.3 (48.7–60.2)| 23.1 (17.5–29.0)| high                        |                 |
| 3 h                       | 1771 (5)            | 322/746         | 776/1025       | 1.67 (1.52–1.82)            | 38.0            |
|                           |                     | 63.5 (57.8–69.2)| 25.5 (19.8–31.2)| high                        |                 |
| 4 h                       | 1771 (5)            | 371/746         | 828/1025       | 1.56 (1.44–1.69)            | 49.0            |
|                           |                     | 76.4 (70.6–82.8)| 27.4 (21.6–33.8)| high                        |                 |
| 6 h                       | 1220 (3)            | 320/618         | 473/602        | 1.51 (1.39–1.65)            | 52.9            |
|                           |                     | 79.9 (73.5–87.3)| 27.0 (20.6–34.4)| high                        |                 |
| No photophobia            |                     |                 |                |                             |                 |
| 2 h                       | 1587 (4)            | 153/738         | 328/849        | 1.77 (1.21–2.60)            | 17.0            |
|                           |                     | 30.1 (20.6–44.2)| 13.1 (3.6–27.2)| high                        |                 |
| 6 h                       | 1220 (3)            | 195/618         | 353/602        | 1.85 (1.62–2.12)            | 33.0            |
|                           |                     | 61.1 (53.5–70.0)| 28.1 (20.5–37.0)| high                        |                 |
| No phonophobia            |                     |                 |                |                             |                 |
| 2 h                       | 1586 (4)            | 173/737         | 351/849        | 1.66 (1.20–2.30)            | 19.9            |
|                           |                     | 33.0 (23.9–45.8)| 13.1 (4.0–25.9)| high                        |                 |
| 6 h                       | 1220 (3)            | 206/618         | 353/602        | 1.76 (1.55–2.00)            | 34.0            |
|                           |                     | 59.8 (52.7–68.0)| 25.8 (18.7–34.0)| high                        |                 |
| No nausea at              |                     |                 |                |                             |                 |
| 2 h                       | 1587 (4)            | 426/737         | 552/850        | 1.10 (1.00–1.20)            | 57.0            |
|                           |                     | 70.1 (65.0–75.8)| 13.1 (8.0–18.8)| high                        |                 |
| 6 h                       | 1220 (3)            | 371/618         | 448/602        | 1.23 (1.14–1.33)            |                |
|                           |                     | 70.1 (65.0–75.8)| 13.1 (8.0–18.8)| high                        |                 |
| No/little funct. dis.     |                     |                 |                |                             |                 |
| 2 h                       | 1220 (3)            | 210/618         | 356/602        | 1.74 (1.53–1.98)            | 34.0            |
|                           |                     | 59.2 (52.0–67.3)| 25.2 (18.0–33.3)| high                        |                 |
| 6 h                       | 1220 (3)            | 250/618         | 414/602        | 1.70 (1.52–1.90)            | 38.0            |
|                           |                     | 64.6 (57.8–72.2)| 26.6 (19.8–34.2)| high                        |                 |
| AE                        | 3202 (6)            | 88/1124         | 226/2078       | 1.71 (1.34–2.17)            | 10.8            |
|                           |                     | 18.5 (14.5–23.4)| 7.7 (3.7–12.6) | high                        |                 |
| Serious AE                | 3306 (7)            | 0/1159          | 0/2147         | ./0                        | 0.0             |
|                           |                     | 0.0             | 0.0            | high                        |                 |

Note: The rate in the APC group and the RD (and their 95% CIs) are calculated from the assumed rate in the placebo group and the relative effect (RR) of ACP (and its 95% CI).

Abbreviations: AE, adverse event; APC, aspirin, paracetamol, caffeine; CI, confidence interval; RD, rate difference; RR, rate ratio.

<sup>a</sup>Median placebo rate across studies.

<sup>b</sup>Downgrading due to imprecision.
corresponding absolute RD was 23.1% (95% CI 17.5–29.0), and the
NNT was 4.3 (95% CI 3.4–5.7). Heterogeneity among the placebo
rates in the individual studies was relatively small. The heterogeneity
of the single RR was not important, at $I^2 = 0\%$. The same results were
obtained in the fixed-model analysis (data not shown). A model with
absolute differences shows a similar result, with an RD $= 27\%$ (95%
CI 22–32), and the same homogeneity ($I^2 = 0\%$).

Analysis of the further secondary outcomes (e.g., pain responses
at different time points, response rates for nausea, photophobia,
phonophobia, restoration of daily activities) complemented these
findings (Table 1, Figure 4). In two studies, significant positive
outcomes for APC compared to placebo were mentioned (pain relief,
improvement of functional ability, phonophobia and photophobia
[16,18]), but the results were not reported in detail and could there-
fore not be included in the analysis. Significantly better restoration
of daily activities compared to placebo was also shown in the study
from Germany (no impairment of daily activities at 2 h: 49.9% for
APC, and 26.7% for placebo [7]), but the readout was slightly dif-
ferent from the other studies, and therefore this outcome was not
included in the analysis. Information on the use of rescue medication
was given in the study by Lipton et al. [17] (12.5% patients in the
APC arm, 27.2% in the placebo arm; $p < 0.001$) and in the study by
Goldstein et al. [18] (1.5% in the APC arm, 14.3% in the placebo arm;
$p = 0.043$).

Adverse events
All included studies made some mention of AEs, but did not always
report the numbers of participants in each treatment group who
experienced at least one AE. The incidence of AEs varied consid-
erably among studies, which might be explained by differences
in study procedures to collect these data (e.g., a diary vs. spon-
taneous reporting), or by contamination with migraine-associated
symptoms.

Six studies report the numbers of participants in each treat-
ment group who experienced at least one AE. For the three studies
included in Lipton et al. [17], only the pooled frequencies of AEs are
reported. Goldstein et al. [18] reported the frequencies of individ-
ual AE types, but no frequencies for patients with at least one AE.
Diener et al. [7] reported only AEs for the pooled dataset, includ-
ing patients with episodic tension-type headache or unclassified
type headache (23% for APC and 21% for placebo). In the present
study, instead of ignoring the data, all information is used in the
meta-analysis for AEs. Absolute rates are shown in the Supporting
Information.

The relative frequencies adverse events reported in the individ-
ual studies are shown in Figure 5.

The relative risk for APC compared with placebo was 1.71 (95%
CI 1.3–2.2; Table 1). The median placebo rate was 10.8%, the corre-
sponding APC rate was 18.5% (95%-CI 14.5–23.48) and the corre-
sponding absolute RD was 7.7% (95%-CI 3.7–12.6). Most of the AEs
were in line with those known for aspirin (gastrointestinal effects
such as dyspepsia, nausea) and caffeine (e.g., nervousness).

Heterogeneity among APC and placebo AE rates was large, but
the RR showed a good homogeneity among the studies, with $I^2 = 0$.
A model including absolute differences showed large inhomogene-
ity, with $I^2 = 65\%$. This suggests that the methodology used to as-
sess AEs differed among studies, but not between treatment groups
within one study.

Lipton et al. [17] reported some severe AEs in both the APC and
placebo groups (12 vs. 11: 1.9% vs. 1.7%). No study reported any
serious AEs in participants treated with APC or placebo.
DISCUSSION

The present meta-analysis of APC versus placebo for the treatment of acute migraine attacks is, as far as we know, the first of its kind, and shows a significant benefit of APC with regard to the primary endpoint of being pain-free after 2 h and the secondary endpoint of pain relief after 2 h, as well as efficacy outcomes for other time points (Table 1, and Supporting Information). In the network meta-analysis by Xu et al. [19], APC was not considered, although, as the present analysis demonstrated, this combination has been investigated in almost 3000 migraine patients, is recommended by headache societies as first-line treatment, and is used in many countries worldwide. We observed heterogeneity among the studies for the outcome of being pain-free at 2 h. This heterogeneity might be attributable to the different settings and patient types in the analysed studies. The high response rate reported in the study from Germany [7] could be due to the fact that this study exclusively recruited patients who used OTC drugs and had no experience with triptans or ergots. Interestingly, the dose used in that study was slightly lower compared to the others. Other studies excluded people with high levels of disability or vomiting. All studies showed a positive, and in most cases significant, benefit for APC over placebo without qualitative interaction. Homogeneity was observed for the outcome of pain relief.

Different incidences of AEs were reported, indicating an important heterogeneity. The relative risk, however, showed homogeneity across studies. No serious AEs occurred with APC. AEs were mostly related to the gastrointestinal system, which is not surprising for medication containing acetylsalicylic acid and caffeine. These data might be contaminated, however, by the gastrointestinal symptoms induced by the migraine attacks themselves.

The quality of the seven individual studies with regard to risk of bias was acceptable (low risk of bias). The certainty of evidence was graded for most endpoints as high, but for being pain-free and pain-relief at 0.5 h and no nausea at 2 h this was graded as moderate.

Because the methods used in the present meta-analysis to calculate absolute rates from the pooled placebo rates and the RRs were calculated according to the recent standard, the results regarding rate differences and NNTs are not directly comparable with those of less recent meta-analyses and Cochrane reviews (e.g., on aspirin or paracetamol [1,2]). In the Supporting Information (Table S2) we present the results using the calculations used in these reviews [12].

In a head-to-head study, APC was superior to aspirin and paracetamol [7]. This finding is in line with the higher RR for being
pain-free at 2 h associated with APC (2.2/1.74), compared to aspirin (2.08/1.64), and paracetamol (1.8/1.55) [1,2] (see also Table S2).

The strength of the present analysis is the high power of the APC versus placebo comparison resulting from the high number of patients. A major shortcoming is the contamination of data beyond 2 h by rescue medication (although the higher frequency of rescue medication use in the placebo group, as reported in Lipton et al. [17] and Goldstein et al. [18], would seemingly underestimate the efficacy of APC). The extent of the possible underestimation of the treatment effect induced by rescue medication could not be evaluated. For this analysis, an individual data meta-analysis would have to be performed; however, the available published data do not allow for this analysis.

In conclusion, the present meta-analysis demonstrates good efficacy for APC versus placebo in terms of both the International Headache Society-recommended primary outcome, “rate of pain-free patients at 2 h” and the secondary outcome, “rate of pain relief at 2 h”. The tolerability was good and indicates that APC is an effective and well-tolerated OTC treatment for acute migraine attacks.

CONFLICT OF INTERESTS
H.C.D. has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Alder, Allergan, Amgen, Electrocore, Ipsen, Lilly, Medtronic, Novartis, Pfizer, Teva and Weber & Weber. Electrocore provided financial support for research projects. The German Research Council (DFG), the German Ministry of Education and Research (BMBF) and the European Union support his headache research. H.C.D. serves on the editorial boards of Cephalalgia and Lancet Neurology, chairs the Clinical Guidelines Committee of the German Society of Neurology and is a member of the Clinical Trials Committee of the International Headache Society. C.G. has received honoraria for contribution to advisory boards or oral presentations from: Allergan, Hormosan Pharma, Lilly, Novartis, Teva, Weber & Weber, Sanofi-Aventis, Perfood and Gruenenthal within the past 3 years. He is honorary general secretary of the German Migraine and Headache Society (DMKG). He does not hold any stocks of medical device or pharmaceutical companies. W.L. has received honoraria for statistical consulting in clinical and epidemiological studies and contribution to Independent Data Monitoring Committees and Advisory Boards from: Bayer, Biotronik, Boehringer-Ingelheim, Cassella, ClinCompetence Cologne, CRM Biometrics, Merz, Occlutech, Oxular, Sanofi, Schwabe, and Scope International. T.W. is an employee of Sanofi-Aventis Deutschland GmbH.

AUTHOR CONTRIBUTIONS
Hans Christoph Diener: Conceptualization (equal); Methodology (equal); Writing – original draft (lead). Charly Gaul: Conceptualization (equal); Writing – review and editing (equal). Walter Lehmacher: Conceptualization (equal); Formal analysis (equal); Methodology (lead); Software (equal); Validation (equal); Writing – review and editing (equal). Thomas Weiser: Conceptualization (equal); Data curation (equal); Project administration (equal); Writing – review and editing (equal).

DATA AVAILABILITY STATEMENT
The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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