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ABSTRACT & COMMENTARY

Effects of Aspirin on Risk of Early Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, David Geffen School of Medicine at UCLA

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: Aspirin administered early after the onset of transient ischemic attack symptoms substantially reduces the risk of developing a stroke.

SOURCE: Rothwell PM, Algra A, Chen Z, et al. Effects of aspirin on risk and severity of early recurrent stroke after transient ischemic attack and ischemic stroke: Time course analysis of randomized trials. *Lancet* 2016;388:365-375.

The risk of recurrent stroke is up to 10% in the week after a transient ischemic attack (TIA) or minor stroke occurs,[1-4] and despite the fact that urgent medical treatment reduces that risk by as much as 80%, many patients inappropriately delay seeking medical attention for days or weeks, even when they make a correct self-diagnosis.[5,6] Antithrombotic therapy, such as aspirin, has been recommended for the immediate management of most acute ischemic vascular events,[7,8] but prehospital self-adminstration of aspirin has been discouraged after a TIA or stroke because of concerns about possible intracerebral hemorrhage. However, one must recognize that hemorrhages rarely cause TIA symptoms, accounting for < 5% of minor strokes.[10,11]

Because of the absence of published randomized evidence regarding the effect of aspirin on risk and severity of early recurrent stroke after TIA and minor stroke, Rothwell et al analyzed individual patient data and reviewed original paper records on early outcomes from all available trials of aspirin vs. placebo in secondary prevention after TIA or ischemic stroke. Investigators pooled data from 15,778 participants from 12 trials of aspirin vs. control in secondary prevention. They found that aspirin reduced the six-week risk of recurrent ischemic stroke by about 60% and disabling or fatal ischemic stroke by about 70%, with greatest benefit noted in patients presenting with TIA or minor stroke. The reduction in risk of recurrent ischemic stroke was most evident in patients with less severe baseline deficits and was

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substantial by the second day after starting aspirin treatment.

■ COMMENTARY

After analyzing the results of the pooled data, Rockwell et al concluded that the results confirmed the findings from previous nonrandomized studies regarding the effect of urgent treatment on the early risk of recurrent stroke,[5,6,13] supporting the benefits of urgent treatment on the early risk of recurrent stroke. They suggested that most of the benefit of urgent treatment in these previous multi-intervention studies simply was due to aspirin and, therefore, believed it essential to emphasize that patients presenting with TIA or minor strokes should not be sent home from EDs with advice to add aspirin to their next prescription; rather, these patients should be treated acutely with aspirin. It follows that physicians should consider recommending the initiation of aspirin therapy if they suspect TIA — even on an initial telephone contact — if there are no obvious contraindications to aspirin therapy. Furthermore, Rothwell et al concluded that to initiate aspirin as soon as possible after the onset of symptoms, paramedics should administer aspirin therapy in appropriate instances when assessing patients at home. The authors found that other anticoagulant therapy, such as dipyridamole, was not as effective as aspirin, whereas clopidogrel plus aspirin appeared to be more effective than aspirin alone in terms of prevention of early recurrent stroke after TIA and minor ischemic stroke, but had no effect on the severity of the stroke. For longer-term prevention after TIA and ischemic stroke, aspirin demonstrated no significant effect on risk or severity of recurrent ischemic stroke after 12 weeks. However, the early benefit of aspirin was maintained on longer-term follow-up, even though no additional benefit accrued.

Clinicians should be aware that early treatment of TIA with aspirin reduced the six-week and 12-week risk of recurrent ischemic stroke by about 60%, and that adding dipyridamole was of no benefit except after 12 weeks, when it appeared to reduce the risk of recurrent ischemic stroke. The considerable benefits from early aspirin therapy in TIA patients warrants widespread patient education. However, one should recognize that this positive effect occurred for approximately 12 weeks, and that there was no reduction in risk of recurrent ischemic stroke after 12 weeks with aspirin therapy alone. ■

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ABSTRACT & COMMENTARY

The Growing Threat of Pyelonephritis Caused by Antibiotic-resistant *Escherichia coli*

By Richard R. Watkins, MD, MS, FACP, FIDSA

Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General Medical Center, Akron, OH

Dr. Watkins discloses that he has received research support from Actavis.

SYNOPSIS: In patients with acute pyelonephritis due to *Escherichia coli* presenting to one of 10 EDs, the prevalence of fluoroquinolone resistance ranged from 6.3% to 19.9%, and the prevalence of extended-spectrum beta-lactamase production was 2.6% to 12.2%.

SOURCE: Talan DA, Takhar SS, Krishnadasan A, et al. Fluoroquinolone-resistant and extended-spectrum ß-lactamase-producing *Escherichia coli* infections in patients with pyelonephritis, United States. *Emerg Infect Dis* 2016;22:1594-1603.

Escherichia coli is the most common cause of community-acquired pyelonephritis and is becoming increasingly resistant to first-line empiric antibiotics. Traditionally, extended-spectrum beta-lactamase (ESBL)-producing *E. coli* has been associated with healthcare acquisition and rarely originated in the community. Talan et al investigated the prevalence of antibiotic-resistant *E. coli* in adults with acute pyelonephritis who were seen in U.S. EDs.

The study was conducted using a network of 10 university-affiliated urban EDs called EMERGEncy ID NET. Enrolled patients included those ≥ 18 years of age who presented with flank pain or costovertebral tenderness, fever ≥ 38°C, a presumptive diagnosis of acute pyelonephritis, and a urine specimen that grew a single uropathogen at ≥ 10^4 CFU/mL. Urine cultures that grew more than one organism were considered to be contaminated and were excluded from the study. Furthermore, patients were designated with complicated pyelonephritis if they met one of the following criteria: pregnant, male, preexisting urinary tract abnormality, or current immunocompromising condition.

After exclusions, the study population included 521 patients. The median age was 37 years and the majority of patients (87.3%) were female. Most infections were community-acquired (85.6%) and uncomplicated (54.9%). E. coli was the most common pathogen cultured (86.9%). Among those with uncomplicated pyelonephritis, 17 of 272 *E. coli* isolates (6.3%) were resistant to fluoroquinolones. The range of prevalence by site was 0.0% to 23.1%. For complicated pyelonephritis, 36 (19.9%) were fluoroquinolone-resistant (range by site was 0.0% to 50.0%). ESBL production was found in seven of 272 *E. coli* isolates (range 0.0% to 8.3%) from cases of uncomplicated pyelonephritis and in 22 of 181 *E. coli* isolates (range 0.0% to 17.2%) in patients with complicated pyelonephritis.

When analyzed by site, the prevalence of ESBL-producing *E. coli* corresponded with the prevalence of fluoroquinolone-resistant strains. Only 41% of the ESBL-producing strains were susceptible to trimethoprim-sulfamethoxazole, 18% to ciprofloxacin, 21.7% to levofloxacin, and 41.4% to gentamicin.

Another disconcerting finding from the study was the number of patients with pyelonephritis who received the wrong empiric antibiotics. Of the 53 patients with a fluoroquinolone-resistant uropathogen, 24 were treated initially with an antibiotic that was inactive in vitro. Moreover, 22 out of the 29 patients with an infection from ESBL-producing *E. coli* were started initially on an inactive antibiotic. Of nine patients with ESBL-producing *E. coli* pyelonephritis who were discharged from the ED, seven were sent out with an in vitro-inactive antibiotic. The investigators did not include any information regarding outcomes in these patients, such as mortality or whether they re-presented to the ED and were then hospitalized. Among 20 patients admitted with ESBL-producing *E. coli* pyelonephritis, 15 initially were treated with inactive antibiotics.

■ COMMENTARY

Talan et al have presented data that show an alarming increase in the prevalence of antibiotic-resistant *E. coli* in patients presenting to EDs with pyelonephritis. This unfortunate situation makes the decision about empiric antibiotics more challenging. The latest Infectious Diseases Society of America (IDSA) guidelines for treating pyelonephritis in women recommend a threshold of 20% for using trimethoprim-sulfamethoxazole. After crossing this threshold, use an alternative antibiotic.[1] Talan et al provided solid evidence indicating that the current IDSA guidelines should be updated. Moreover, since the spread of antibiotic resistance is ongoing and shows no signs of abating, it seems likely

that the resistance patterns presented will soon be out of date.

Until new guidelines are published, clinicians should make empiric antibiotic choices based on local resistance patterns. Also, it is important to keep in mind risk factors for fluoroquinolone resistance and the possibility of an ESBL-producing organism, such as recent antibiotic use, travel outside North America, recent hospitalization, and a previous urinary tract infection from a fluoroquinolone-resistant or ceftriaxone-resistant pathogen. However, in this study, approximately one-third of patients with an ESBL-producing *E. coli* had none of these risk factors. One rational empiric antibiotic for pyelonephritis, especially if the patient has a risk factor(s) for antibiotic resistance, is ertapenem. All of the uropathogens in the Talan et al study were susceptible to this drug. However, potential drawbacks of ertapenem include disruption of the anaerobic gut flora, no easy oral conversion, and the very real risk of increasing carbapenem resistance. When treating pyelonephritis, clinicians should be pragmatic about the risks and benefits of empiric antibiotics and mindful about antibiogram data for urinary isolates from their community. ■

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ABSTRACT & COMMENTARY

Headaches in the Elderly: A Non-specific Marker for Stroke Risk

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Bayer and Boehringer-Ingelheim.

SYNOPSIS: Non-migrainous headaches, for which there are many causes, appear to be a risk factor for stroke in an elderly population, but the mechanism is uncertain.

SOURCE: Norton J, Portet F, Gabelle A, et al. Are migraine and non-migrainous headache risk factors for stroke in the elderly? Findings from a 12-year cohort follow-up. *Eur J Neurol* 2016;23:1463-1470.

Norton et al expanded the proposition that migraine is a risk factor for stroke, examining the incidence of stroke in an elderly population with migraine and with the more common non-migrainous headache (NMH). Investigators sent invitation letters to randomly selected community-dwelling persons, ≥ 65 years of age, living in Montpellier, France, between March 1999 and February 2001. These elderly persons were invited to attend a half-day clinical examination to check eligibility for the retrospective study. The 2,259 eligible subjects who responded were interviewed about their medical history and underwent a neuropsychiatric interview and a neurological examination. Among subjects reporting headaches, a diagnosis of NMH was made only after excluding a diagnosis of migraine, as based on the International Headache Society (IHS) criteria. After recruitment, all subjects were to be followed up at two, four, seven, nine, and 11 years. The 136 subjects who were lost to follow-up, and thus excluded from the analysis, were older, more disabled, and less educated with lower income, with more vascular risk and cognitive impairment. Despite more medical and social impairment, these excluded participants demonstrated no significant differences in current or lifetime NMH and migraine. The 1,919 remaining subjects with no history of stroke at baseline and no missing values for the main covariates were followed for stroke incidence for a median follow-up period of 8.8 years. At each follow-up, subjects reported neurological events that occurred since the previous visit. Strokes, either hemorrhagic, ischemic, or unknown, were adjudicated, but brain imaging, mainly CT, was available for "more than 80% of validated stroke cases." Lifetime migraine by IHS criteria was reported in 17.4%, and current migraine was reported in 5.4% of the subjects. The diagnosis of NMH, made during their lifetime, was 11.4% of subjects, and was diagnosed in 8.9%. The majority of subjects were said to report only one type of headache. The NMH diagnoses were varied: "tension headaches" 36.5%, "rheumatology-related" 25.1%, "Arnold's neuralgia" (occipital neuralgia) 12.9%, "hypertension-related" 4.5%, "glaucoma-related" 3.3%, "trigeminal neuralgia" 3.3%, "intracranial" 3.3%, "ear, nose, and throat-related" 2.8%, "histaminic cephalalgia" 2.2%, and "other aetiologies" 6.1%. In the elderly subjects with a migraine history at study recruitment, 1.9% suffered a stroke during the follow-up period, as compared to 6.2% of baseline NMH sufferers, and 4.3% of subjects with a past history of migraine or NMH. Cox proportional hazard models indicated that current migraine his-

tory in the elderly population (mean age for migraine and NMH: 72 years) was not a risk factor for stroke; however, NMH sufferers were twice as likely to suffer a stroke (hazard ratio, 2.00; 95% confidence interval, 1.00-3.93; $P = 0.049$).

■ COMMENTARY

Convincing epidemiological studies have shown that migraine with aura is a risk factor for ischemic stroke in a younger population, most notably in women. Yet stroke is more common in an older population, whose headaches, including migraine, are likely to have dissipated with age. Norton et al evaluated a possible correlation between headaches, both migraine and non-migraine, and stroke in an older population. Unfortunately, a small, selected population of older individuals and a lack of granularity in disease categories, lead to few viable conclusions from these data.

The authors commented on some of the limitations of this retrospective epidemiological study. The small number of strokes detected in follow-up (n = 73), with only two strokes in elderly subjects with migraine, may obscure the correlation that was found in studies with a larger population. Because of the small number of elderly migraineurs in the study, the population was not stratified according to migraine without or with aura or to sex, variables of importance in other epidemiological studies. The authors noted the heterogeneous mix of NMHs, including both primary and secondary headache types. The number of subjects with each headache type was too small to conduct a sub-group analysis. Likewise, because of the small number of events, there was no sub-analysis according to stroke type. The correlation with migraine is much more robust for ischemic stroke than for intraparenchymal hemorrhage. Given that these details may differentiate between a connection and a coincidence, the study population was too small to make a clear conclusion about a migraine and stroke linkage in the elderly. Another limitation of the study is that the population analyzed was self-selected participants who volunteered for the study, and more disabled individuals were lost to follow-up. The population followed over the long term were more likely to be the healthy elderly with headache, as opposed to a more representative cross-section of the elderly.

One important inference that can be made from these data is that headache in the elderly deserves investigation and monitoring. The authors suggested that elderly individuals with NMH be followed closely because of an increased stroke risk. In general, headaches are less common in the elderly and, if present, are more likely to be secondary to an underlying systemic disease or identifiable brain lesion. Therefore, secondary headaches in the elderly may be a marker for poor health in general, and may be indicative of greater cerebrovascular risk specifically. Why elderly individuals with multiple headache types should have a somewhat greater stroke risk than those with migraine, the tenuous conclusion from this study, does not have any mechanistic explanation. ■

PHARMACOLOGY UPDATE

Aspirin and Omeprazole Delayed-release Tablets (Yosprala)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved two fixed doses of aspirin (ASA) and omeprazole (OMP) for reducing the risk of aspirin-associated gastric ulcers in patients who need aspirin for secondary prevention of cardiovascular and cerebrovascular events. This combination is marketed as Yosprala.

INDICATIONS

ASA/OMP is indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of aspirin-associated gastric ulcers.[1]

DOSAGE

The recommended dose is one tablet at least 60 minutes before a meal.[1] The combination is not interchangeable with the individual components of aspirin and omeprazole.[1] ASA/OMP is available as 81 mg and 325 mg delayed-release aspirin and 40 mg of immediate-release omeprazole.

POTENTIAL ADVANTAGES

The combination is more effective than enteric-coated aspirin (EC-ASA) in reducing the risk of gastric ulcers with a lower discontinuation rate due to adverse reac-

tions, 7% vs. 11%.[1] It provides the convenience of both drugs in one tablet.

POTENTIAL DISADVANTAGES

ASA/OMP has not been shown to reduce the risk of gastrointestinal bleeding due to aspirin.[1]

COMMENTS

The formulation of ASA/OMP releases omeprazole to raise the gastric pH before releasing aspirin. The efficacy of ASA/OMP was evaluated in two randomized, double-blind trials compared to EC-ASA. Participants presented with a cerebrovascular or cardiovascular diagnosis, were > 55 years of age, had been on aspirin 325 mg for at least three months, and were expected to require ASA for at least six months. Those between 18 and 55 years of age also were required to present with a documented history of gastric or duodenal ulcer within the past five years.

Participants were randomized to ASP/OMP (325 mg/40 mg; n = 524) or EC-ASA 325 mg (n = 525). The primary efficacy endpoint was the incidence of endoscopically determined gastric ulcers. At six months, the incidences were 2.7% and 3.8% for ASA/OMP for the two studies, and 8.5% and 8.7% for EC-ASA, respectively. The cumulative incidence of gastric and/or duodenal ulcers was 3% compared to 12%. In a posthoc analysis, ASA/OMP reduced the risk of subjects with baseline gastric erosions developing gastric ulcers compared to EC-ASA.[2] One subject in each group experienced a gastric/duodenal hemorrhage. The most common adverse event was gastritis, and the frequency was similar between the two groups (18% for ASA/OMP, and 16% for EC-ASA). ASA/OMP has not been compared to aspirin nor a proton pump inhibitor or histamine-2 antagonist taken separately, which has been found to be effective in reducing upper gastrointestinal ulcers and bleeding.[3,4]

CLINICAL IMPLICATIONS

The U.S. Preventive Services Task Force recommends low-dose aspirin for the prevention of both cardiovascular-related events and colorectal cancer, mainly in men and women 50-59 years of age who have a ≥ 10% risk of developing cardiovascular disease over 10 years and who are not at increased risk for bleeding.[5] However, low-dose aspirin increases the risk of gastroduodenal injury.[5,6] Potential risk factors include male gender; elderly (> 70 years of age); having a peptic ulcer; prior gastrointestinal bleed; *Helicobacter pylori* infection; uncontrolled hypertension; those using antiplatelet drugs, anticoagulants, steroids, or other nonsteroidal anti-inflammatory drugs; and chronic renal failure. The combination of ASA/OMP provides

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Clinical Briefs

By Louis Kuritzky, MD

Motivational Interviewing Improves CPAP Adherence

SOURCE: Bakker JP, Wang R, Weng J, et al. Motivational enhancement for increasing adherence to CPAP: A randomized controlled trial. *Chest* 2016;150:337-345.

Even though obstructive sleep apnea (OSA) causes immediate (daytime sleepiness, memory impairment, decreased functionality) and long-term (hypertension, increased cardiovascular event rate) problems, it may come as a surprise that the majority of users of continuous positive airway pressure (CPAP) machines do not even achieve four hours of use nightly, on average. This is particularly concerning since benefits of CPAP on adversities related to OSA are most substantial when using CPAP for 5.5 hours or more per night.

Motivational interviewing is a technique that has been successfully employed to improve outcomes ranging from smoking cessation to compliance with antihypertensive medication. Practitioners of motivational interviewing believe patients naturally often feel some ambivalence about interventions offered to them and that by helping the patient identify such ambivalence, steps can be taken to address obstacles to success. Central to the mechanism of motivational interviewing success is the role of the interviewer as facilitator rather than director. That is, patients are encouraged both to identify their own sources of ambivalence and also to explore which obstacles they might wish to address, as well as how they might best address them. Considering that the textbook explaining motivational interviewing (Miller WR, Rollnick S. *Motivational Interviewing: Helping People Change*. Third Edition. Guilford Press; 2012) encompasses more than 400 pages, the above explanation obviously is a dramatic over-simplification. Nonetheless, practitioners of motivational interviewing techniques (psychologists, physicians, and other clinicians) often find it a useful tool.

In a 12-month, randomized, controlled trial of motivational interviewing vs. placebo (n = 83), Bakker et al found that recipients of motivational interviewing demonstrated (on average) more than 90 minutes greater utilization of CPAP per night than those in the placebo group. This benefit was achieved through two in-person, hour-long motivational interviewing sessions with a psychologist, followed by six phone sessions over 32 weeks (10-30 minutes each) with the same psychologist. ■

Empagliflozin Improves Renal Outcomes in Type 2 Diabetes

SOURCE: Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323-334.

Sodium glucose transporter 2 (SGLT2) inhibitors are the newest class of medications approved to treat type 2 diabetes (T2DM). Although there have been isolated reports of acute kidney injury associated with SGLT2 treatment, FDA registration trials have noted a short-term decline in glomerular filtration rate, which returns to normal over ensuing weeks. The EMPA-REG trial (n = 7,020) was performed primarily as a cardiovascular safety trial for the SGLT2 inhibitor empagliflozin, as mandated for all new pharmacologic agents indicated for T2DM. In addition to the cardiovascular risk reduction reported in earlier published EMPA-REG results, renal outcomes were another important prespecified endpoint.

New or worsening nephropathy was meaningfully reduced by empagliflozin treatment (hazard ratio = 0.61, a 39% reduction). Similarly, the incidence of a doubling of serum creatinine was reduced by almost half, and likelihood of initiation of renal replacement treatment was reduced by more than half.

In addition to favorable effects on glucose control and cardiovascular outcomes, treatment with empagliflozin was associated with meaningful reductions in adverse renal outcomes. ■

Patients Make Multiple Errors in Inhaler Use

SOURCE: Sanchis J, Gich I, Pedersen S; Aerosol Drug Management Improvement Team (ADMIT). Systematic review of errors in inhaler use: Has patient technique improved over time? *Chest* 2016;150:394-406.

Despite various technical advances in inhaler devices, the skill with which patients actually use such devices has shown little improvement over four decades. Certainly, most clinicians have experienced or will experience suboptimal outcomes attributable to non-nefarious misuse of intended treatments.

Inhalation devices include metered dose inhalers (MDI), breath-activated MDIs, dry powder inhalers, and MDIs with inhalation chambers. Sanchis et al reported on data from patients in 144 publications about observed inhaler technique (n = 54,354).

Although the steps for each device vary, errors in use (failure to place teeth/lips on mouthpiece, failing to fully exhale before inhalation, failure to breath-hold after medication inhalation, etc.) were the rule rather than the exception.

Only 31% of users exhibited correct inhaler technique, with an equal number demonstrating poor technique. The authors documented that skillfulness of technique has not improved over 40 years of observation. Obviously, something has to change in the process of educating patients about inhaler technique if clinicians expect different results in the future. ■

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an option to reduce the risk of developing aspirin-associated gastric ulcers in susceptible patients. However, there currently is no evidence that it works any better than aspirin and a proton pump inhibitor taken separately. The projected cost for ASA/OMP is $5 per tablet. ■

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CME QUESTIONS

1. Aspirin administered orally after a transient ischemic attack:

a. should be given at least five days after the onset of symptoms.

b. should be given as soon as possible after the onset of symptoms.

c. should be given at least three days after the onset of symptoms.

d. should never be given.

2. Which of the following is correct with regard to the proportion of *Escherichia coli* isolates from patients with complicated pyelonephritis that were resistant to fluoroquinolone antibiotics?

a. 1.9% were resistant.

b. 10.9% were resistant.

c. 19.9% were resistant.

d. 29.9% were resistant.

3. Which statement best describes headache and the elderly?

a. Headaches are not indicators of disease risk.

b. Headache prevalence decreases with age.

c. Both migraine without and with aura increase stroke risk.

d. Tension-type headache is a rare cause of headache.