Fortunately, we live and work in an era when several interventions are known to prevent or treat ischemic stroke. For patients like this 81-year-old woman, secondary prevention of vascular disease with aspirin provides statistically and clinically significant absolute reductions in all serious vascular events, in all stroke, and in coronary events that offset the nonsignificant increase in the risk of intracranial hemorrhage.1 So, prescribing aspirin for this patient after her transient ischemic attacks was the right thing to do.

However, we cannot be sure that aspirin was responsible for her intracerebral hemorrhage (ICH). After all, the ICH could be attributable to the age-related small vessel diseases that probably underlay her transient ischemic attacks, cognitive decline, and microbleeds. Whether the aspirin caused, or even just precipitated, the ICH is unknown.

The only known intervention for secondary prevention of recurrent ICH is lowering blood pressure, so that should be started. However, we cannot be sure that aspirin was responsible for her intracerebral hemorrhage (ICH). After all, the ICH could be attributable to the age-related small vessel diseases that probably underlay her transient ischemic attacks, cognitive decline, and microbleeds. Whether the aspirin caused, or even just precipitated, the ICH is unknown.

The only known intervention for secondary prevention of recurrent ICH is lowering blood pressure, so that should be started. However, the proven treatment that this patient was taking for secondary prevention of ischemic events, aspirin, has been stopped. So is restarting the aspirin, which may have played no role in the ICH, safe?

This particular dilemma has not been addressed in a randomized controlled trial (RCT). However, the paradigm has been tested in an RCT in another bleeding condition; a small short-term RCT of aspirin continuation after peptic ulcer bleeding found a significant reduction in all-cause death despite a nonsignificant increase in recurrent ulcer bleeding.2 In the absence of RCTs, we know of 3 published observational studies that address our patient’s dilemma.3–5 One study found a 2-fold reduction in all vascular events (ie, ischemic and hemorrhagic combined) among patients who restarted aspirin after any ICH (52 per 1000 patient-aspirin years versus 113 per 1000 patient-years; P=0.04).5 None of the studies found an increase in the risk of recurrent ICH associated with restarting aspirin in univariate analyses.3–5 However, one of these studies, which included 104 adults with lobar ICH like our patient, identified 29 recurrent ICHs during a median follow-up of almost 3 years and found an association between aspirin use after ICH and recurrent ICH in a multivariable analysis (adjusted hazard ratio, 3.95; 95% confidence interval, 1.6–8.3), possibly explained by microbleeds.4 However, this study’s multivariable model may have been overfitted, which may have exaggerated the association, so the finding requires replication. Furthermore, if the association between aspirin use and ICH recurrence after lobar ICH is real, the magnitude of the effect would not be considered sufficiently large to discount the effects of bias or confounding according to conventional criteria.6

Because none of the observational studies show dramatic harmful effects,6 we cannot dismiss the potential benefits of restarting aspirin in this patient. Furthermore, there is evidence of variation between hospitals in the proportion of patients

**The Case**
An 81-year-old woman presented with sudden onset of aphasia and delirium. Her history is noted for cognitive decline and transient ischemic attacks. Head computed tomography showed a left temporal intracerebral hemorrhage; MRI showed few additional microbleeds. She was taking aspirin daily; it was withheld.

**The Question**
Should aspirin be restarted in this patient?

**The Controversy**

**CONTINUATION OF ANTIPLATELET THERAPY AFTER INTRACEREBRAL HEMORRHAGE**

**Antiplatelet Therapy May Be Continued After Intracerebral Hemorrhage**
Rustam Al-Shahi Salman, MA, PhD, FRCP Edin; Martin S. Dennis, MD, FRCP Edin

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restarting antithrombotic drugs after ICH in clinical practice, not explained by patient characteristics. Therefore, this dilemma needs to be resolved in an RCT. If this patient was resident in the United Kingdom, she could be invited to participate in the REstart or STop Antithrombotics Randomised Trial (RESTART, ISRCTN71907627, http://www.RESTARTtrial.org), which includes a brain MRI substudy to investigate an interaction between brain microbleeds and the effect of restarting antiplatelet drugs and has enrolled 70 participants at 89 hospital sites to date.

So, are we pro restarting aspirin in this patient? Yes, in the context of an RCT embedded within routine clinical practice, because such learning healthcare systems are surely the most expedient and ethical way to resolve this and many other dilemmas in everyday clinical practice for the benefit of this patient and others like her.

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References

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Key words: aspirin (aspirin), intracerebral hemorrhage, magnetic resonance imaging, platelet aggregation inhibitors

Clinical case

An 81-year-old woman presented with an acute aphasia and delirium. In her history, she had reduced cognitive functions and transient ischemic attacks (TIAs). A computerized tomography of the head showed intracerebral hemorrhage in the left temporal lobe; additional microhemorrhages were found in the MRI. The patient had been taking aspirin daily; the medication was discontinued due to the development of symptoms.

Question

Should the patient continue taking aspirin?

Discussion

Fortunately, we live in an era when there are proven methods of prophylaxis and treatment of ischemic stroke. For patients such as this 81-year-old woman, secondary prophylaxis with aspirin ensures statistically and clinically significant reduction in the risk of such serious events as stroke and myocardial infarction [1]. What is more important is the insignificant increase in the risk of intracerebral hemorrhage [1]. Therefore, starting aspirin treatment after TIAs was the right decision.

However, we cannot be sure that aspirin alone caused the intracerebral hemorrhage (ICH). In the end, ICH might have been related to the age-related changes of small vessels, which were probably the reason for the TIA, and cognitive impairments and microhemorrhages. It is not known whether aspirin was the cause of ICH or simply accelerated its development.

The only secondary prophylactic intervention with proven efficacy is lowering blood pressure, so it should start exactly with this. However, the patient was prescribed aspirin, a medicine with proven efficacy in secondary prophylaxis of ischemic events. So the question arises: is it safe to continue aspirin treatment? There are no randomized controlled trials (RCTs) to resolve this specific dilemma. In a small short-term RCT, aspirin was continued after peptic ulcer hemorrhage. As a result, a significant decrease in mortality was noticed in the treated group, despite the insignificant increase in the risk of repeat peptic ulcer hemorrhage [2].

Despite the absence of RCTs, three published observational studies have been performed to resolve the patient dilemma [3–5]. In one of these studies, it was found that continuing the use of aspirin after development of any ICH (52 out of 1000 patient-aspirin years compared to 113 out of 1000 patient-years; \( p = 0.04 \)) [5]. None of these studies found an increase in the risk of recurrent ICH associated with the resumption of aspirin treatment [3–5]. However, in one of these studies, which included 104 adults with lobar ICH, as in this case, they had 29 recurrent ICH over a median period of almost 3 years. In the multivariate analysis, it was found that the use of aspirin after ICH was associated with a higher risk of recurrent ICH (relative risk 3.95; 95% confidence interval 1.6 to 8.3), which, possibly, was due to the development of microhemorrhages [4]. However, the multivariate model in this study might have been too simplistic, which led to the overestimation of the observed connection. Consequently, the conclusion requires repetition. In addition, if there is a real association between the use of aspirin and recurrent ICH after partial ICH, the effect size will not be...
считаться достаточно большим для снижения влияния систематической ошибки или вмешивающихся факторов в соответствии с традиционными критериями [6].

Поскольку ни в одном из обсервационных исследований не показали наличия драматически вредных последствий [6], мы не можем игнорировать потенциальную выгоду продолжения приема аспирина этой пациенткой. Кроме того, существуют доказательства наличия вариации между клиниками по пациентам, продолжающим принимать антитромботические препараты после ВМК в клинической практике, которая не объясняется характеристиками самих пациентов [7]. Таким образом, эту дилемму необходимо разрешить путем проведения РКИ. Если бы эта пациентка проживала в Соединенном Королевстве, ее могли бы пригласить для участия в рандомизированном испытании Возобновление или остановка приема антитромботических препаратов (REstart or STop Antithrombotics Randomised Trial – RESTART, ISRCTN71907627, http://www.RESTARTtrial.org). В нем проводится субисследование с МРТ головного мозга для изучения связи между развитием церебральных микрокровоизлияний и влиянием возобновления приема антиагрегантов. На сегодняшний день в это испытание зачислили 70 пациентов в 89 клиниках.

Следует ли продолжить прием аспирина этой пациентке? Да, в контексте РКИ, внедренных в повседневную клиническую практику. Такие обучающие системы здравоохранения являются наиболее целесообразным и этичным способом решения этой проблемы и многих других дилемм в повседневной клинической практике на благо этой пациентке и ей подобных [8].

ЛИТЕРАТУРА