

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

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Abstract

BACKGROUND

Stroke is common during the first few weeks after a transient ischemic attack (TIA) or minor ischemic stroke. Combination therapy with clopidogrel and aspirin may provide greater protection against subsequent stroke than aspirin alone.

METHODS

In a randomized, double-blind, placebo-controlled trial conducted at 114 centers in China, we randomly assigned 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA to combination therapy with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to placebo plus aspirin (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Treatment differences were assessed with the use of a Cox proportional-hazards model, with study center as a random effect.

RESULTS

Stroke occurred in 8.2% of patients in the clopidogrel–aspirin group, as compared with 11.7% of those in the aspirin group (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.81; $P<0.001$). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group ($P=0.73$); the rate of hemorrhagic stroke was 0.3% in each group.

CONCLUSIONS

Among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage. (Funded by the Ministry of Science and Technology of the People's Republic of China; CHANCE ClinicalTrials.gov number, [NCT00979589](#).)

Introduction

TRANSIENT ISCHEMIC ATTACK (TIA) AND ACUTE MINOR ISCHEMIC STROKE ARE common and often lead to disabling events. In China, there are approximately 3 million new strokes every year, and approximately 30% of them are minor ischemic strokes.^{1,2} The incidence of TIA in China has not been determined, but on the basis of the incidence in other countries, there are probably more than 2 million TIAs annually in China.³⁻⁵ The risk of another stroke occurring after a TIA or minor stroke is high, with approximately 10 to 20% of patients having a stroke within 3 months after the index event; most of these strokes occur within the first 2 days.⁵⁻⁸

The role of antiplatelet therapy for secondary stroke prevention has been well established. However, aspirin is the only antiplatelet agent that has been studied in the acute phase of stroke, during which its benefit is modest.^{9,10} Aspirin and clopidogrel synergistically inhibit platelet aggregation,^{11,12} and such dual therapy reduces the risk of recurrent ischemic events in patients with the acute coronary syndrome.^{13,14} Large-scale trials of secondary prevention of ischemic events after stroke have not shown a benefit of the combination of clopidogrel and aspirin.¹⁵⁻¹⁷ However, these trials did not study

the early, high-risk period after stroke, they included some patients with strokes of moderate severity, and they included few if any patients with TIA. Three small pilot trials have shown trends toward a benefit of the combination therapy and minimal safety concerns in patients with minor stroke or TIA.¹⁸⁻²⁰

We conducted the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial to test the hypothesis that 3 months of treatment with a combination of clopidogrel and aspirin would reduce the risk of recurrent stroke, as compared with aspirin alone, among patients with acute high-risk TIA or minor ischemic stroke.

Methods

STUDY OVERSIGHT

We conducted this study according to the [protocol](#) and statistical analysis plan, which are available with the full text of this article at NEJM.org. The trial was designed by three of the authors and was overseen by the executive committee, which had full access to the data. Data collection and entry were performed by staff at the Tiantan Clinical Trial and Research Center for Stroke, where the data analysis was performed. One of the authors had full access to an independent database for any questions regarding the analyses. All members of the writing committee contributed to and approved an earlier draft of this manuscript, which was prepared without professional editorial assistance. The first and last authors made the decision to submit the manuscript for publication. All the authors assume responsibility for the accuracy and completeness of the data and the fidelity of this report to the study protocol. There was no confidentiality agreement between the study sponsor (the Ministry of Science and Technology of the People's Republic of China) and the investigators. There was no commercial support for this study.

All the participants or their legal proxies provided written informed consent. The CHANCE protocol was approved by the ethics committee at each study center. Clopidogrel and the matching placebo were purchased from Sanofi-Aventis, which had no other role in the study.

STUDY POPULATION

Patients who met the following inclusion criteria were eligible: age of 40 years or older; diagnosis of an acute minor ischemic stroke or TIA; and ability to start the study drug within 24 hours after symptom onset, which was defined as the point at which the patient reported no longer being in a normal condition. Acute minor stroke was defined by a score of 3 or less at the time of randomization on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits). TIA was defined as focal brain ischemia with resolution of symptoms within 24 hours after onset plus a moderate-to-high risk of stroke recurrence (defined as a score of ≥ 4 at the time of randomization on the ABCD,² which assesses the risk of stroke on the basis

of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes; scores range from 0 to 7, with higher scores indicating greater short-term risk).

All patients with possible clinical neurologic events during the follow-up period underwent computed tomography (CT) or magnetic resonance imaging (MRI) of the head. Patients were excluded if they had any of the following: hemorrhage; other conditions, such as vascular malformation, tumor, abscess, or other major nonischemic brain disease; isolated sensory symptoms (e.g., numbness), isolated visual changes, or isolated dizziness or vertigo without evidence of acute infarction on baseline CT or MRI of the head; a score of more than 2 on the modified Rankin scale (scores range from 0 [no symptoms] to 6 [death]) immediately before the occurrence of the index ischemic stroke or TIA, indicating moderate disability or worse at baseline; an NIHSS score of 4 or more at randomization; a clear indication for anticoagulation therapy (presumed cardiac source of embolus, such as atrial fibrillation or prosthetic cardiac valve) or a contraindication to clopidogrel or aspirin; history of intracranial hemorrhage; anticipated requirement for long-term nonstudy antiplatelet drugs or for nonsteroidal antiinflammatory drugs affecting platelet function; heparin therapy or oral anticoagulation therapy within 10 days before randomization; gastrointestinal bleeding or major surgery within the previous 3 months; planned or probable revascularization (any angioplasty or vascular surgery) within 3 months after screening (if clinically indicated, vascular imaging was to be performed before randomization, whenever possible); planned surgery or interventional treatment requiring cessation of the study drug; TIA or minor stroke caused by angiography or surgery; or severe noncardiovascular coexisting condition, with a life expectancy of less than 3 months. Women of childbearing age who were not practicing reliable contraception and did not have a documented negative pregnancy test and patients receiving other investigational drugs or devices were also excluded (see Table S1 in the [Supplementary Appendix](#), available at NEJM.org). No patients included in the study were treated with thrombolysis around the time of randomization.

STUDY DESIGN

CHANCE was a randomized, double-blind, placebo-controlled clinical trial conducted at 114 clinical centers in China; details of the rationale for the study and its design have been published previously.²¹ Patients meeting the enrollment criteria were randomly assigned to one of the two treatment groups with the use of a double-blind, double-dummy design. The site investigator called into an automated system that randomly assigned a number corresponding to a medication kit stored at the study site, and the medication in the kit was administered to the patient.

Both groups received open-label aspirin on day 1 (with the dose ranging from 75 to 300 mg, at the discretion of the treating physician). Patients randomly assigned to the clopidogrel–aspirin group received a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg per day on days 2 through 90, aspirin at a dose of 75 mg per day on days 2 through 21, and placebo aspirin on days 22 through 90. Patients randomly assigned to the aspirin group received a placebo version of clopidogrel on days 1 through 90 and aspirin at a dose of 75 mg per day on days 2 through 90. Randomization was

stratified according to clinical center and interval between symptom onset and enrollment (<12 hours vs. 12 to 24 hours). The primary objective was to assess the effects of the two treatment regimens on the incidence of stroke in the first 90 days after acute minor stroke or high-risk TIA.

STUDY OUTCOMES

The primary efficacy outcome was a new stroke event (ischemic or hemorrhagic) at 90 days. Ischemic stroke was defined as an acute focal infarction of the brain or retina with one of the following: sudden onset of a new focal neurologic deficit, with clinical or imaging evidence of infarction lasting 24 hours or more and not attributable to a nonischemic cause (i.e., not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurologic disease); a new focal neurologic deficit lasting for less than 24 hours and not attributable to a nonischemic cause but accompanied by neuroimaging evidence of new brain infarction; or rapid worsening of an existing focal neurologic deficit lasting more than 24 hours and not attributable to a nonischemic cause, accompanied by new ischemic changes on MRI or CT of the brain and clearly distinct from the index ischemic event. Hemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurologic symptoms. Recurrent stroke was considered to be disabling if the score on the modified Rankin scale was 2 or more.

The primary safety outcome was a moderate-to-severe bleeding event, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.²² Severe hemorrhage was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention. Moderate hemorrhage was defined as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention.²²

Key secondary efficacy outcomes included a new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), analyzed as a composite outcome and also as individual outcomes. Vascular death was defined as death due to stroke (ischemic or hemorrhagic), systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmia. Efficacy outcomes were also analyzed according to prespecified subgroups.

All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was unaware of the study-group assignments. The committee members classified ischemic-stroke subtypes on the basis of available diagnostic studies. A data and safety monitoring board whose members were selected by the sponsor was in place to ensure the safety of patients during the study, with predetermined periodic assessments of safety and stopping rules.

STATISTICAL ANALYSIS

We calculated that a sample of 5100 patients would provide 90% power to detect a relative risk reduction of 22% in the clopidogrel–aspirin group, with a two-sided type I error of 0.05, assuming an

event rate of 14% in the aspirin group and a 5% overall rate of withdrawal (defined as medication nonadherence).²¹

No patient withdrew between the time of randomization and the administration of the first dose of study medication; all analyses were based on the population of patients who underwent randomization. We compared the baseline characteristics of the patients in the two study groups. Proportions were used for categorical variables, and medians with interquartile ranges were used for continuous variables. Time to randomization was calculated as a group mean. Differences between study groups in the rate of stroke (ischemic or hemorrhagic) during the 90-day follow-up period were assessed with the use of a Cox proportional-hazards model, with pooled study centers (≥ 20 patients) as a random effect.

Hazard ratios with 95% confidence intervals are reported. When there were multiple events of the same type, the time to the first event was used in the model. Data from patients who had no events during the study were censored at the time of study termination or death. We used this approach to maximize the time-dependent information in the trial while maintaining the ease of interpretation of risks. For each model, the proportional-hazards assumption was assessed by testing the interaction between treatment and time. In addition, we assessed whether the treatment effect differed in certain prespecified subgroups by testing the treatment-by-subgroup interaction effect with the use of Cox models. All tests were two-sided, and a P value of 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.0 (SAS Institute).

Results

STUDY PATIENTS AND FOLLOW-UP

Table 1.

Baseline Characteristics of the Patients.

Between October 2009 and July 2012, a total of 41,561 patients with stroke or TIA were screened at 114 clinical sites; 5170 patients were enrolled, with 2584 randomly assigned to the clopidogrel–aspirin group and 2586 to the aspirin group. The most common reasons for exclusion were delayed presentation (26.4% of screened patients); moderate or severe stroke (10.4%); intracranial hemorrhage (7.0%); low-risk TIA, defined as a score of <4 on the ABCD² (6.5%); or contraindication to clopidogrel or aspirin (6.0%) (Fig. S3 in the [Supplementary Appendix](#)). The two groups were well balanced regarding baseline characteristics ([Table 1](#)).

The median age was 62 years, and 33.8% of the patients were women. A total of 65.7% of the patients had a history of hypertension, 21.1% had diabetes, and 43.0% were current or former smokers. The median time from the onset of the qualifying minor stroke or TIA to randomization was 13 hours. The index event was a TIA in 1445 patients (27.9%). A total of 36 patients (0.7%) — 20 in the clopidogrel–aspirin group and 16 in the aspirin group — were lost to follow-up; 165 patients (6.4%) in the clopidogrel–aspirin group and 146 (5.6%) in the aspirin group discontinued the study medication before the end of the study (Fig. S3 in the [Supplementary Appendix](#)).

PRIMARY OUTCOME

Table 2.

Efficacy and Safety Outcomes.

Figure 1.

Probability of Survival Free of Stroke.

Stroke occurred in 212 patients (8.2%) in the clopidogrel–aspirin group, as compared with 303 patients (11.7%) in the aspirin group (hazard ratio, 0.68; 95% confidence interval [CI], 0.57 to 0.81; $P<0.001$) ([Table 2](#) and [Figure 1](#)). Fatal or disabling stroke occurred in 135 patients (5.2%) in the clopidogrel–aspirin group and in 177 (6.8%) in the aspirin group (hazard ratio, 0.75; 95% CI, 0.60 to 0.94; $P=0.01$). Ischemic stroke occurred in 204 patients (7.9%) in the clopidogrel–aspirin group and in 295 (11.4%) in the aspirin group (hazard ratio, 0.67; 95% CI, 0.56 to 0.81; $P<0.001$). Hemorrhagic stroke occurred in 8 patients in each of the two study groups (0.3% of each group).

KEY SECONDARY AND OTHER EFFICACY OUTCOMES

The composite outcome of vascular events occurred in 216 patients (8.4%) in the clopidogrel–aspirin group, as compared with 307 patients (11.9%) in the aspirin group (hazard ratio, 0.69; 95% CI, 0.58 to 0.82; $P<0.001$) ([Table 2](#), and Fig. S4 in the [Supplementary Appendix](#)). Death from any cause occurred in 0.4% of the patients in each group. Vascular death (including death from hemorrhagic stroke) occurred in 6 patients (0.2%) in the clopidogrel–aspirin group and in 5 (0.2%) in the aspirin group. TIA occurred in 39 patients (1.5%) in the clopidogrel–aspirin group and in 47 (1.8%) in the aspirin group ($P=0.36$).

BLEEDING EVENTS

Moderate or severe hemorrhage, as defined by means of the GUSTO criteria, occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group ($P=0.73$) ([Table 2](#)). The rate of any bleeding event was 2.3% in the clopidogrel–aspirin group as compared with 1.6% in the aspirin group (hazard ratio, 1.41; 95% CI, 0.95 to 2.10; $P=0.09$) ([Table 2](#)).

Figure 2.

Hazard Ratio for the Primary Outcome in Prespecified Subgroups.

The reduction in the rate of stroke and combined secondary vascular events with clopidogrel and aspirin was consistent across all major subgroups ([Figure 2](#), and Fig. S5 in the [Supplementary Appendix](#)). There were no significant interactions in any of the 11 predefined subgroups ($P>0.10$ for all comparisons).

SAFETY

Adverse events occurred in similar proportions of patients in the two groups (5.8% in the clopidogrel–aspirin group and 5.0% in the aspirin group). The proportions of patients with serious adverse events were also similar (1.0% and 0.8% in the clopidogrel–aspirin and aspirin groups, respectively) (Table S4 in the [Supplementary Appendix](#)).

Discussion

In this large-scale trial involving patients with high-risk TIA or minor ischemic stroke, we found that the addition of clopidogrel to aspirin within 24 hours after symptom onset reduced the risk of subsequent stroke by 32.0%, as compared with aspirin alone. Event rates during this early period were very high, and clopidogrel was associated with an absolute risk reduction of 3.5 percentage points, equivalent to a number needed to treat of 29 patients to prevent one stroke over a period of 90 days. Combination therapy with clopidogrel and aspirin, as compared with aspirin alone, was not associated with an increased incidence of hemorrhage, although there was a worrisome trend in overall bleeding toward more events with the combination therapy.

The results of our trial differ from those of other trials of combination therapy with clopidogrel and aspirin after cerebral ischemic events.^{7,8,17} One possible explanation is that, unlike previous trials, our trial targeted a population at particularly high risk for recurrent ischemia and at low risk for hemorrhage. Previous trials included patients with more severe strokes than our trial did, and they did not enroll patients in the first hours after an index minor stroke or TIA, during which the risk of recurrent ischemia is particularly high. This may explain why other trials did not show a reduction in the risk of ischemic events but did show an increased risk of hemorrhage.

In our study, the curves for survival free of stroke were particularly steep in the first few days, during which the curves representing the treatment groups diverged dramatically. Subsequently, the rates of stroke were similar. This suggests that the requirement for randomization within 24 hours after the

onset of symptoms, with nearly half the patients enrolled within 12 hours (and treated shortly thereafter), was important. Although we did not see a relative difference in the efficacy outcome between patients randomly assigned to a study group within 12 hours and those assigned after a longer interval, absolute event rates were higher among those who were enrolled within 12 hours. In clinical practice, treatment with clopidogrel and aspirin as soon as possible after symptom onset is likely to produce the greatest absolute benefit, since ischemic event rates are highest in the initial hours after symptoms appear.

Our trial was conducted entirely in China, a country with approximately 150 to 250 deaths from stroke per 100,000 persons per year, which is five times as high as the rate in the United States.²³ Although diagnostic tools and therapies commonly used in the United States and Europe are available in most hospitals in China, some patients cannot afford this level of care.^{24,25} Secondary prevention practices are also less rigorous in China, where rates of treatment of hypertension, diabetes, and hyperlipidemia are low, as shown in our study population (Table S3 in the [Supplementary Appendix](#)). Furthermore, the distribution of stroke subtypes in China differs from that in more developed countries; China has a higher incidence of large-artery intracranial atherosclerosis²⁵ and a higher prevalence of genetic polymorphisms that affect the metabolism of clopidogrel.²⁶ The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (ClinicalTrials.gov number, NCT00991029), sponsored by the National Institutes of Health, which is similar to our trial, is now enrolling patients at sites primarily in the United States.²⁷ The POINT trial is assessing a higher loading dose of clopidogrel (600 mg) and a narrower time window (treatment within 12 hours after symptom onset) than were used in our study.

Several common clinical conditions mimic TIA, including seizures, migraine, peripheral vertigo, syncope, and anxiety.²⁸ To minimize the risk of enrolling patients with TIA mimics, we excluded all patients with isolated sensory symptoms, isolated visual changes, or isolated dizziness or vertigo without evidence of acute infarction on baseline CT or MRI of the head. In addition, enrollment of patients with TIA was limited to those with a high ABCD² score (≥ 4) to increase the likelihood that spells were due to true TIAs and to ensure that we were enrolling patients who were at high risk for subsequent ischemic events.²⁹ The risk of subsequent stroke in the trial was high for this patient population, suggesting that our strategy was successful. Our findings may not apply to other populations of patients with ischemic events.

In conclusion, our study shows that among patients with high-risk TIA or minor ischemic stroke who are initially seen within 24 hours after symptom onset, treatment with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone for a total of 90 days, is superior to aspirin alone in reducing the risk of subsequent stroke events. The combination of clopidogrel with aspirin did not cause more hemorrhagic events in this patient population than aspirin alone.

Funding and Disclosures

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[Disclosure forms](#) provided by the authors are available with the full text of this article at NEJM.org

No potential conflict of interest relevant to this article was reported.

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A complete list of investigators and institutions participating in the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial is provided in the [Supplementary Appendix](#), available at NEJM.org.

Supplementary Material

Protocol	PDF	1930KB
Supplementary Appendix	PDF	653KB
Disclosure Forms	PDF	408KB

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FERNANDO MENESES-TERAN, MD ▾

Jul 10, 2013

About CHANCE

In cohort studies, the risk of recurrent stroke after indices TIA or minor stroke is 10 to 20% at three months. But, in controlled studies, the risk varies between 3.4% (with aspirin) and 3.9% (with placebo); but, aspirin alone, compared with placebo, reduces by 13% the relative risk of stroke in patients who have had a prior ischemic stroke (Cochrane Database of Systematic Reviews 2008, Issue 3 CD000029). The CHANCE study has shown that the combination of clopidogrel and aspirin reduces the risk of

recurrent stroke by 32%, as compared with aspirin alone, without increasing the risk of bleeding or adverse events. The NNT was of 29, which is suitable.

Well-designed, rigorous, multicenter study; with high number of patients and moderate of events; without selection, or patients allocation, or endpoints detection or attrition, or reporting biases.

But, it is a study whose clinical application should be specific: Chinese population, minor acute stroke or TIA at high risk, with a high burden of risk factors for recurrent stroke, with a short follow-up period, probably without genetic polymorphisms of cytochrome P-450 which inhibit hepatic conversion of clopidogrel to active metabolite.

DR JAVAID SHAFI, MD ▾

Jul 07, 2013

IT IS MORE RELEVANT TO FIND ,THE REASON FOR THE BENEFITED GROUP.

A MULTIPLE FACTORS DEFINE THE BENEFITS. THIS MAY INCLUDE PLATELETS FUNCTION

VARIABILITY TO CRANIAL BLOOD VESSELS TO MICROCIRCULATION TO COLLATERALS.

Thomas Mooe ▾

Jul 05, 2013

Information about aspirin loading dose necessary

Both groups received open-label aspirin on day 1 (with the dose ranging from 75 to 300 mg, at the discretion of the treating physician). There is, however, no data about the proportion of patients given an adequate loading dose (300 mg) in the paper as far as I can see. A start dose of 75 mg would leave the patients in the control group without protection for several days while the intervention group were loaded with clopidogrel according to the protocol. Detailed data concerning aspirin dose day 1 is necessary to assess this study. A 75 mg start dose in a considerable proportion of the patients in the control group would completely invalidate the study.

ROBERT DUNN, MD ▾

Jul 04, 2013

What was the aspirin loading dose?

Unfortunately the aspirin loading dose was not standardised in this trial (75-300mg at the treating physician's discretion), whereas the clopidogrel loading dose was. As most stroke events occurred within the first few days an alternative explanation for the trial results could be that inadequate aspirin loading is inferior to adequate clopidogrel loading. Publishing the outcomes stratified by aspirin loading dose would be helpful in determining if this is the case.

Michael Carlsen ▾

Jun 30, 2013

Care and respect

The conflict of ideas about results should reference the discoverers and give better context to argument. Clopidogrel is not a given, but a new discovery by Burnstock referenced here <http://www.abc.net.au/radionational/programs/scienceshow/geoffrey-burnstock/4053892#transcript> . The discoverers of cox 1 and cox 2 surely did not expect companies to end up in the courts re their

discoveries. (Though respect should always be given to the companies for promoting the cost of research and discovery).

The point is that the discoverers whilst discovering a sub atomic field, so as to speak, did not come that field from within but arrived through argument and lateral, thinking.

This is lacking here.

An idea of better thinking is given by Burnstock himself when he points to his recent new field of discovery, It is that neural pathways do not flow in recognised directions as once believed..

And such a man would notice the social effect of the patient who, following a cardiac event, attends regularly, a professional for a period of two years . Such patient is 95 percent less likely to present to an intensive care ward. Good argument requires context



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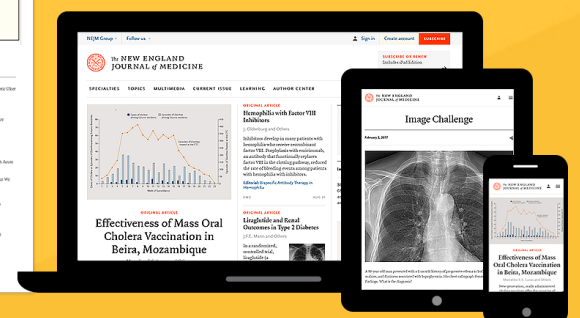
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