

ADAPTABLE provides answers on aspirin dosing, conduct of pragmatic trials

Among patients with atherosclerotic CVD, there was no difference in CV events or major bleeding according to aspirin dose, researchers reported at the American College of Cardiology Scientific Session.

The open-label, pragmatic, randomized controlled ADAPTABLE trial was the first to use PCORnet, a network established by the Patient-Centered Outcomes Research Institute for comparative effectiveness research. The results were simultaneously published in *The New England Journal of Medicine*.



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W. Schuyler Jones

“Despite its widespread use, there is not clear evidence to support the best dose of daily aspirin,” **W. Schuyler Jones, MD**, interventional cardiologist, director of the Duke University Cardiac Catheterization Laboratory, medical director of Duke Heart Center Clinical Research Unit and investigator at the Duke Clinical Research Unit, said during a presentation. “U.S. guidelines have not specified which dose is most appropriate for patients with heart disease. Our study was designed to answer a simple important clinical question: In people with preexisting heart disease, is a strategy of 81 mg or 325 mg of daily aspirin better?”

Patients with ASCVD at 40 centers and one health plan were recruited to participate through their electronic health record systems, Jones said. Through the network’s patient portal, each patient was randomly assigned to aspirin 325 mg daily or 81 mg daily, and purchased their medication over the counter. Patients had an early encounter through the portal to assess compliance and had routine follow-up encounters by email (87.4%) or phone (12.6%) every 3 to 6 months, according to the researchers.

“We identified patients with preexisting heart disease via electronic records queries termed a computable phenotype,” Jones said during the presentation. “Patients were enrolled using a multimodal, multi-touch approach, and participants used the online patient portal to enroll, provide electronic consent and self-randomize to 81 mg or 325 mg of daily aspirin. The computable phenotype allowed our study partners to

generate listings of eligible patients with known cardiovascular disease and at least one common enrichment risk factor so that screening could be minimal, and the approach could be pragmatic, generalizable and large-scale.”

The researchers planned to enroll 20,000 patients, but in 2017, after an analysis of recruitment rates and event rates, they reduced the size of the trial to 15,000 patients.

Of the 15,076 patients (median age, 68 years; 69% men; 9% Black) in the study, 96% [reported taking aspirin](#) before enrollment, and of those, 85.3% were taking 81 mg daily, 2.3% were taking 162 mg daily and 12.2% were taking 325 mg daily. Median follow-up was 26.2 months (interquartile range, 19-34.9).

During the study period, the primary effectiveness endpoint of all-cause death, hospitalization for MI or [hospitalization for stroke](#) occurred in 7.28% of those assigned aspirin 81 mg daily and in 7.51% of those assigned aspirin 325 mg daily (HR = 1.02; 95% CI, 0.91-1.14; $P = .75$), the researchers found.

The primary safety endpoint of hospitalization for major bleeding associated with a blood product transfusion — which Jones said was easier to ascertain in a pragmatic trial than traditional bleeding measures, and roughly correlated with Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe bleeding — occurred in 0.63% of the 81 mg group and 0.6% of the 325 mg group (HR = 1.18; 95% CI, 0.79-1.77; $P = .41$), Jones said during the presentation.

There were also no differences between the groups in the individual components of the primary effectiveness endpoint, and there was no difference in primary effectiveness endpoint in any prespecified subgroups, he said.

Dose switching was more common in the 325 mg group than in the 81 mg group (41.6% vs. 7.1%), Jones said, and the median days of exposure to the assigned dose was less in the 325 mg group than in the 81 mg group (434 days vs. 650 days).

In a sensitivity analysis based on doses patients reported taking regardless of randomization, the primary effectiveness endpoint occurred more often in those who actually took 81 mg aspirin compared with those who actually took 325 mg aspirin (HR = 1.25; 95% CI, 1.1-1.43), Jones said during the presentation, noting the corresponding bleeding analysis has not yet been performed.

“As with any post-randomization analysis, this approach has many inherent biases, and further explorations of dose-switching and adherence to study dose are warranted,” Jones said.

At a press conference, Jones said the key message for patients is that “aspirin is safe and effective for patients with established heart disease, and there really doesn’t seem to be a difference between the two doses. I would advise doctors to tell patients that if they are on 81 mg, they should stay on it; if they discontinued aspirin and resume it, they should restart at 81 mg because we didn’t find any conclusive evidence that 325 mg is better; and there is a signal that if the patient can tolerate 325 mg, potentially they should stay on it if they discuss it with their physician.”

“This is a pioneering large pragmatic trial, and we’re going to need to see more of these over the next few years,” **Donald M. Lloyd-Jones, MD, SM, FACC, FAHA**, chair of the department of preventive medicine, Eileen M. Foell Professor and professor of preventive medicine, medicine and pediatrics at Northwestern



Donald M.
Lloyd-Jones

University Feinberg School of Medicine, said during a discussion after the presentation. “There were some clear limitations [with] the open-label design and the unfortunate large crossover, and perhaps fewer Black Americans and fewer women than we might have desired. Nonetheless, the most important legacy of this trial for me is that you did it, and you showed us many of the promises and some of the pitfalls of these large pragmatic designs.”

In a related editorial published in *NEJM*, **Colin Baigent, FMedSci**, professor of epidemiology at the Nuffield department of population health at Oxford University and director of the Medical Research Council Population Health Research Unit, wrote that the trial “is a major achievement ... because it has shown a method of conducting trials efficiently and at low cost in the United States, and this method can now be adapted and used more widely. This should allow many more clinical questions to be answered, with obvious benefits to health care consumers.”

He wrote the trial itself was less successful because so many patients from the 325 mg group switched doses, often before the early encounter, which means that “bias arising from this degree of crossover could have obscured a true difference of efficacy or safety (or both).”

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References:

[Baigent C. *N Engl J Med*. 2021;doi:10.1056/NEJMe2106430.](#)

[Jones WS, et al. *N Engl J Med*. 2021;doi:10.1056/NEJMoa2102137.](#)

PERSPECTIVE



Erin D. Michos, MD, MHS, FACC, FAHA, FASE

ADAPTABLE attempted to answer once and for all: What is the optimal dose of aspirin for secondary prevention among patients with ASCVD? It was a clinical question in need of more evidence.

The bottom line is that it is reassuring that low-dose aspirin appears to be equally effective to high-dose aspirin in reduction of major vascular events with similar risk for bleeding, so we can continue using low-dose aspirin (81 mg), as is common standard practice for patients already taking this dose. Additionally, for patients who are currently treated with higher-dose aspirin (325 mg) who are stable and doing well, there also is not a compelling reason to automatically switch them to a lower dose either.

However, the caveat is that these trial results were limited by major dose switching, a problem from the open-label design. Patients and their clinicians knew what dose they were taking. So, patients at elevated risk of bleeding – such as those with a history of gastrointestinal bleeding or peptic ulcer disease, those with chronic kidney disease, those with thrombocytopenia, those taking NSAIDs and those older than 70 years – might be more likely to be advised to switch down to the lower dose. That may be why the bleeding risk was similar between the higher dose and the lower dose.

Aspirin still remains a class I indicated therapy for the secondary prevention of ASCVD. These results don't change that. But for decisions about which dose can be decided between patients and their clinicians based on their own unique risk factors for recurrent vascular events compared with bleeding events, patients and their clinicians should have a conversation, discuss the study results, and decide which dose makes sense for them.

Of note, contrary to prior studies, in ADAPTABLE, the authors did not see any interaction among key subgroups defined by age, sex, race/ethnicity, prior use of dual antiplatelet therapy, or coexisting diabetes or chronic kidney disease.

The traditional ways of recruiting, following participants and ascertaining events in large CV outcome trials are burdensome and very expensive. The pragmatic approach as used in ADAPTABLE could cut costs by one-third or so. The PREVENTABLE trial examining whether statins can help prevent dementia or physical disability is also using this approach.

While overall I am a big fan of this pragmatic trial design using electronic health records, I also have some concern about pragmatic design enrollment related to socioeconomic disparities and inequity related to access to internet and mHealth technology.

Another important key feature of the ADAPTABLE trial was its patient-centered design. Patient representatives, known as “adaptors,” served on the steering and executive committees, gave input on trial design and reviewed all patient-facing materials. This is important to make sure that any patient barriers are overcome by design considerations, and that study materials represent the diversity of the participants that are hoped to be recruited. The patient adaptors will also play a key role in dissemination of study results. Going forward, patient-centered design – trials designed with the input of patients – should be a critical component of all studies.

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PERSPECTIVE



Jeffrey S. Berger, MD

Aspirin is one of the most commonly used medicines for the prevention of CV events. However, practice patterns are variable. Even before ADAPTABLE, there were little data to support using a higher dose than 81 mg to 100 mg daily for secondary CVD prevention, but there appeared to be widespread belief that more may be better. Hopefully, ADAPTABLE will reinforce to the medical community that there is no clinical benefit for a higher dose of aspirin.

While this study demonstrates that 325 mg is not superior to 81 mg of aspirin, we should remember that aspirin remains a cornerstone in the secondary prevention of CV events. I think some questions remain: What is the optimal dose of aspirin in very obese individuals? Does anyone benefit from aspirin for the prevention of a first CV event (ie, primary prevention)? In the future, I believe we will be measuring platelet activity when we determine an aspirin regimen; in the future, we will be able to use an individual’s information about platelet genetics and/or function to figure out the drug and dose they should be taking.

The most important aspect of ADAPTABLE is that it provides a new platform for how to conduct a large clinical trial. It changed the landscape for how the medical community can perform large clinical trials. The investigative team should be complimented for that; it is a big step forward. It would be impossible to continue trials in the current state, with many trials costing hundreds of millions of dollars. Testing aspirin dose was a great way to prove the concept; it may be more difficult with a drug that people are not as comfortable with. I look forward to the challenge.

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PERSPECTIVE



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Some of the most frequently asked questions by patients to a preventive cardiologist involve aspirin therapy. In regards to primary prevention, the questions usually revolve around the issue if they should take aspirin. What if I have diabetes, elevated Lp(a) or pre-clinical ASCVD as documented by a high coronary calcium score, should I take aspirin 81 mg per day? This question is difficult to answer based on the lack of evidence from randomized trials. We clinicians have to provide our best judgment knowing we need more data.

Now thanks to the ADAPTABLE trial, we can at least answer the question regarding the dose for patient with ASCVD. This trial was a randomized but open label with a pragmatic design to allow flexibility to address this important question. The conclusion is that for patients with ASCVD, aspirin 81 mg was equivalent to 325 mg for prevention of major adverse events. Safety was also similar, but more patients decided to downtitrate to the lower dose vs. uptitrate to the higher dose.

This is a landmark trial for two reasons. It confirms that aspirin 81 mg is the correct dose for most patients with ASCVD, and perhaps more importantly, it has finally broken through the barrier of requiring double-blind, placebo-controlled trials with multiple visits to track outcomes. A pragmatic design is the hope for many future CV outcome trials because the cost of the more rigorous designed studies is not feasible to answer many of our important clinical questions.

My hope is that the learnings from the ADAPTABLE trial set the stage for more pragmatic trials in the future in which an open-label design can be implemented with remote data capture through electronic medical record systems.

One significant learning from the ADAPTABLE trial is that patients prefer lower doses of drugs even if the safety of the higher dose appears similar. This has ramifications for many of the prevention guidelines in which higher doses of drugs are recommended (eg, statins) due to the data generated from large rigorous outcome trials.

This is potentially the beginning of a new era of CV prevention trials in which clinical decision-making can be based on high quality data that meets an appropriate standard through a pragmatic design but not to the same standard that we have been accustomed to in the past. Is it not better to get a good answer to an important clinical question than no answer at all?

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PERSPECTIVE



Robert S. Rosenson, MD

Many patients are on long-term aspirin therapy and develop chronic anemia from gastritis or may have frequent bruising they may find unpleasant, so the question of the correct dose of aspirin for patients with CVD is an important one.

The event rates were no different between the dosage groups, but the study raises a lot of questions. The large-scale approach lowers costs, but there may be some important issues that are obscured by the nature of the study.

No. 1, we know that in patients taking enteric-coated aspirin, not everybody has an antiplatelet effect. One study of stroke survivors found that 20% of patients taking aspirin 325 mg daily and 45% taking aspirin 81 mg daily did not have an antiplatelet effect. An important issue is what type of aspirin is being taken. Coated or noncoated? Chewable or swallow-at-once?

No. 2, it is unclear why some patients stopped taking aspirin or decided to reduce their dose. There are other therapies that may have been causing symptoms and prompted them to make the change. For example, perhaps they were on NSAIDs for arthritis that could have caused gastritis, so they down-titrated the dose of the aspirin. The granularity of those issues is not easily addressed with this type of study design.

The take-home message is that low-dose aspirin is equally effective to higher-dose aspirin in patients with stable ASCVD. It's hard to say that this is transformative because other studies have shown lower doses of aspirin are equally effective.

The trial design could be useful for future comparative studies of BP medications. To do a randomized, double-blind, controlled trial, it would require tens of thousands of patients. That is impractical. This type of study design has the ability to address those kinds of questions very effectively. For example, it would be useful to study chlorthalidone,

which has not been widely used in the U.S., and hydrochlorothiazide, which is often used in combination pills. Whether chlorthalidone is superior to hydrochlorothiazide is an important question that could be addressed with this type of study. As would a comparison of ACE inhibitors and angiotensin receptor blockers.

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