JAMA Cardiology | Special Communication

Rationale and Design of the Aspirin Dosing—A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial

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IMPORTANCE Determining the right dosage of aspirin for the secondary prevention treatment of atherosclerotic cardiovascular disease (ASCVD) remains an unanswered and critical question.

OBJECTIVE To report the rationale and design for a randomized clinical trial to determine the optimal dosage of aspirin to be used for secondary prevention of ASCVD, using an innovative research method.

DESIGN, SETTING, AND PARTICIPANTS This pragmatic, open-label, patient-centered, randomized clinical trial is being conducted in 15 000 patients within the National Patient-Centered Clinical Research Network (PCORnet), a distributed research network of partners including clinical research networks, health plan research networks, and patient-powered research networks across the United States. Patients with established ASCVD treated in routine clinical practice within the network are eligible. Patient recruitment began in April 2016. Enrollment was completed in June 2019. Final follow-up is expected to be completed by June 2020.

INTERVENTIONS Participants are randomized on a web platform in a 1:1 fashion to either 81 mg or 325 mg of aspirin daily.

MAIN OUTCOMES AND MEASURES The primary efficacy end point is the composite of all-cause mortality, hospitalization for nonfatal myocardial infarction, or hospitalization for a nonfatal stroke. The primary safety end point is hospitalization for major bleeding associated with a blood-product transfusion. End points are captured through regular queries of the health systems' common data model within the structure of PCORnet's distributed data environment.

CONCLUSIONS AND RELEVANCE As a pragmatic study and the first interventional trial conducted within the PCORnet electronic data infrastructure, this trial is testing several unique and innovative operational approaches that have the potential to disrupt and transform the conduct of future patient-centered randomized clinical trials by evaluating treatments integrated in clinical practice while at the same time determining the optimal dosage of aspirin for secondary prevention of ASCVD.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02697916

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Author Audio Interview

Supplemental content

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JAMA Cardiol. 2020;5(5):598-607. doi:10.1001/jamacardio.2020.0116
Published online March 18, 2020.

Atherosclerotic cardiovascular disease (ASCVD) is a major public health problem in the US and worldwide and remains a leading cause of morbidity and mortality.[1,2] Cardiovascular diseases are the leading drivers of health-associated expenses in the US, exceeding $300 billion, a figure expected to soar to more than $900 billion by 2035.[3] Since pivotal trials showed substantial benefits with aspirin in acute coronary syndrome (ACS), it has been an anchor treatment for the secondary prevention of ASCVD for almost 3 decades.[4-7] The benefits of aspirin have also been reaffirmed in recent cardiovascular outcomes trials that demonstrated no difference in ischemic events when compared with a new-generation oral anticoagulant in the post-ACS and chronic atherosclerotic vascular disease settings.[8,9]

While there is strong evidence to support aspirin treatment for the secondary prevention of ASCVD in contemporary practice guidelines,[10-13] registries and post hoc analyses from randomized clinical trials have shown discordant results with respect to aspirin dosage on ischemic events in the post-ACS setting.[14-16] Moreover, variable use of aspirin in low or high dosages for post-ACS treatment in clinical practice exists,[17] reflecting the uncertainty among clinicians regarding the optimal dosage for long-term secondary prevention. Determining the right dosage of aspirin has the potential to prevent thousands of myocardial infarctions (MIs) and bleeding events worldwide.

The cost and operational complexity of conducting a properly powered, traditional randomized clinical trial testing 2 aspirin dosages in ASCVD would be prohibitive and unlikely to receive support from the industry. Within the context of the growing complexity and cost of cardiovascular trials,[18] a strong need has arisen to develop and execute more streamlined, pragmatic trials leveraging real-world data and technologies to generate real-world evidence to answer important clinical questions that have a direct outcome on public health.[19,20] Given the epidemic of ASCVD, the availability of aspirin as an over-the-counter drug, the equipoise regarding the optimal dosage of aspirin for secondary prevention, and the opportunities created for conducting large-scale electronic health record (EHR)–based pragmatic clinical trials using the National Patient-Centered Clinical Research Network (PCORnet), several factors have come together to finally address the question of aspirin dosage selection.[21,22]

The Aspirin Dosing: a Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness of Aspirin (ADAPTABLE) trial (NCT02697916) is a multicenter, open-label, pragmatic, superiority randomized clinical trial designed to compare a low dosage vs a high dosage of aspirin (81 mg daily vs 325 mg daily) for the secondary prevention treatment of ASCVD in 15 000 patients.[23] This large-scale innovative trial addresses a clinically important and patient-centered question while simultaneously testing novel and streamlined clinical research methods within a national EHR-enabled research network. This article reports the rationale and the design of the ADAPTABLE trial in conformance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[24] The original trial protocol was approved on October 22, 2015, and was amended in December 18, 2017.

Key Points

Question What is the most appropriate dosage of aspirin in patients with established atherosclerotic cardiovascular disease?

Findings This report highlights the intricate design and details of study conduct for the Aspirin Dosing: a Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) trial. This is the first pragmatic trial using the Patient-Centered Outcomes Research network, which was developed to perform large scale comparative-effectiveness clinical trials.

Meaning The ADAPTABLE study will help to determine the optimal dosage of aspirin in patients with established atherosclerotic cardiovascular disease.

Rationale

Aspirin for the Secondary Prevention Treatment of ASCVD

Aspirin has been studied in more than 135 000 patients with high ASCVD risk in randomized trials and has been shown to lead to a relative approximate 20% decrease in serious vascular events at the expense of a concomitant increase in bleeding risk.[5] Although aspirin is available in many countries as an over-the-counter analgesic drug, the optimal dosage to balance the trade-off between ischemic event reduction vs increased bleeding risk for the treatment of ASCVD remains uncertain. Low dosages of aspirin commonly used in clinical practice are sufficient to irreversibly suppress cyclooxygenase (COX)–1-mediated platelet activation and aggregation.[25] Increasing dosages also inhibit COX-2 activity, a prostaglandin with vasodilatory and platelet-aggregation inhibition properties. Consequently, increasing the dosage paradoxically decreases the antiplatelet effect of aspirin.[25]

The optimal daily dosage of aspirin has been evaluated in 1 dedicated short-term, prospective clinical trial[26] focused on a post-ACS population, which showed no differences in ischemic and bleeding events through 30 days with a low dosage (75-100 mg/d) vs a high dosage (300-325 mg/d) of aspirin. This study, however, did not provide evidence about the optimal aspirin dosage for long-term secondary prevention. Thus, considerable uncertainty remains regarding the optimal dosage of aspirin for the treatment of chronic ASCVD in patients with or without previous ACS, as reflected by lack of clear recommendations in practice guidelines.[10-12]

Use Case for More Pragmatic, Efficient Trials

Observed trends of the increasing cost and complexity of conducting trials and the relative stagnation of investigational new-drug applications for cardiovascular disease received by the US Food and Drug Administration (FDA)[18] have contributed to the strong need for low-cost, efficient, pragmatic, and technology-enabled trials.[20,27] Funded by the Patient-Centered Outcomes Research Institute (PCORI), the PCORnet is a data network made possible by aggregated EHR and claims data platforms and created to facilitate the conduct of pragmatic, patient-centered clinical research.[22,28] Its mission is to "conduct patient-centered and data-enabled clinical research to deliver results that matter, faster."[29] In a survey of PCORnet stakeholders, the evaluation of aspirin dosing was selected as the first pragmatic trial leveraging PCORnet because of its potential benefit to public health, its feasibility of being addressed with a network leveraging EHRs, and its position as a clear way to evaluate the capacity for completing pragmatic trials in PCORnet.

As the first randomized trial executed within the PCORnet data infrastructure, the ADAPTABLE trial represents, to our knowledge, the first large-scale, EHR-enabled clinical trial executed within the US and uses several innovative and transformational operational patient-centered approaches previously untested in cardiovascular outcomes trials. The data network is a critical component of the inno-

vation of the ADAPTABLE trial to facilitate recruitment, consent, and follow-up; PCORnet is poised to answer the specific research question for ADAPTABLE by enabling the use of EHR technology to identify eligible patients, conduct remote outreach and randomization at scale, and ascertain end points. By putting some resources that have already been assembled to dual purposes, this approach has the potential to decrease costs associated with clinical research. Through its broad eligibility criteria and the absence of in-clinic study visits, the pragmatic design of the ADAPTABLE trial seeks to deviate as little as possible from routine health care delivery to help support real-world clinical decisions.[30]

Methods

Trial Organization, Oversight, and Inclusion and Exclusion Criteria

Information on the research network organization, patient partners, steering committee, data and safety monitoring board, and protocol development are in the eAppendix and eFigure 1 in the Supplement. Because the results of the ADAPTABLE trial are meant to be generalized to the population of patients with established ASCVD treated in routine clinical practice, eligibility criteria were selected to broadly reflect criteria used during clinical care to confirm the presence of ASCVD. The study was approved by local institutional review boards.

Before the initial protocol was finalized in October 2015, it was posted for public review and comment. Key eligibility criteria were finalized based on this feedback, including answers to dedicated questions regarding specific topics of interest. Additionally, enrichment criteria were required to ensure that a group of patients with ASCVD who are at moderate to high risk would be included, to ensure an adequate event rate would be achieved. Trial participant recruitment began in April 2016. Enrollment was completed in June 2019. Final follow-up is expected to be completed by June 2020.

The inclusion and exclusion criteria were transformed into programming coding algorithms using *International Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision* (*ICD-10*) codes that were used to query the local health systems' EHR data warehouses to identify eligible patients. It became apparent that the initial inclusion criteria designed to select patients with prior cardiovascular events or procedures and/or with obstructive coronary disease identified during coronary angiography did not adequately capture patients with established ASCVD. For example, patients with a prior MI or prior revascularization procedures that occurred before the period covered by the query in the health system EHR data warehouse were not identified, since these events and procedures are typically only included as unstructured data elements in problem lists during outpatient encounters. Additionally, angiographic details are also often included only as unstructured data elements. Given that unstructured EHR data elements are not captured with programming algorithms, several participating health systems collaborated to augment *ICD-9* and *ICD-10* codes that captured chronic ASCVD conditions typically submitted as billable diagnoses during outpatient encounters. The protocol was amended in October 2016 to incorporate these changes to the key inclusion criteria and also incorporate additional enrichment criteria identifiable as structured data elements in the EHR data warehouses. Inclusion and exclusion criteria and enrichment criteria from the original protocol and the first protocol amendment are shown in the **Box**.

Innovative Operational Approaches

Recruitment Methods

The testing of novel, large-scale recruitment strategies within the PCORnet network has been one of the core goals of the trial. As described previously,[31] the data coordinating center developed programming algorithms reflecting the initial and revised trial eligibility criteria (termed *computable phenotypes*). These codes are publicly available online[32] and were distributed to all participating health systems and the participating health plan research networks that customized and applied them to their local EHR data warehouses to identify a local cohort of potentially eligible participants.[31,33] These novel methods resulted in the identification of hundreds of thousands of potentially eligible patients who were approached for participation during the recruitment period of the trial. Additional layers of verification were implemented to confirm eligibility of patients identified with the use of this computable phenotype.

While there has been no mandatory recruitment method for this trial, each participating health system and clinical research network queried their EHR data warehouses with the study computable phenotype to identify a large number of potentially eligible patients and developed strategies to contact those patients through multifaceted approaches to inquire about their interest in participating in the trial. Cross-network sharing and learning about best recruitment practices was an important way of informing local recruitment and retention approaches. Multimodal high-touch and low-touch methods were used to connect with potential participants at various sites. The most common recruitment approaches have been remote or virtual contact via email, mailed letters, online messaging embedded within EHRs, or telephone calls leveraging patient-centric recruitment material developed through collaboration with the Adaptor patient partners (a group of patient partner investigators composed of patient representatives from each participating clinical research network). Several health systems developed information technology applications to embed email recruitment approaches within their pre-existing EHR patient portals, while other health systems used embedded EHR prompts and/or prescreening methods together with tablet-based or computer-based electronic informed consent for high-throughput screening and enrollment during scheduled outpatient clinical encounters (**Figure 1**). Emphasis has been placed on explaining trial concepts to clinicians so that they could serve as a resource for patients without slowing clinical workflow. Projected and actual enrollment rates are depicted in eFigure 2 in the Supplement.

Electronic Informed Consent

After potentially eligible patients are identified, they are provided with a link to the trial web portal (through the various recruitment approaches detailed) and a personalized access code that allows them to access the portal. The web portal is available in English, with Spanish-language versions at some sites. A web-based, electronic informed consent platform, including an informational video, is presented to participants. The electronic consent process follows the FDA's guidance on the use of electronic health consent[34] and was developed with the patient partners. The content of the consent forms was customized locally and approved by the institutional re-

Box. Original and Amended Eligibility Criteria

Original Protocol (October 22, 2015)

Known atherosclerotic cardiovascular disease, defined as any of the following:
- A prior myocardial infarction
- Prior coronary revascularization procedures (either percutaneous coronary intervention or coronary artery bypass grafting)
- Prior coronary angiography showing 75% or greater stenosis of 1 or more epicardial coronary vessels

An age of 18 years or older

No known safety concerns or adverse effects considered to be associated with aspirin, including
- A history of clinically significant allergy to aspirin, such as anaphylaxis, urticaria, or significant gastrointestinal intolerance
- A history of clinically significant gastrointestinal bleeding within the past 12 months
- Clinically significant bleeding disorders that preclude the use of aspirin

Access to the internet[a]

No current treatment with an oral anticoagulant (either warfarin or a novel anticoagulant [dabigatran, rivaroxaban, apixaban, edoxaban]) and no plan to be treated in the future with an oral anticoagulant for existing indications, such as atrial fibrillation, deep vein thrombosis, or pulmonary embolism

No current treatment with ticagrelor and no plan to be treated in the future with ticagrelor

For women, not being pregnant or nursing an infant

Estimated risk of major adverse cardiovascular event greater than 8% over next 3 years, as defined by the presence of 1 or more of the following enrichment factors:
- An age older than 65 years
- Serum creatinine level greater than 1.5 mg/dL
- Diabetes mellitus (type 1 or type 2)
- Three-vessel coronary artery disease
- Cerebrovascular disease and/or peripheral artery disease
- Left ventricular ejection fraction less than 50%
- Current cigarette smoking

Amended Protocol (October 3, 2016)

Known atherosclerotic cardiovascular disease, defined as any of the following:
- A prior myocardial infarction
- Prior coronary revascularization procedures (either percutaneous coronary intervention or coronary artery bypass grafting)
- Prior coronary angiography showing 75% or greater stenosis of 1 or more epicardial coronary vessels
- History of chronic ischemic heart disease, coronary artery disease, or atherosclerotic cardiovascular disease[b]

An age of 18 years or older

No known safety concerns or adverse effects considered to be associated with aspirin, including
- A history of clinically significant allergy to aspirin, such as anaphylaxis, urticaria, or significant gastrointestinal intolerance
- A history of clinically significant gastrointestinal bleeding within the past 12 months
- Clinically significant bleeding disorders that preclude the use of aspirin

Access to the internet[a]

No current treatment with an oral anticoagulant (either warfarin or a novel anticoagulant [dabigatran, rivaroxaban, apixaban, edoxaban]) and no plan to be treated in the future with an oral anticoagulant for existing indications such as atrial fibrillation, deep vein thrombosis, or pulmonary embolism

No current treatment with ticagrelor and no plan to be treated in the future with ticagrelor

For women, not being pregnant or nursing an infant

Estimated increased risk of major adverse cardiovascular event over next 3 years, as defined by the presence of 1 or more of the following enrichment factors[b]:
- An age of 65 years of older
- Serum creatinine level of 1.5 mg/dL or more
- Diabetes mellitus (type 1 or type 2)
- Current cigarette smoking
- Cerebrovascular disease
- Peripheral artery disease
- Three-vessel coronary artery disease
- Systolic or diastolic heart failure[b]
- Left ventricular ejection fraction less than 50%
- Systolic blood pressure level of 140 mm Hg or more documented within prior 12 months[b]
- Low-density lipoprotein cholesterol level of 130 mg/dL or more documented within prior 12 months[b]

SI conversion factors: To convert serum creatinine to µmol/L, multiply by 88.4; to convert low-density lipoprotein to mmol/L, multiply by 0.0259.

[a] In the event that the clinical research networks are notified that a cohort of patients without internet access can be included, then patient agreement will be obtained during the consent process to provide follow-up information by telephone contact with the Duke Clinical Research Institute call center.

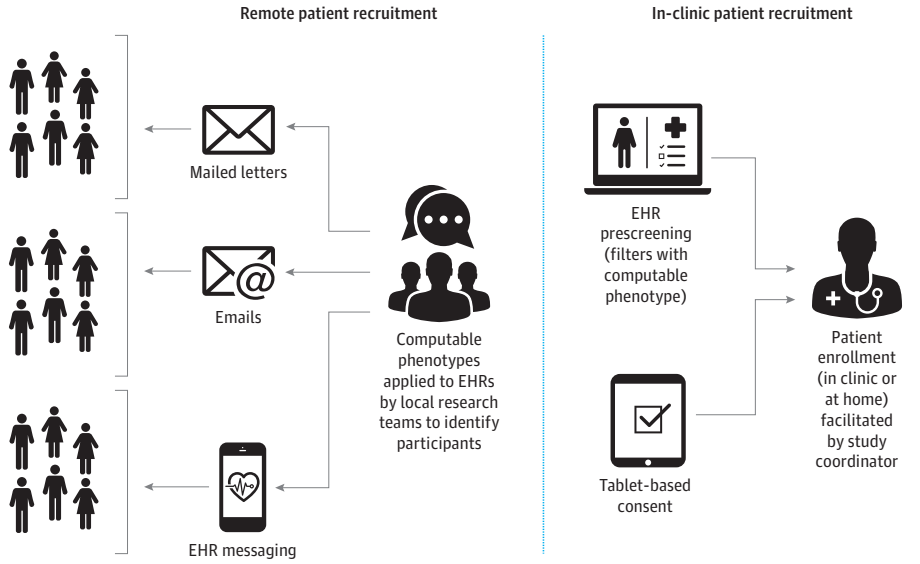
[b] Changes after the amendment.

view boards of each participating health system. After answering several questions that determine trial ineligibility and verify the understanding of the commitments associated with trial participation, participants electronically sign the consent form. To address the potential limited generalizability of the study results for those who have no access to the internet or are uncomfortable with technology, the informed consent process has been facilitated by research coordinators using electronic tablets during scheduled outpatient clinical encounters (noninternet participation).

Direct-to-Patient Randomization

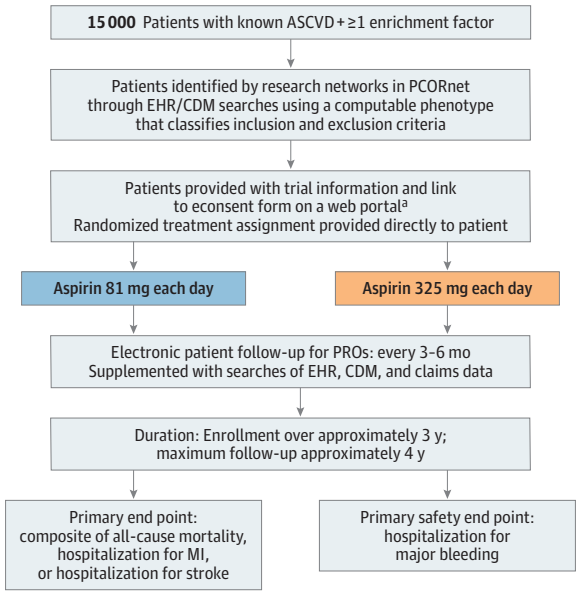
Following electronic signature of the consent form, participants are randomized in a 1:1 fashion to either 81 mg or 325 mg of daily aspirin and are provided with their randomized aspirin-dosage assignment via the trial web portal, independently from a health care professional, or in person during outpatient clinic encounters with tablet-facilitated enrollment (**Figure 2**). Additionally, a secondary randomization to follow-up intervals of 3 months or 6 months was also performed to determine the most effective

Figure 1. Recruitment Approaches



EHR indicates electronic health record.

Figure 2. The Aspirin Dosing: a Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Study Design



ASCVD indicates atherosclerotic cardiovascular disease; CDM, common data model; EHR, electronic health record; PCORnet, Patient-Centered Clinical Research Network; PROs, patient-reported outcomes.

method to optimize patient retention and adherence to the randomized aspirin dosage in this pragmatic trial. Because of the size of the trial, it was deemed unnecessary to stratify randomization. After randomization, participants are asked to buy their assigned dosage of aspirin at their local pharmacy and told to adhere to the assigned aspirin dosage. Given the clinical equipoise underlying the optimal dosage of aspirin, the centralized confirmation of end points, and the pragmatic nature of the trial, the aspirin dosage assignment is open-label.

Efficiently translating clinical trial findings into routine clinical practice can be complex. To minimize this challenge, the trial intervention in the ADAPTABLE trial was delivered as closely as possible as it would be in routine clinical practice (ie, participants bought their aspirin over the counter), and only an open-label design would permit that. Potential observation and performance bias associated with the open-label design are minimized with strategies to ensure participants are educated about the clinical equipoise between the 2 study dosages of aspirin (eg, online video, study comprehension questions). Participants receive a $25.00 gift card for their participation in the trial.

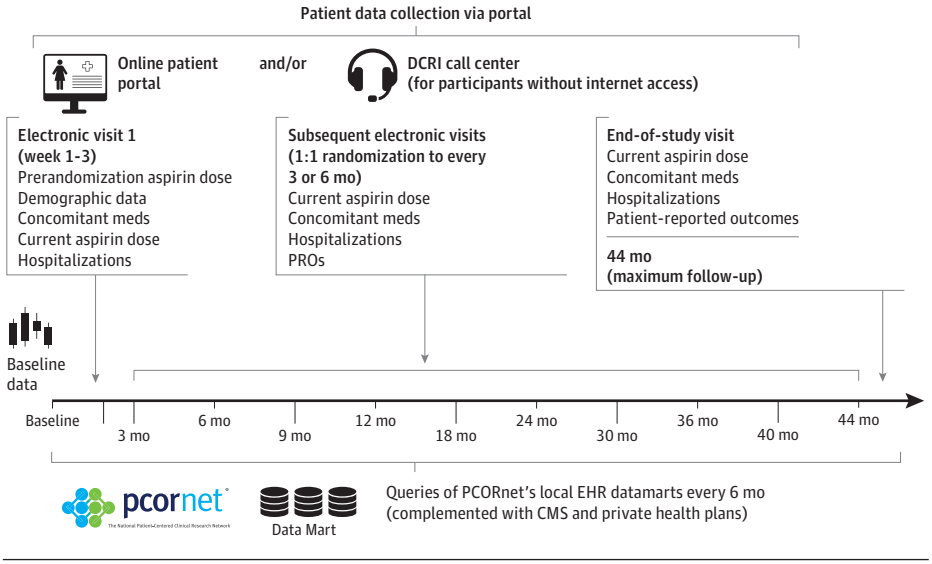
Direct-to-Patient Data Collection

All study visits, including randomization, are completed within the web portal and do not require clinic visits. During the early study visit (approximately 1-3 weeks after initial randomization), contact information and limited health status data are obtained from participants, and participants confirm that they started taking the study dosage of aspirin. At the time of the scheduled electronic follow-up visits (randomized to every 3 months vs every 6 months), information on adherence to the randomized aspirin dosage, hospitalizations (and reasons for hospitalizations), and patient-reported outcomes are collected from trial participants. Participants enrolled as noninternet participants are contacted via a central telephone call center at the Duke Clinical Research Institute. Participants who initially chose electronic follow-up but have not completed an electronic visit in 6 months via the trial web portal are also contacted by the call center. If participants do not wish to continue their scheduled trial contacts via the trial web portal or the call center, they are offered limited-participation options, including less frequent telephone calls, a call only at the end of the study, or data collection only through the scheduled queries of the data infrastructure.

Data Collection Through Queries of PCORnet's Common Data Model

Within the structure of PCORnet's distributed data environment, regular queries of the health systems' common data model (CDM) are per-

Figure 3. Data Collection



CMS indicates Centers for Medicare and Medicaid Services; DCRI, Duke Clinical Research Institute; EHR, electronic health record; PCORnet, Patient-Centered Clinical Research Network; PROs, patient-reported outcomes.

formed by the data coordinating center to ascertain hospitalizations of trial participants in hospitals within the research network. Results of these queries are reviewed by local data teams, returned to the study coordinating center, curated, and aggregated into a harmonized, trial-specific database that also includes patient-reported data. A schematic of trial data collection approaches is shown in **Figure 3**.

End Point Ascertainment, Reconciliation, and Confirmation

The primary effectiveness end point is a composite of all-cause mortality, hospitalization for nonfatal MI, or hospitalization for nonfatal stroke. Prespecified secondary end points include coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft) and the individual components of the primary end point. The primary safety end point is hospitalization for major bleeding associated with a blood-product transfusion. End points are identified with algorithms applied to multiple data sources (PCORnet's CDM, health plans, and claims data). Because of the pragmatic nature of the study, these end points are not confirmed with source documents or traditional independent adjudication by a clinical events committee. Because of patient preferences (in that the cause of death was deemed meaningless to patients) and for practical reasons, all-cause mortality (rather than cardiovascular mortality) was included as a component of the primary end point, because EHR and claims data do not routinely record cause-of-death information. Patient-reported outcomes are confirmed and reconciled through several iterative methods. A prespecified end point validation plan is being conducted throughout the trial, through which random samples of nonfatal end points (25 per clinical research network) are selected across sites and health systems at periodic intervals and then adjudicated in a traditional manner using collected source documents. The validation-associated adjudication results will not lead to reclassification of end points in the primary analysis of the study.

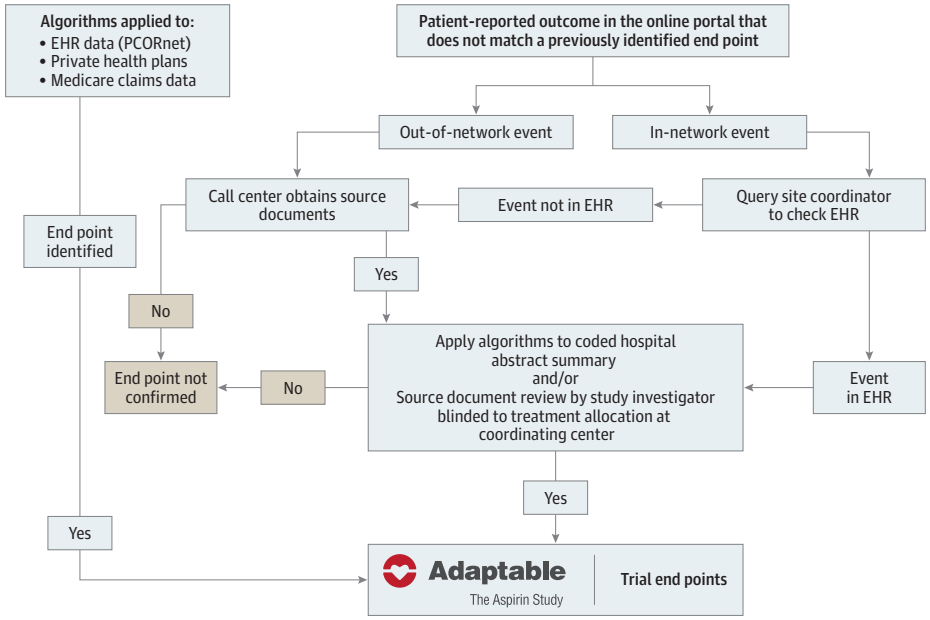
Programming algorithms were developed by the data coordinating center and distributed to each health system to identify end points captured in their local CDM through the aforementioned data queries. Both *ICD-9* and *Current Procedural Terminology* codes were used to classify the hospitalizations for nonfatal end points (MI, stroke, and bleeding) and updated with *ICD-10* codes once those were available (eTable 2 in the Supplement). The accuracy of the coding algorithms used to identify MI, stroke, and bleeding have been previously validated.[35-37] Furthermore, linkages are performed with Medicare and PCORnet partner health plan administrative claims databases to identify and confirm potential end points not captured in the local health system EHR data warehouses (termed *out-of-network events*) using the same programming algorithms.[38] Inpatient deaths are captured through these approaches, but out-of-hospital deaths are confirmed with queries to the Medicare data and/or via notification by family or friends of the participant. Given the long data latency associated with the National Death Index of approximately 18 months, queries to this information source have not been pursued.

If patient-reported hospitalizations that could be potential study end points (MI, stroke, or bleeding) cannot be reconciled with queries to the CDM or administrative claims databases, medical records, including hospitalization discharge summaries and procedure reports, are obtained by the Duke Clinical Research Institute coordinating center and analyzed by disease-specific experts using the same prespecified criteria used in the EHR end point queries. The process and approaches for end point ascertainment and reconciliation are shown in **Figure 4**. Statistical analysis is explained in the eAppendix and sample size calculation is summarized in eTable 1 in the Supplement.

Discussion

Aspirin has been used for decades for the treatment of ASCVD and is available over the counter, but the safest and most effective dosage of aspirin for this indication remains a critical and unanswered question. Despite the lack of established effectiveness of aspirin for the primary prevention of ASCVD as highlighted in the recently published prevention guidelines,[39,40] the role of aspirin for the secondary prevention treatment of patients with established ASCVD has

Figure 4. End Point Ascertainment and Reconciliation



EHR indicates electronic health record; PCORnet, Patient-Centered Clinical Research Network.

not been questioned[5] and is recommended by clinical practice guidelines.[10-13] While recently published post hoc analyses have examined the effectiveness and safety of different dosages of aspirin for the treatment of vascular disease, particularly with respect to body weight, only a prospective, properly designed, sufficiently powered randomized clinical trial, such as the ADAPTABLE trial, can definitively resolve the uncertainty and equipoise surrounding aspirin dosages.[41,42] The 2016 American College of Cardiology/American Heart Association Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease writing group endorses the ADAPTABLE trial and expects it to provide meaningful evidence to support practice in the future.

As a pragmatic study and the first interventional trial conducted within the PCORnet electronic data infrastructure, the ADAPTABLE trial is testing several unique and innovative operational approaches that have the potential to disrupt and transform the conduct of future randomized clinical trials, with better efficiency and at a lower cost, and incorporates multistakeholder engagement including patients, communities, and clinicians. The scale of this study incorporating EHRs, claims data, and a web portal makes it the first of its kind.[20] As a demonstration study, ADAPTABLE is set up as a benchmark on which iterative improvements of the pragmatic methods developed for recruitment and end point ascertainment will be made for future trials within the PCORnet network. The innovative methodological components of the ADAPTABLE trial may help inform the regulatory science needed for future hybrid trials that combine new methods for patient identification and enhanced follow-up using electronic methods and/or other integration of data generated from routine health care encounters. As FDA completes its guidance for real-world evidence and the supporting assessment of fit-for-use procedures and data, hybrid studies may be possible using some of the features of ADAPTABLE, especially in phase IV settings. Given that ADAPTABLE is studying an approved over-the-counter medication, implementation is easier compared with other trials operating under investigational new drug regulations. Nevertheless, creative approaches developed from ADAPTABLE, such as electronic enrollment and remote follow-up, could be used for trials evaluating drugs requiring prescription or experimental treatments within the PCORnet network.

Conclusions

As the interest in real-world evidence evolves, the combination of patient engagement, clinicians, and health systems offers a platform to address routine questions that influence outcomes. In this context, the focus on patient engagement offers the ability to focus on the right questions, using the best settings to address them. In ADAPTABLE, the widespread involvement of patient partners, from identification of the question to cocreation of the trial, is an advance for real-world evidence needs. This model had an undeniable influence on ADAPTABLE, from design to execution. As patient-oriented clinical research evolves, EHR data networks mature, and valuable experience with pragmatic trial operational approaches is gained and shared, the clinical research ecosystem is expected to evolve to facilitate the conduct of trials of the future. Within this context, the growing interest and emphasis by the FDA on the use of real-world data to generate real-world evidence for the effectiveness and safety of medical therapeutics synchronizes directly with the goals and objectives of the ADAPTABLE trial.[43]

ARTICLE INFORMATION

Accepted for Publication: January 9, 2020.

Published Online: March 18, 2020. doi:10.1001/jamacardio.2020.0116

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Author Contributions: Dr Jones had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Obtained funding: Roe, Berdan, Hernandez.
Administrative, technical, or material support: Marquis-Gravel, Roe, Robertson, Harrington, Berdan, Hammill, Faulkner, Fintel, Zhou, Daugherty, Nauman, Kraschnewski, Ahmad, Benziger, Haynes, Metkus, Shah, McClay, Geary, Lampert, Whittle, Alvarado, Goldberg, VanWormer, Farrehi, McTigue, Rothman, Hernandez, Jones.
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Conflict of Interest Disclosures: Dr Marquis-Gravel reported grants from Canadian Institute of Health Research during the conduct of the study and personal fees from Servier and Novartis outside the submitted work. Dr Robertson reported grants from Patient Centered Outcomes Research Institute (PCORI) during the conduct of the study. Dr Harrington reported grants from PCORI during the conduct of the study and grants from Sanofi, AstraZeneca, Portola, Janssen, Bristol-Myers Squibb, and the Medicines Company outside the submitted work. Dr Pencina reported grants from PCORI during the conduct of the study and grants from Sanofi/Regeneron and Amgen and personal fees from Merck and Boehringer Ingelheim outside the submitted work. Dr Berdan reported grants from PCORI during the conduct of the study. Dr Hammill reported grants from PCORI during the conduct of the study. Dr Nallamothu reported serving as a a principal investigator or coinvestigator on research grants from the National Institutes of Health, VA Health Services Research & Development, the American Heart Association, Apple Inc, and Toyota; he also receives compensation as editor-in-chief of *Circulation: Cardiovascular Quality & Outcomes*, a journal of the American Heart Association, and is a co-inventor on US utility patent number US15/356,012 (US20170148158A1) entitled "Automated Analysis of Vasculature in Coronary Angiograms" that uses software technology with signal processing and machine learning to automate the reading of coronary angiograms, held by the University of Michigan and licensed to AngioInsight Inc, in which Dr. Nallamothu holds ownership shares (yet to be funded). Dr Ford reported grants from PCORI during the conduct of the study. Dr Nauman reported grants from PCORI during the conduct of the study. Dr Kraschnewski reported grants from PCORI and the National Institutes of Health during the conduct of the study; grants from PCORI, the National Institutes of Health, Health Resources and Services Administration, and the Pennsylvania Department of Health, Merck Corporation, and the Substance Abuse and Mental Health Services Administration outside the submitted work. Dr Haynes reported grants from PCORI during the conduct of the study. Dr Gupta reported grants from PCORI during the conduct of the study. Dr Shah reported grants from PCORI and People-Centered Research Foundation during the conduct of the study and grants from the National Institutes of Health outside the submitted work. Dr McClay reported grants from PCORI during the conduct of the study. Dr Re reported grants from PCORI grant during the conduct of the study. Dr Geary reported grants from PCORI during the conduct of the study. Dr Jain reported grants from Medtronic and Boston Scientific and personal fees from St Jude outside the submitted work. Dr Whittle reported grants from PCORI during the conduct of the study. Dr VanWormer reported grants from PCORI during the conduct of the study. Dr Farrehi reported grants from PCORI during the conduct of the study. Dr Rothman reported grants from PCORI during the conduct of the study; personal fees from Abbott outside the submitted work. Dr Hernandez reported personal fees from Bayer; grants and personal fees from AstraZeneca, Merck, and Novartis; and grants from Verily outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (ASP-1502-27029).

Role of the Funder/Sponsor: PCORI approved the design and conduct of the study. They had no role in collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors, or its Methodology Committee. Dr Fonarow is an Associate Editor for *JAMA Cardiology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Additional Contributions: We thank Amber Sharlow, BS, and Elizabeth E. S. Cook, BA, Duke Clinical Research Institute, and the Adaptors (patient partner investigators) involved in the conduct of the trial: Desiree Davidson, Kevin Edgley, Greg Merritt, PhD, Linda S. Brown, Henry Cruz, Nadina Zemon, Tom E. McCormick III, MS,

Jacqueline Alikhaani, BA, Ken C. Gregoire, and Bill Larsen (in memoriam). These individuals [were or were not] compensated for their contributions.

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Editor's Note

Lessons From the Rationale and Design Features of the ADAPTABLE Trial

Patrick T. O'Gara, MD

Leading clinical trialists have for several years called for fundamental changes to the clinical research enterprise. Although randomized clinical trials remain the gold standard by which the efficacy and safety of an intervention are best assessed, their associated costs, size, complexity, duration, and limited generalizability have accentuated the need for innovative trial designs to facilitate simpler, faster, and more efficient means to answer meaningful clinical questions that matter to patients and the public. The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial[1] combined randomized treatment assignment (manual thrombus aspiration plus primary percutaneous coronary intervention vs primary percutaneous coronary intervention alone) within a high-quality, large-scale national registry, thereby highlighting the exciting potential for the approach termed *randomized registry trials* to be executed more quickly and at a fraction of the cost of a traditional randomized clinical trial posing the same question. A small randomized clinical trial embedded within the CathPCI Registry, supported by the American College of Cardiology, was subsequently reported,[2] but to date there has been very little movement in this direction within the United States.

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How else can we move forward? In this issue of *JAMA Cardiology*, Marquis-Gravel and colleagues[3] present the rationale and design features of the prospective, randomized Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) trial, the first study of its type supported by the Patient-Centered Outcomes Research Institute and executed through its distributed and multistakeholder research network (PCORnet).[3] The many collaborators who participated in this multiyear effort, including academicians, patients, health systems, and payers, built and then embedded within the electronic health record a platform to allow determination of the optimal dose of aspirin for secondary prevention of atherosclerotic cardiovascular disease. In doing so, they created an infrastructure that allows for the conduct of clinical research within the routine workflow of one's daily practice. Elements include the use of programming algorithms to enhance patient recruitment (termed *computable phenotypes*), strategies to streamline informed consent and automated patient randomization, and structured patient-initiated data collection and end-point validation.

JAMA Cardiology has not previously published trial-design articles. The editors believe the methods incorporated in the ADAPTABLE trial represent important next steps in the more rapid and less expensive generation of reliable real-world evidence to enable better decision-making. The efficacy and safety outcomes of this 15 000-patient study are awaited with interest. In the interim, the design features should spur further efforts to improve the clinical research ecosystem.

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Published Online: March 18, 2020. doi:10.1001/jamacardio.2020.0328

Conflict of Interest Disclosures: None reported.

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