


Appraisals in Meta-journal Hour 19

By Salwana, and BH Chew

The paper:

Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease DOI: 10.1056/NEJMoa2102137

Why was this study conducted?

The introduction section of the paper discusses the disagreement between previous findings from Observational and Randomized Control Trial studies on the different dosages that had different risks on patients with atherosclerotic cardiovascular diseases. In the US, aspirin was recommended in patients with established atherosclerotic cardiovascular disease to lower the risk of adverse health outcomes. 60% of patients discharged from the hospital after myocardial infarction were treated with 325mg of aspirin daily and the dose was changed by 25 by a factor in the proportional use of high-dose aspirin varying across participating centers (Hall et al. 2014). The European Society of Cardiology (Montalescot et al., 2014) provides clinical guidelines on the definitive recommendations for aspirin dosage, however, the American College of Cardiology – American Heart Association (Amsterdam et al. 2014) does not have similar guidelines. As such, the appropriate dose of aspirin for patients with established atherosclerotic cardiovascular disease is controversial. The author found that there was uncertainty about which aspirin dose clinicians should recommend. Still, questions exist regarding the side-effect profile, including potential differences in major bleeding or discontinuation due to minor bleeding or dyspepsia. The evidence supporting a preferred aspirin dosage for atherosclerotic cardiovascular disease (ASCVD) can have significant public health implications for outcomes such as death, myocardial infarction, stroke, and major bleeding.

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The study was based on ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) (Gravel et al., 2020), an open-label, pragmatic design to provide real-world evidence on the optimal aspirin dosing strategy for these patients. The study aimed to compare the effectiveness of two different doses of aspirin (81 mg and 325 mg per day) in reducing the risk of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke among patients with established atherosclerotic cardiovascular disease.

The authors used an open-label, pragmatic, randomized, controlled trial comparing the effectiveness of 81-mg- and 325-mg daily aspirin doses as secondary prevention in patients with established atherosclerotic cardiovascular disease

How was it done?

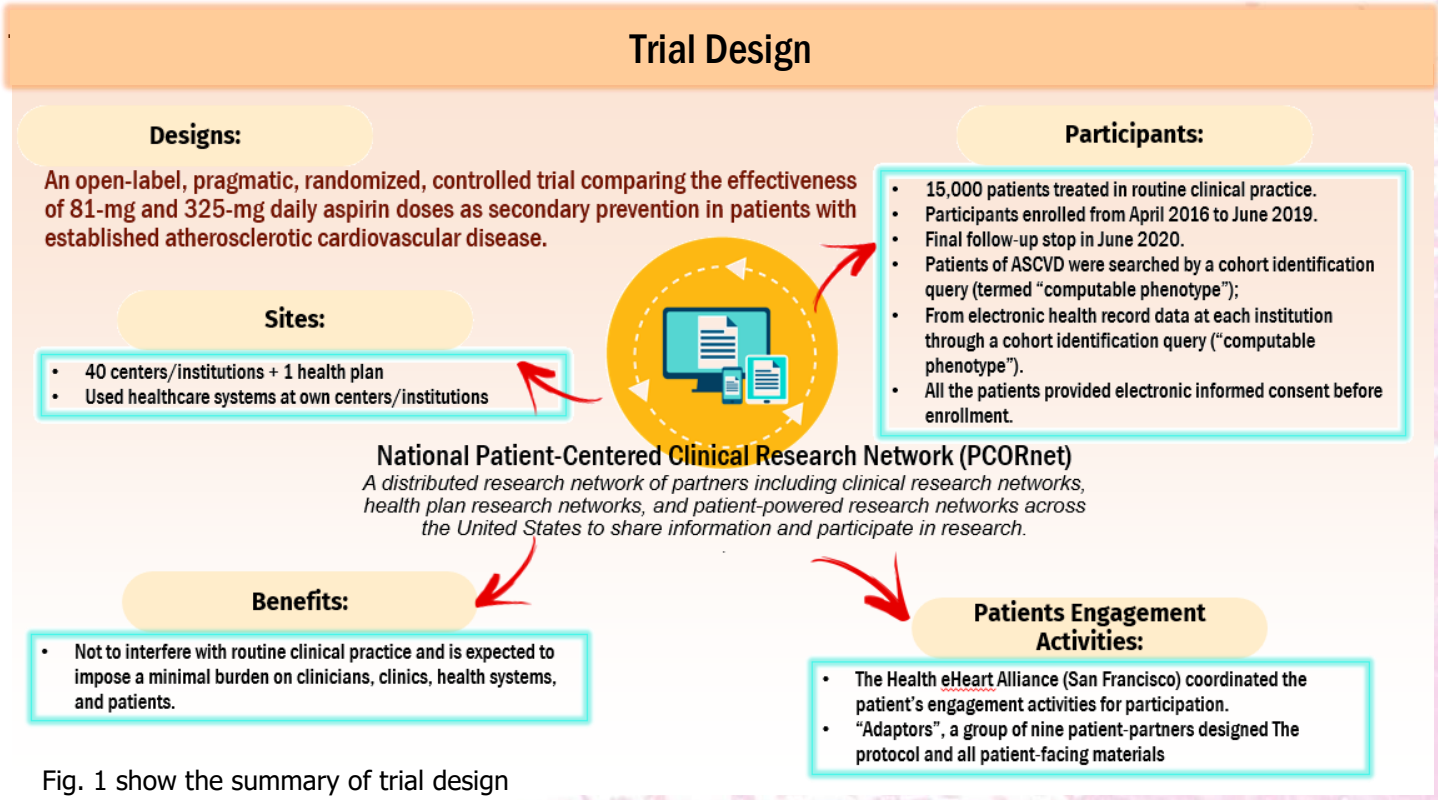


Fig. 1 show the summary of trial design

Trial Population and Recruitment Strategies

INCLUSION AND EXCLUSION CRITERIA

Patients with established atherosclerotic cardiovascular disease following criteria below:

INCLUSION

Established ASCVD was defined by any of the following:

1) prior myocardial infarction;
2) prior coronary revascularization procedure (percutaneous coronary intervention or coronary-artery bypass grafting surgery);
3) prior coronary angiography demonstrating ≥75% stenosis of at least 1 epicardial coronary artery; or
4) history of chronic ischemic heart disease, coronary artery disease, or ASCVD.

ENRICHMENT CRITERIA

Have at least 1 enrichment criterion:

- age ≥65 years
- serum creatinine ≥1.5 mg/dL,
- diabetes mellitus
- current cigarette smoking
- cerebrovascular disease
- peripheral artery disease
- heart failure (systolic or diastolic)
- left ventricular ejection fraction <50%
- systolic blood pressure ≥140 mm Hg, o
- low density lipoprotein cholesterol ≥130 mg/dL.

EXCLUSION

Exclusion criteria included:

- History of significant allergy to aspirin,
- History of gastrointestinal bleeding within 12 months.
- Bleeding disorder that precluded aspirin use.
- Current or planned use of an oral anticoagulant or ticagrelor.
- Female patients who were pregnant or nursing.
- There were no exclusion criteria for upper age limit, comorbid conditions, or other concomitant
- medications.

- There were no exclusion criteria for upper age limit, comorbid conditions, or other concomitant medications.

Randomization and Trial Treatment

T0

Baseline

Demographic characteristics:

- Reported by patients.
- Age, sex, race, ethnic group, current tobacco use, and medication use

Clinical characteristics and medical history:

- Retrieved by means of a trial-specific query of **the electronic health record (with the use of the PCORnet Common Data Model format)** at enrolling health centers.
- A look-back period of 5 years from the date of enrollment.

The PCORI Patient-Reported Outcomes Common Measures short form was administered through the patient portal (or call center) baseline

T2

Consent

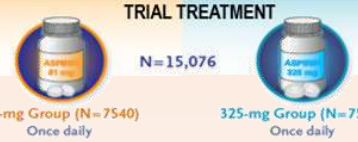
RANDOMIZATION

- In patient portal
- Buy aspirin over the counter

PATIENT PORTAL FOR AN EARLY STUDY ENCOUNTER

- By telephone contact the call center for non-Internet participants.
- Between 1-3 weeks after randomization.
- To confirm adherence to the appropriate dosage and answer questions about secondary contact information.

TRIAL TREATMENT



- 1:1 ratio for 3 months or 6 months follow-up.
- Were followed for a median duration of 26 months.

Routine follow-up (no n-person visits at the trial centers during follow up)

T2

3 months Follow-up

T3

6 months Follow up

Asked about adherence to the trial medication, the use of concomitant medications, recent hospitalizations (and primary diagnoses of hospitalizations), and patient-reported outcomes.

- Internet participants were sent email reminders to complete the trial visits.
- Non-Internet participants received telephone calls from the call center.
- Internet participants who had not completed a trial follow-up encounter for 6 months were converted to non-Internet participation and contacted by the call center in order to complete follow-up.
- When patients missed an encounter and returned for a subsequent encounter, they were asked to complete information on hospitalizations (trial outcomes) that had occurred since the last complete encounter.

The PCORI Patient-Reported Outcomes Common Measures short form was administered through the patient portal (or call center) at 6 months

- 1:1 ratio to follow-up visits every 3 months or every 6 months to better understand the effect of the frequency of clinical trial assessments on patient engagement and follow-up.
- $25 remuneration for each participant

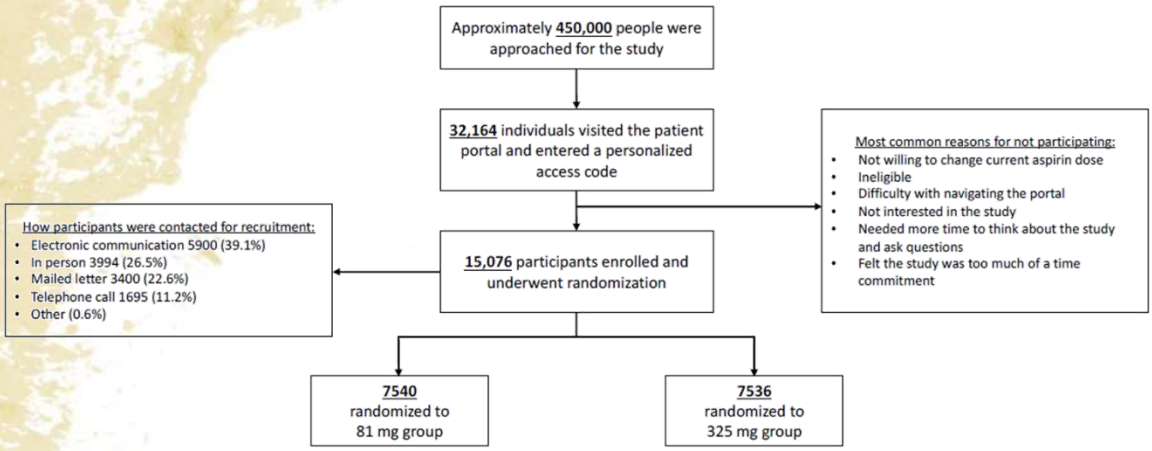


Fig. 2 Randomization, treatment, and follow-up of participants.

Its Data Sources

Multiple data sources:

- Patient report at the scheduled trial encounters.
- Queries of electronic health record data organized according to the PCORnet Common Data Model format.
- Linkage with data sources from PCORnet private health plan partners (Aetna, Anthem, and Humana); and
- Linkage with fee-for-service Centers for Medicare and Medicaid Services claims data.

Sample Size Calculation

Early sample size was 20,000

- 85% power to detect a 15% relative risk reduction assuming a primary effectiveness outcome rate of 5% per year in the higher-risk arm.
- 24 months recruitment/maximum follow-up of 30 months/5% annualized rate of loss to follow-up.

Longer by 14 months

- Slower recruitment
- Longer follow up duration
- Limited fundings

Reduced sample size to 15,000.

- 88% power to detect a 15% relative risk reduction in the primary outcome, assuming an annualized event rate of 4.6% in the higher-risk arm, leading to an overall event rate below 5%
- 38 months recruitment/maximum follow-up of 50 months/5% annualized rate of loss to follow-up.

- Slower recruitment
- Longer follow up duration
- Limited fundings

Table 6

Overall annualized event rate (%)	Relative Risk	Annualized event rate in low risk group (%)	Annualized event rate in high risk group (%)	Number of Events	Power
4.2	0.800	3.7	4.7	1321	0.99
4.2	0.825	3.8	4.6	1320	0.96
4.2	0.850	3.9	4.5	1322	0.88
4.4	0.800	3.9	4.9	1381	0.99
4.4	0.825	4.0	4.8	1381	0.97
4.4	0.850	4.1	4.8	1383	0.89
4.6	0.800	4.1	5.1	1441	0.99
4.6	0.825	4.2	5.0	1442	0.97
4.6	0.850	4.2	5.0	1439	0.90
4.8	0.800	4.3	5.3	1501	1.00
4.8	0.825	4.3	5.3	1502	0.98
4.8	0.850	4.4	5.2	1503	0.92

Table 6 in the article presents calculations performed for a sample size of 15,000 using PASS software

Table 6 shows the primary effectiveness endpoint:

- Rates of 4.6%, 4.8%, 5.0%, and 5.2% per year in the higher-risk arm.
- Annualized rate of loss to follow-up of 5%, 2-sided significance level alpha of 0.05.
- Clinically meaningful RR reduction for the treatment effect between aspirin doses for primary effectiveness endpoint of 20%, 17.5%, and 15%.
- Assuming an annualized event rate of 4.6% in the higher risk arm and a 15% RR reduction (annualized event rate of 3.8% in the lower risk arm) leads to 88% power and requires 1322 primary outcome events.

Table 7 shows the primary safety endpoint for:

- Hospitalization for major bleeding, power calculations were based on estimated primary event rates of 2%, 2.5%, and 3% per year (in the higher dose arm); Annualized rate of loss to follow-up of 5%; 2-sided significance level alpha of 0.05;
- 7,500 participants in each treatment arm; total enrollment of 38 months; and a maximum follow-up period of 50 months.
- Power greater than 85% to detect an RR reduction of 25%, and for event rates of 2.5% or greater, power will be close to 80% to detect an RR reduction of 20%.

Table 7

Annualized event rate in higher-dose arm	Relative risk reduction	No. of events	Power
2%	25%	436	86%
	20%	449	66%
	15%	461	42%
2.5%	25%	544	92%
	20%	559	76%
	15%	575	50%
3%	25%	651	96%
	20%	669	83%
	15%	688	58%

Table 7 in the article presents calculations performed for a sample size of 7,500 each arm using PASS software.

Clinical Outcomes

1. **Primary effectiveness outcomes**
   The time to the first occurrence of any event in the composite of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke.
2. **Pre-specified secondary outcomes**
   Including coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), the individual components of the primary outcome, and hospitalization for transient ischemic attack.
3. **Primary safety outcomes**
   Hospitalization for major bleeding with an associated blood-product transfusion.

Statistical Analysis

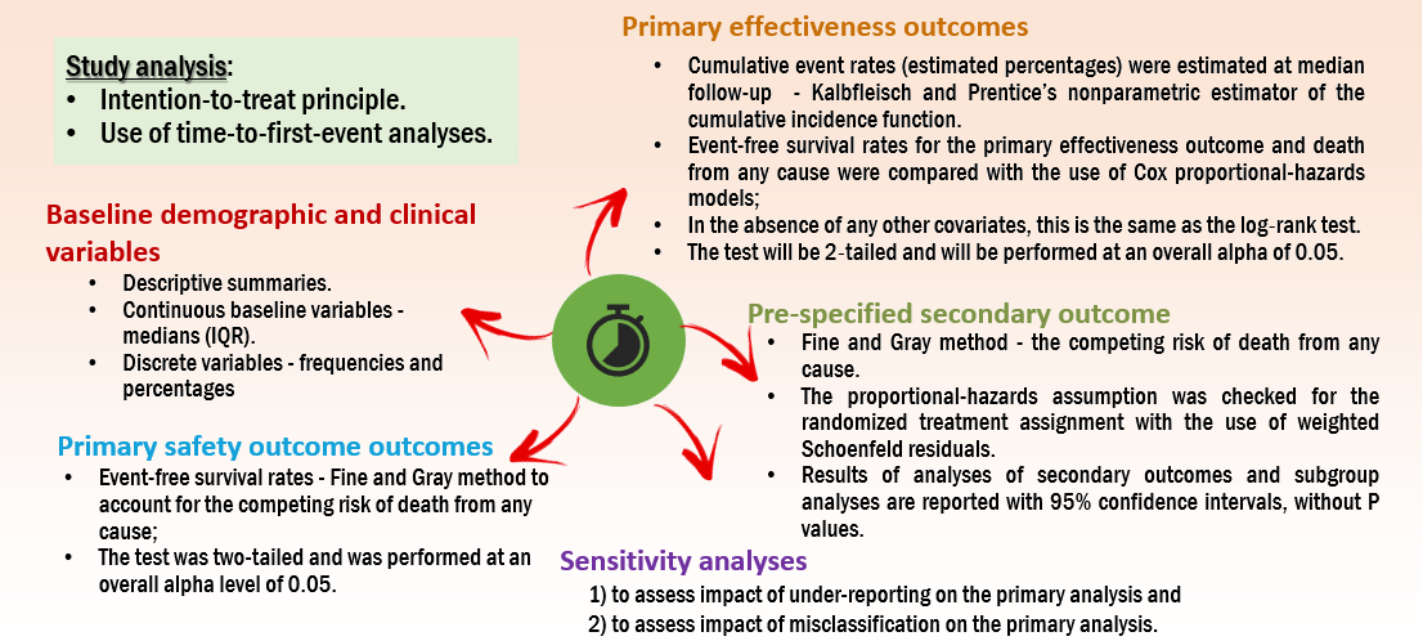


Fig. 3 show the summary of statistical analysis used in this study

What was the finding?

1. **Patients, Medication Use, And Follow-Up**
   - **Demographic information:** The median age was 67.6 years, 68.7% were men, 8.7% were Black, 3.2% were Hispanic, 1.0% were Asian, and 6.5% and 6.9% had undetermined race and ethnic group, respectively.
   - **Clinical characteristics at baseline** (List of figure: Table 1)**:**
     - 35.3% of the patients had previous myocardial infarction and 53.0% had previous coronary revascularization procedures within 5 years before enrolment.
     - 96.0% of the patients had been taking daily aspirin before enrolling in the trial.
       - 85.3% reported taking 81 mg, 2.3% reported taking 162 mg, and 12.2% reported taking 325 mg.
     - A total of 3081 of 13,818 patients (22.3%) were taking a P2Y12 inhibitor at the time of enrolment, with 2849 of those patients (92.5%) taking clopidogrel.

2. **Primary effectiveness outcome:**
   - 590 patients (estimate at median follow-up, 7.28%) in the 81-mg group and 69 patients (estimate at median follow-up, 7.51%) in the 325-mg group (hazard ratio, 1.02; 95% confidence interval [CI], 0.91 to 1.14) (List of figure: Figure 1A and Table 2).
   - The treatment effect on the primary effectiveness outcome appeared similar across the prespecified subgroups.
   - There was no difference in treatment effect according to the secondary randomization to 3 months or 6 months of follow-up. I
   - Individual components:
     - Death from any cause:
       - 315 patients (estimate at median follow-up, 3.80%) in the 81-mg group and 357 patients (estimate at median follow-up, 4.43%) in the 325-mg group (hazard ratio, 0.87; 95% CI, 0.75 to 1.01)
     - Hospitalizations for myocardial infarction and stroke:
       - Similar between 2 groups.

3. **Pre-specified secondary outcomes:**
   - Similar between 2 groups.
   - Mean scores for patient-reported outcome measures were similar in the two groups at baseline and follow-up.

4. **Safety Outcomes:**
   - Hospitalization for major bleeding with an associated blood-product transfusion (primary safety outcome).
   - 53 patients (estimate at median follow-up, 0.63%) in the 81-mg group and 44 patients (estimate at median follow-up, 0.60%) in the 325-mg group (hazard ratio, 1.18; 95% CI, 0.79 to 1.77).

5. **Adherence to trial Medication**
   - Aspirin discontinuation: 7.0% of the patients assigned to the 81-mg dosing strategy and 11.1% of those assigned to the 325-mg dosing strategy.
   - Dose switching: 7.1% in the 81-mg group and 41.6% in the 325-mg group (List of figure: Table 3)
   - Reason for discontinuations:
     Table 1 below shows the reasons and the number of patients for each arm.

Reasons	81mg of daily aspirin	325mg of daily aspirin
Patient preference	65 (18.6%)	84 (15.9%)
Need for oral anticoagulant -	74 (21.2%)	110 (20.8%)
Bleeding or bruising	18 (5.2%)	24 (4.5%)
Other medical condition	102 (29.2%)	204 (38.6%)
Cited the primary prevention studies or ACC/AHA guidelines.	33 (9.5%)	36 (6.8%)
"Other" as reasons	57 (16.3%)	70 (13.3%)

6. **Sensitivity Analysis**
   - Robustness of results to potential underreporting and misclassification of outcomes:
     - Potential missing data when patients moved or left the enrolling health system - No changes in results.
     - Potential misclassification of outcomes - No changes in results.
   - Prespecified landmark analysis that omitted outcomes during the first 10 days of follow-up after randomization for events that were probably related to previous aspirin use - No changes in results.
   - Time-dependent covariates (regardless of randomized dose):
     - Patients who took 81 mg had a higher risk of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke than those who took 325 mg (hazard ratio, 1.25; 95% CI, 1.10 to 1.43).

Discussion

According to a 2014 study retrieved from the National Cardiovascular Data Registry, 60% of patients released after a heart attack were prescribed 325 mg of aspirin daily, indicating uncertainty about the optimal dosage. Before the study, the majority of the patients (85.3%) were taking 81 mg of aspirin daily, however many switched their assigned dose during the trial, possibly due to patient preference, clinician practices, or development of side effects or concurrent illnesses. The publication of updated guidelines from the American College of Cardiology-American Heart Association Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease in 2016 may also have influenced dose switching, particularly for patients on long-term dual antiplatelet therapy or those who had percutaneous coronary intervention. Patients discontinued the 325-mg dosing strategy more frequently than the 81-mg dosing strategy, possibly due to published reports questioning the effectiveness of aspirin in preventing cardiovascular events; efforts to combat misinformation and confusion about aspirin's role in preventing secondary outcomes in people with atherosclerotic cardiovascular disease were challenging.

Lesson learned:

- Lessons learned from this trial include the feasibility of identifying a large cohort of eligible patients, engaging and recruiting them, and ensuring long-term retention and adherence to trial protocols through value-added methods.

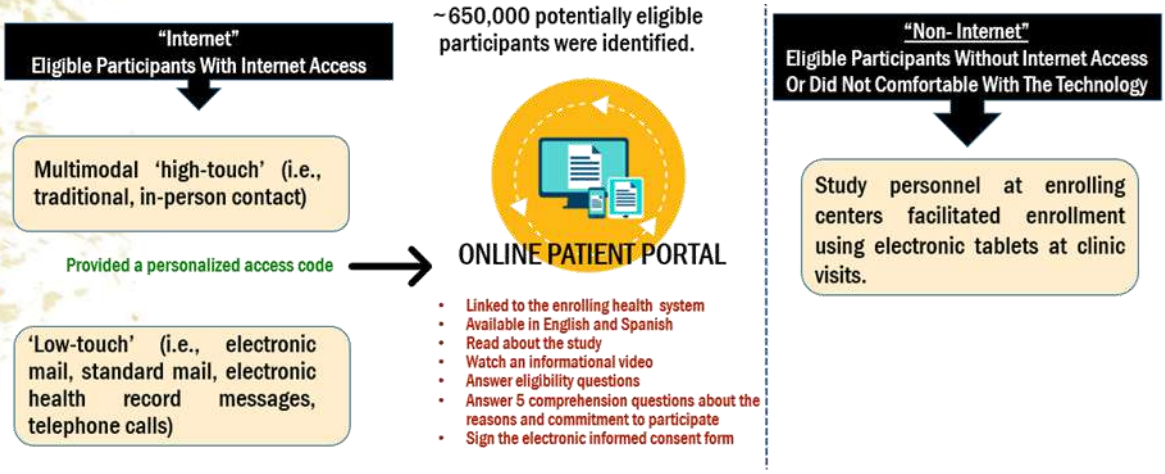


Fig. 4 show the recruitment strategies used in this study

Implications:

- This trial was the first demonstration project for pragmatic clinical trials within PCORnet and recruited over 15,000 patients from 40 centers in the US using electronic methods and low-touch recruitment strategies.
- The trial involved nine patient partners who provided input throughout the trial and incorporated electronic health record data and patient-reported information to reduce the burden on patients and sites.
- Lessons learned from this trial include the feasibility of identifying a large cohort of eligible patients, engaging and recruiting them, and ensuring long-term retention and adherence to trial protocols through value-added methods.

Limitations:

- The trial was open-label, which means that both the patients and the clinicians knew which dose of aspirin the patient was taking. This could have led to biases or perceptions about the risks and benefits of aspirin dosing, which may have influenced the dose changes over time.
- Patients who primarily took 81 mg of daily aspirin before the trial were included in the study. This could have affected the results since the patients commonly switched their randomized dose during the trial.
- Enrollment of women and traditionally underrepresented groups with atherosclerotic cardiovascular disease fell short of expectations and short in duration. This resembled past typical cardiovascular study enrolment and may affected the results.
- The study did not assess nonserious or minor bleeding adverse events.

Conclusions:

The study found no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily in patients with established cardiovascular disease. The results suggest that there is uncertainty about the recommended dose of aspirin for patients with atherosclerotic cardiovascular disease. The study highlights the need for evidence to support a preferred dosage of aspirin, as it can have a major public health impact on outcomes such as death, myocardial infarction, stroke, and major bleeding in patients with atherosclerotic cardiovascular disease.

How much can we take out from this research/paper?

The paper contributes to the understanding of the appropriate dose of aspirin in patients with established atherosclerotic cardiovascular disease. It compares the effectiveness and safety of two different doses of aspirin (81 mg and 325 mg) in reducing the risk of death, myocardial infarction, stroke, and major bleeding. Based on the findings, the study provides evidence that there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily. The results of this study have implications for clinical practice and public health, as they contribute to the ongoing discussion on the recommended dose of aspirin for patients with atherosclerotic cardiovascular disease.

As researchers, we can extract several important insights from this study. First and foremost, it provides valuable insights into the comparative effectiveness of different aspirin dosing strategies in patients with established atherosclerotic cardiovascular disease. The study utilized an open-label, pragmatic design, which reflects real-world clinical practice and allows for a broader understanding of the comparative effectiveness of different aspirin dosing strategies. Many large-scale cardiovascular clinical studies are impacted by rising costs and restricted recruitment. Implementing a computable phenotype, which is a set of executable algorithms for identifying a group of clinical features derived from electronic health records or administrative claims data, is critical for successful enrollment in large-scale pragmatic clinical trials. The practical implications of this finding would benefit clinicians and patients in terms of selecting the appropriate aspirin dose for cardiovascular disease management, to address the high prevalence of aspirin use among patients with established cardiovascular disease and the predominance of the 81 mg dose in this population. Clinicians may consider individual patient factors, such as bleeding risk when deciding on the aspirin dose for cardiovascular disease prevention.

Although the findings suggest that there is no significant difference in the primary effectiveness outcome (composite of death, hospitalization for myocardial infarction, or hospitalization for stroke) between the 81 mg and 325 mg dosing strategies, one should look closely into the findings. Studies often combine several events, for example, death myocardial infarction, or stroke, into a single study outcome. This is called a composite endpoint. It is usually used in a modern phase-III trial, especially for cardiovascular disease and cancer. The purported benefits of combining multiple types of outcome is to collect more events, which usually increase statistical power, decrease sample-size requirements, shorter trial duration, and decrease cost (Freemantle et al., 2003). However, the selected individual components of a composite endpoint, are not always clinically meaningful and not important for individual patients (not similar), as the combinations might not establish a relationship of outcome variables (Montori et al. 2005). Following that, the author suggested that some clinical and regulatory requirements need to be fulfilled to ensure the correct interpretation of composite endpoints and for the validation of these types of outcomes (Freemantle et al., 2003) (Montori et al. 2005). In the end, the treatment can be considered to affect all components or just a single outcome.

In addition to the addressed issue, Santamaría et al. (2023) also suggested that deeper considerations should be taken care of when analyzing the outcomes corresponding to the time-to-first-event analysis, which was introduced by Pocock et al. (2012). The analysis should be done following the distinct individual events that happen within the composite outcome that lead to separate events with their clinical significance. The components of a composite outcome will be analysed by putting severity into account by assigning weights severity and evaluated of pairs patients based on their risk estimates. On note to the article on appraised, the study employed a time-to-event analysis to assess the primary effectiveness outcome (composite of death, hospitalization for myocardial infarction, or hospitalization for stroke) and the primary safety outcome (hospitalization for major bleeding). This approach should provide a comprehensive evaluation of the outcomes over time.

However, it is crucial to acknowledge some limitations of the study. This study was based on an open-label and pragmatic design, thus it may introduce biases and confounding factors. Failure to assess other potential factors that could influence aspirin effectiveness and safety. Other than that, reliance on self-reporting of aspirin use may introduce recall bias and inaccuracies. Related to the relatively short follow-up period, it may not capture long-term outcomes and potential dose effects over time. As suggested by the authors, further studies are required to understand the following; Whether a high incidence of dose switching in the group assigned to the 325-mg dose affected trial results; How results might differ with longer-term follow-up and a more diverse trial population; and what the incidences of non-serious adverse events and minor bleeding are and whether these affect adherence.

In conclusion, this research offers valuable insights into three aspects; Effectiveness, safety outcomes, and adherence., in quote "Effectiveness and safety outcomes did not differ significantly with daily use of 81 mg as compared with 325 mg of aspirin in patients with established atherosclerotic cardiovascular disease, and adherence was better with the 81-mg dose".

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