Circulation: Cardiovascular Quality and Outcomes

DATA REPORT

Aspirin for Primary Prevention of Cardiovascular Disease

A Trial Sequential Analysis

Babikir Kheiri, MD
Mahmoud Barbarawi, MD
Ghassan Bachuwa, MD
Michael D. Shapiro, DO, MCR

Aspirin therapy is a standard component of optimal medical therapy in the secondary prevention of established atherosclerotic cardiovascular disease. Although the bleeding risk is minimal with short-term administration during acute cardiovascular events, it increases substantially with prolonged use. Nonetheless, the evidence base has clearly established a favorable risk-benefit ratio in support of aspirin in the secondary prevention of atherosclerotic cardiovascular disease.[1] On the other hand, the risk-benefit ratio is less clear in the setting of primary prevention. In a recent trial-level meta-analysis, Zheng and Roddick[2] reported a significant reduction of the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke with aspirin in primary prevention, though the risk of major bleeding was higher. However, several potentially serious issues with this study require critical evaluation.

The meta-analysis conducted by Zheng and Roddick[2] represents an updated meta-analysis which might be prone to false positive (type-I errors) and false negative (type-II errors) results due to large numbers of significance tests and inadequate power.[3] In a single randomized clinical trial (RCT), a priori calculation of power is required to produce a true treatment effects estimates before declaring significant results. In meta-analyses, such a priori information calculations are often unreported which may lead to unreliable conclusions. Therefore, to draw meaningful conclusions, meta-analyses require the same degree of rigor as RCTs. Thus, we have conducted a trial sequential analysis which combines a priori information regarding sample size calculation and adaptation of monitoring boundaries, to evaluate the efficacy and safety of aspirin for primary prevention of atherosclerotic cardiovascular disease.

METHODS AND RESULTS

Accuracy of meta-analyses have been focused on issues such as quality assessment of the included studies, publication bias, heterogeneity in the conduct and design of the studies, and meta-analyses registration.[4] However, meta-analyses may report inaccurate treatment effects, particularly if they fail to include a sufficient number of studies or events.[3] Therefore, some propose the notion that meta-analyses should be evaluated with the same rigorous standards as RCTs, especially those related to power calculations. To avoid the overestimation of treatment effects and the possibility that the results of a cumulative meta-analysis of sparse data are due to chance findings, the aggregated population size should be as large as that of an adequately powered RCT. To fulfill this criterion, some meta-analyses require construction of sequential monitoring boundaries (similar to interim monitoring in RCTs).[5] The O'Brien-Fleming α-spending function to control the risk of type-I error may provide a valid tool to assess the inferences obtained from meta-analyses before sufficient evidence has been reached.[3,6] In addition, trial sequential analyses adjust for the heterogeneity in cumulative meta-analyses.[3]

Key Words: aspirin ■ diabetes mellitus ■ longevity ■ myocardial infarction ■ sample size

https://www.ahajournals.org/journal/circoutcomes

Table. **Trial Sequential Analysis Results**

Variable	Control Incidence (%)	Cumulative Information Size (n)	Diversity (%)	I^2 (%)	Result					
					Trials Driven			A Priori		
					RRR	Required Information Size (n)	Conclusion	RRR	Required Information Size (n)	Conclusion
Overall population										
Composite outcome	3.9	157864	0	0	9.6%	82032	Inconclusive	25%	10768	Inconclusive
All-cause mortality	4.5	161680	0	0	2.8%	787361	Inconclusive	25%	9473	Futile
Cardiovascular mortality	1.2	161680	0	0	5.3%	1008417	Inconclusive	25%	36244	Futile
Myocardial infarction	2.0	161680	66	61	13.9%	216992	Inconclusive	25%	64098	Significantly lower
Any stroke	1.7	161680	0	0	5.8%	509479	Inconclusive	25%	24841	Futile
Ischemic stroke	1.5	129068	0	0	12.5%	120474	Significantly lower	25%	28109	Futile
Major bleeding	1.1	147858	0	0	–41.8%	19472	Futile	25%	38075	Inconclusive
Intracranial bleeding	0.3	160404	0	0	–33.3%	109500	Futile	25%	169343	Significantly higher
GI bleeding	0.5	140801	0	0	–55.5%	25465	Significantly higher	25%	95509	Significantly higher
High-risk (10-y risk of cardiovascular events ≥10%)										
Composite outcome	6.1	45298	0	0	8.1%	72078	Inconclusive	15%	19741	Futile
All-cause mortality	6.9	47838	0	0	6.0%	116669	Inconclusive	15%	17689	Futile
Cardiovascular mortality	2.2	24773	17	9	3.9%	795144	Inconclusive	15%	46935	Futile
Myocardial infarction	3.2	47838	56	47	11.7%	151865	Inconclusive	15%	88641	Inconclusive
Any stroke	2.4	47838	0	0	6.7%	277921	Inconclusive	15%	52586	Futile
Ischemic stroke	2.2	43512	0	0	11.4%	102071	Inconclusive	15%	57475	Inconclusive
Major bleeding	1.6	47838	12	3	–41.0%	15481	Futile	15%	90190	Significantly higher
Intracranial bleeding	0.4	47838	0	0	–18.7%	277503	Inconclusive	15%	321483	Inconclusive
GI bleeding	0.7	42699	26	9	–55.1%	24813	Significantly higher	15%	225348	Inconclusive
Diabetes mellitus										
Composite outcome	6.6	27047	0	0	9.7%	45113	Inconclusive	15%	18363	Inconclusive
All-cause mortality	9.4	20326	0	0	5.3%	104394	Inconclusive	15%	12537	Futile
Cardiovascular mortality	2.7	20326	83	52	1.9%	18684125	Inconclusive	15%	273336	Inconclusive
Myocardial infarction	4.2	21896	77	54	9.3%	350627	Inconclusive	15%	130507	Inconclusive
Any stroke	3.6	21363	54	26	19.3%	44067	Inconclusive	15%	75811	Inconclusive
Ischemic stroke	3.2	22406	72	45	21.0%	68997	Inconclusive	15%	138749	Inconclusive
Major bleeding	2.9	20076	0	0	–29.0%	14282	Inconclusive	15%	42296	Significantly higher
Intracranial bleeding	0.6	18019	0	0	–21.3%	122718	Inconclusive	15%	213924	Inconclusive
GI bleeding	1.2	18019	0	0	–35.3%	24742	Inconclusive	15%	106365	Inconclusive
Low-risk (10-y risk of cardiovascular events <10%)										
Composite outcome	3.1	112566	0	0	10.8%	77244	Significantly lower	25%	13987	Inconclusive
All-cause mortality	3.4	112566	39	32	0.32%	169201288	Inconclusive	25%	20610	Inconclusive
Cardiovascular mortality	0.8	112566	0	0	9.2%	486405	Inconclusive	25%	54558	Futile
Myocardial infarction	1.4	112566	76	72	19.4%	226532	Inconclusive	25%	130597	Inconclusive
Any stroke	1.4	112566	42	35	2.5%	4585920	Futile	25%	53253	Futile

(*Continued*)

Table. Continued

Variable	Control Incidence (%)	Cumulative Information Size (n)	Diversity (%)	I^2 (%)	Result					
					Trials Driven			A Priori		
					RRR	Required Information Size (n)	Conclusion	RRR	Required Information Size (n)	Conclusion
Ischemic stroke	1.2	100020	18	13	13.6%	164718	Inconclusive	25%	43956	Futile
Major bleeding	0.9	100020	0	0	–43.3%	22355	Inconclusive	25%	50840	Inconclusive
Intracranial bleeding	0.3	112566	0	0	–40.5%	78207	Inconclusive	25%	169343	Significantly higher
GI bleeding	0.5	98102	0	0	–57.3%	23924	Significantly higher	25%	95509	Significantly higher

RRR indicates relative risk reduction.

We included all the 13 trials in Zheng and Roddick's[2] meta-analysis (Figure I in the Data Supplement). The primary outcome was a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes included all-cause mortality, cardiovascular mortality, myocardial infarction, any stroke, ischemic stroke, major bleeding, intracranial bleeding, and gastrointestinal bleeding. Subgroup analyses were performed for diabetic, high-risk (10-year risk ≥10%), and low-risk (10-year risk <10%) patients. Trials of high- and low-risk populations were derived as calculated in the recent meta-analysis.

The analysis maintained a 2-sided type-I error rate at 5% with 80% power (20% type-II error) to detect statistically significant intervention effects. We calculated the diversity (D^2)-adjusted information size with various relative risk reductions (RRR) in the aspirin group. For all groups, we estimated the RRR as pooled by the included trials. In addition, we estimated a priori calculation of 25% RRR for the overall population and in low-risk patients. In diabetic and high-risk patients, a priori estimation of 15% RRR for the power calculation was used. All analyses were conducted using Trial Sequential Analysis software, v0.9.5.10.[7]

For the overall population, aspirin was not associated with survival benefits (all-cause and cardiovascular mortality), with inconclusive evidence for the primary outcome. Moreover, aspirin was associated with high intracranial and gastrointestinal bleeding risks in the overall population. In patients with diabetes mellitus, there were inconclusive results in the individual ischemic end points. In low-risk patients, there was futile evidence for stroke benefits and inconclusive evidence for myocardial infarction reductions (Table and Figure II in the Data Supplement).

COMMENT

While aspirin reduces risk of cardiovascular events in patients with established atherosclerotic cardiovascular disease, evidence in support of the use of aspirin for primary prevention is less clear. The European Society of Cardiology recommends against aspirin use for primary prevention,[8] whereas the US Preventive Services Task Force recommends aspirin administration only after carefully assessing ischemic and bleeding risks, patient preferences, and longevity.[9]

In a recent meta-analysis, Zheng and Roddick[2] reported significant reductions in ischemic end points, though overall effectiveness is attenuated by significantly increased bleeding events. However, our investigation, which accounted for multiple significance testing associated with an updated meta-analysis, failed to conclusively demonstrate an improvement in the composite cardiovascular outcome. In addition, the lack of survival benefit among the aspirin-treated group in the overall population was similar to a recent meta-analysis using different RRR cutoffs (as low as 5%).[10] However, our results for the high-heterogeneity outcomes should be interpreted carefully.

For low-risk patients, our results demonstrated no beneficial effects of aspirin for primary prevention on cardiovascular mortality and stroke with increased bleeding events. Indeed, the risks of bleeding might outweigh the benefits in reducing ischemic benefits. We chose a lower RRR for diabetics and high-risk patients as even a smaller reduction of cardiovascular events would be clinically important. As the results for the diabetic patients failed to conclusively demonstrate an improvement on several ischemic outcomes, further adequately powered trials are needed. In the meantime, it is reasonable to consider individual patient characteristics and carefully balance the risk of bleeding with the benefit on cardiovascular outcomes, as the US Preventive Services Task Force recommends.

ARTICLE INFORMATION

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCOUTCOMES.119.005846.

Correspondence

Michael D. Shapiro, DO, MCR, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239. Email shapirmi@ohsu.edu

Affiliations

Department of Internal Medicine, Hurley Medical Center/Michigan State University, Flint, MI (B.K., M.B., G.B.). Center for Preventive Cardiology, Knight Cardiovascular Institute at Oregon Health and Science University, Portland, OR (M.D.S.).

Disclosures

Dr Shapiro discloses a position on the advisory board of Esperion and research funding from Akcea. Dr Shapiro is supported by NIH K12HD043488. Dr Shapiro is a consultant for Amarin. The other authors report no conflicts.

REFERENCES

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
2. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA*. 2019;321:277–287. doi: 10.1001/jama.2018.20578
3. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, Gluud LL, Als-Nielsen B, Gluud C. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol*. 2009;38:276–286. doi: 10.1093/ije/dyn179
4. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions 4.6 (updated September 2006)*. In: The Cochrane Library Issue 4. Chichester, UK: John Wiley & Sons Ltd; 2006.
5. Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet*. 1998;351:47–52. doi: 10.1016/S0140-6736(97)08461-4
6. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549–556.
7. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. *User Manual for Trial Sequential Analysis (TSA)*. Copenhagen, Denmark: Copenhagen Trial Unit, Centre for Clinical Intervention Research; 2011:1–115. Available from: www.ctu.dk/tsa
8. Piepoli M, Hoes A, Agewall S, Albus C, Brotons C, Catapano A, Cooney M, Corrà U, Cosyns B, Deaton C, Graham I, Hall M, Hobbs F, Løchen M, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter D, Sattar N, Smulders Y, Tiberi M, van der Worp H, van Dis I, Verschuren W, Binno S. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representati. *Eur Heart J*. 2016;37:2315–2381. doi: 10.1093/eurheartj/ehw106
9. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2016;164:836–845. doi: 10.7326/M16-0577
10. Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J*. 2019;40:607–617. doi: 10.1093/eurheartj/ehy813