Aspirin for the Primary Prevention of Cardiovascular Events

A systematic review and meta-analysis comparing patients with and without diabetes

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OBJECTIVE — The negative results of two randomized controlled trials (RCTs) have challenged current guideline recommendations for using aspirin for primary prevention of cardiovascular events among patients with diabetes. We therefore sought to determine if the effect of aspirin for primary prevention of cardiovascular events and mortality differs between patients with and without diabetes.

RESEARCH DESIGN AND METHODS — We conducted a systematic search of MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus since their inceptions until November 2008 for RCTs of aspirin for primary prevention of cardiovascular events. Blinded pairs of reviewers evaluated studies and extracted data. Random-effects meta-analysis and Bayesian logistic regression were used to estimate the ratios of relative risks (RRs) of outcomes of interest among patients with and without diabetes. A 95% CI that crosses 1.00 indicates that the effect of aspirin does not differ between patients with and without diabetes.

RESULTS — Nine RCTs with moderate to high methodological quality contributed data to the analyses. The ratios of RRs comparing the benefit of aspirin among patients with diabetes compared with patients without diabetes for mortality, myocardial infarction, and ischemic stroke were 1.12 (95% CI 0.92–1.35), 1.19 (0.82–1.17), and 0.70 (0.25–1.97), respectively.

CONCLUSIONS — Whereas estimates of benefit among patients with diabetes remain imprecise, our analysis suggests that the relative benefit of aspirin is similar in patients with and without diabetes.

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Cardiovascular events including myocardial infarction and ischemic stroke are the leading causes of morbidity and mortality in patients with diabetes, and the population burden of cardiovascular disease attributed to diabetes appears to be increasing (1). Several guidelines, including those of the American Diabetes Association, recommend aspirin for the primary prevention of cardiovascular events in patients with diabetes (2,3). Given that trials of aspirin for primary prevention have enrolled too few patients with diabetes, guideline panels have applied indirect evidence from other high-risk groups to formulate this recommendation (4). In contrast, other guidelines such as those of the European Society of Cardiology and the European Association for the Study of Diabetes (5) and the most recent U.S. Preventive Services Task Force (6) provide no specific recommendations regarding the use of aspirin in patients with diabetes.

The best available estimate of the effect of aspirin comes from the most recent study from the Antithrombotic Trialists' Collaborative, an individual-level meta-analysis of randomized controlled trials (RCTs) that reported a 12% reduction in the rate ratio of serious vascular events in patients with diabetes randomized to aspirin prophylaxis, although this finding was not statistically significant (rate ratio 0.88, 95% CI 0.67–1.15) (7). However, this meta-analysis did not include data from the Early Treatment Diabetic Retinopathy Study (ETDRS) (8) nor two recent primary prevention RCTs, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) (9) and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) (10) studies. Results from both JPAD and POPADAD, however, were imprecise and unable to exclude a reduction in the risk for their composite end points of up to 42 and 24%, respectively.

We, therefore, set out to conduct a systematic review of RCTs of aspirin for primary prevention in patients with diabetes to *1*) estimate the efficacy of aspirin for the primary prevention of cardiovascular events among patients with diabetes and *2*) estimate the extent to which the effect of aspirin differs in patients with and without diabetes.

RESEARCH DESIGN AND METHODS

— The report of this protocol-driven systematic review adheres to the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of randomized clinical trials (11).

Eligibility criteria

Eligible studies were RCTs that enrolled patients with diabetes without a prior history of myocardial infarction or stroke

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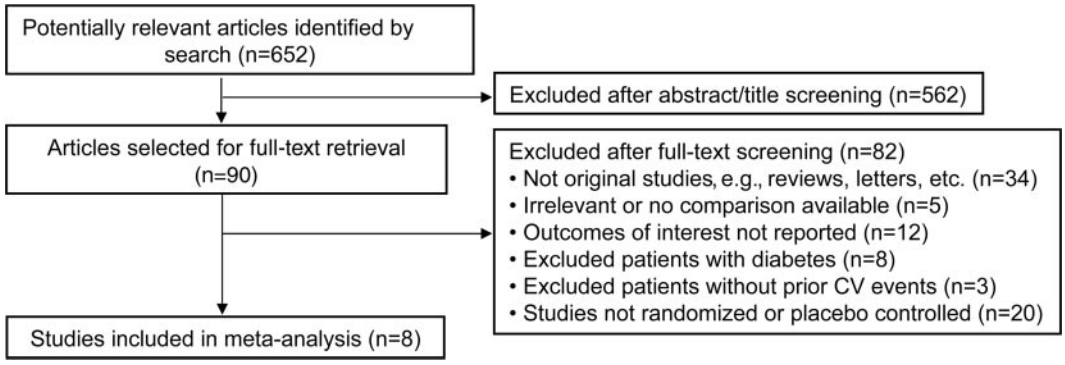

Figure 1—*Flow diagram of the process of study selection. CV, cardiovascular.*

and assessed the efficacy of aspirin at any dosage.

Study identification and retrieval

An expert reference librarian designed and conducted the electronic search strategy. Our systematic search included MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus, since their inceptions until November 2008. We used database-specific controlled language and terms that describe the key concepts: aspirin, diabetes, cardiovascular events, prevention, and randomized trials. We also reviewed the reference sections of identified reviews, published guidelines, and published manuscripts known to the authors. Study inclusion was not limited by publication status or language.

Pairs of reviewers, working independently and in duplicate, identified potentially eligible records for full-text retrieval from the titles and abstracts. Records in which the reviewers disagreed were also retrieved in full text. The reviewers assessed the retrieved full-text articles for eligibility. An independent reviewer resolved disagreements.

Outcomes

The outcomes of interest were ischemic stroke, myocardial infarction, and all-cause mortality.

Data abstraction

Two reviewers extracted the following data from each eligible article: description of study participants, study characteristics, and outcome data.

Quality assessment

Independent reviewers working in duplicate determined the extent to which trials reported concealment of allocation; blinding of patients, providers, and outcome assessors; and the extent of loss to follow-up.

Author contact

We contacted the corresponding and/or first author of each eligible article identified in the screening process by e-mail to confirm data extraction and quality assessment and to request missing information.

Prevention of cardiovascular events with aspirin

We used the κ statistic to quantify chance-adjusted agreement between reviewers for article selection. Random-effects meta-analyses estimated the pooled treatment effects (relative risks [RRs] and their 95% CIs) of aspirin in preventing cardiovascular events and all-cause death in patients with diabetes and without diabetes. The I^2 statistic estimated the percentage of inconsistency across studies that was due to heterogeneity rather than chance or random error (12).

Given that subjects included in the Antiphospholipid Antibody–Acetylsalicylic Acid (APLASA) study were receiving aspirin for antiphospholipid antibody syndrome and had a short duration of follow-up and that a small number of subjects in ETDRS had suffered a prior stroke or myocardial infarction, we conducted sensitivity analysis to determine whether the exclusion of these studies affected the conclusions of this review.

Interaction between the effect of aspirin and diabetes status

We implemented three methods to determine whether a difference exists in aspirin effect in patients with and without diabetes. First, we estimated the ratio of RRs and its 95% CI using the method of Altman and Bland (13). This estimate compares the pooled RRs across subgroups of patients with diabetes and without across trials. Pooled estimates that exclude a ratio of 1 provide evidence of an aspirin-diabetes interaction. Second, we estimated the ratio of RRs comparing the aspirin effect in patients with and without diabetes within trials and then pooled these ratios. Again, pooled estimates that exclude a ratio of RRs of 1 indicate a statistically significant difference in the treatment effect of aspirin in patients with and without diabetes. We used Comprehensive Meta-Analysis version 2 software (Biostat, Englewood, NJ) and StatsDirect 2.5.4 (StatsDirect, Cheshire, U.K.) to conduct these analyses. Finally, we conducted a Bayesian random-effects logistic regression with aspirin use and diabetes status as the main effect factors, and an interaction term of these two was also applied to the included trials. A 95% credible interval of the regression coefficient of the interaction term that excludes 0 indicates that the effect of aspirin is different in patients with and without diabetes. This analysis was carried out using WinBUGS 1.4 (Medical Research Council and Imperial College of Science, Technology and Medicine, U.K.) with noninformative prior distributions and three parallel Markov Chain Monte Carlo chains with overdispersed initials. The Brooks-Gelman-Rubin (14) convergence diagnostic was applied to examine the convergence of the Markov Chain Monte Carlo samplers. Statistical inferences were then drawn based on the resulting posterior distributions of parameters of interest. For RCTs with zero events in one study arm, we used a continuity correction factor of 0.5 and conducted sensitivity analysis using the treatment arm method to test whether the choice of statistical methods affected study conclusions (15).

RESULTS

Search results

Figure 1 describes the process of study selection that yielded eight eligible RCTs

Table 1—*Description of included trials*

	Patient population	Inclusion age (years)	Participants (% female)	Participants with diabetes (%)	Aspirin treatment	Control	Average study duration (years)	Diabetes subgroup outcomes reported
APLASA (18)	Persistently antiphospholipid antibody–positive patients	≥18	98 (90)	6 (6)	81 mg daily	Placebo	2.3	Mortality, MI, stroke
Hypertension Optimal Treatment (19,27)	Patients with hypertension	50–80	18,790 (47)	1,501 (8)	75 mg daily	Placebo	3.8	Mortality, MI
ETDRS (8)	Patients with diabetes and diabetic retinopathy	18–70	3,711 (44)	3,711 (100)	650 mg daily	Placebo	5.0	Mortality, MI
JPAD (9)	Patients with type 2 diabetes	30–85	2,539 (45)	2,539 (100)	81 or 100 mg daily	Open label	4.4	Mortality, MI, stroke
Physicians' Health Study (28)	Healthy male physicians	≥40	22,071 (0)	533 (2)	325 mg every other day	Placebo	5.0	MI
POPADAD (24)	Patients with diabetes, asymptomatic PAD, and no symptomatic CVDs	≥40	1,276 (56)	1,276 (100)	100 mg daily	Placebo	6.7	Mortality, MI
Primary Prevention Project (29)	Patients without history of CVD	≥50	1,031 (52)	1,031 (100)	100 mg daily*	Open label	3.6	MI, stroke
Women's Health Study (17)	Female health care professionals without CVD	≥45	39,876 (100)	1,037 (3)	100 mg every other day†	Placebo	10.1	MI, stroke

CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease. *Also randomized to vitamin E. †Also randomized to β-carotene.

for meta-analysis. The study by Zabel-Langhennig et al. (16) did not report any events of interest and therefore was not included in the main analysis. Table 1 describes the included studies showing important differences in the studies. Authors from 50% of eligible RCTs responded to our data requests (9,17–19).

Methodological quality

Table 2 shows the methodological quality of the included RCTs. The κ statistic for quality assessment identified through the screening process was 0.70 (range 0.64–0.87). Overall, trials had high methodological quality, with more than half of them concealing allocation and blinding patients and caregivers, most reporting minimal loss to follow-up, and only one was stopped earlier than planned because of finding significant benefit during an interim analysis.

Prevention of cardiovascular events with aspirin

Figure 2*A–C* demonstrates the pooled RRs and 95% CI for the effect of aspirin versus control on death, myocardial infarction, and ischemic stroke, respectively, stratified by diabetes status. The estimates of RR and 95% CI among all patients regardless of diabetes status for the outcomes of mortality, myocardial infarction, and ischemic stroke were 0.93 (95% CI 0.85–1.03; I^2 0%), 0.79 (0.66–0.95; I^2 63%), and 0.73 (0.43–1.22; I^2 39%), respectively. Estimates among patients with diabetes were 0.97 (0.87–1.08; I^2 0%), 0.86 (0.67–1.11; I^2 53%), and 0.62 (0.31–1.24; I^2 67%), respectively. The corresponding estimates among patients without diabetes were 0.87 (0.75–1.02; I^2 0%), 0.72 (0.55–0.95; I^2 70%), and 0.89 (0.41–1.94; I^2 0%), respectively.

Table 2—*Risk of bias in included trials*

	Blinding: caregivers	Blinding: patients	Blinding: outcome assessors	Blinding: data collectors	Allocation concealment	Lost to follow-up	Funding source	Trial stopped early
APLASA	Yes	Yes	Yes	Yes	Yes	5%	FP	No
ETDRS	Yes	Yes	Yes	Yes	Yes	>10%	NFP	No
Hypertension Optimal Treatment	Yes	Yes	Yes	No	Yes	3%	FP	No
JPAD	No	No	Yes	Yes	Yes	8%	NFP	No
Physicians' Health Study	Yes	Yes	Yes	NR/NC	NR/NC	<1%	FP	No
POPADAD	Yes	Yes	Yes	Yes	Yes	<1%	FP	No
Primary Prevention Project	No	No	NR	No	Yes	NR/NC	FP	Yes
Women's Health Study	Yes	Yes	Yes	No	NR/NC	NR/NC	FP	No

FP, includes for-profit sources; NFP, does not include for-profit sources; NR/NC, profit status not reported or not clear.

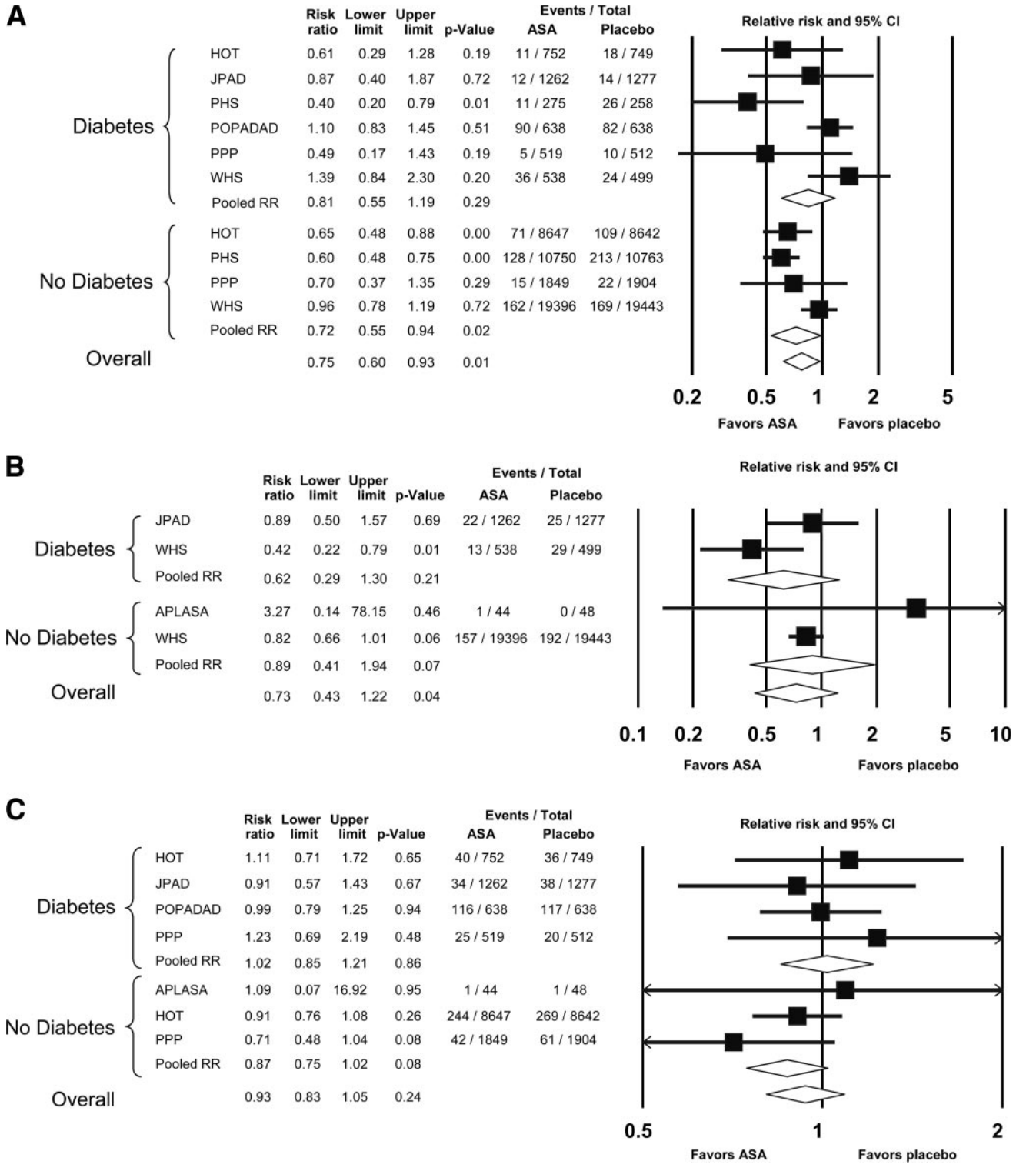

Figure 2—*Forest plots for mortality, myocardial infarction, and ischemic stroke. Forest plots of random-effects meta-analysis for pooled RRs of mortality* (A)*, myocardial infarction* (B)*, and ischemic stroke* (C)*. Results are presented for patients with and without diabetes and for all patients combined. Squares and horizontal lines represent the point estimates and associated 95% CI. The diamonds represent the pooled RR, with the center representing the point estimate and the width representing the associated 95% CI. ASA, aspirin; HOT, Hypertension Optimal Treatment; PHS, Physicians' Health Study; PPP, Primary Prevention Project; WHS, Women's Health Study.*

Interaction between the effect of aspirin and diabetes status

Table 3 describes the results of between-study subgroup analysis, within-study subgroup analyses, and Bayesian random-effects regression analyses. All three methods yielded nonsignificant ratios of RR of aspirin in patients with and without diabetes across all outcomes examined. The choice of continuity correction method for RCTs with zero events in one arm did not substantially affect inferences.

Table 3—*Aspirin-diabetes subgroup interaction analyses*

	RR* with diabetes	RR* without diabetes	$P_{interaction}$	Ratio of RRs pooled across trials†	Ratio of RRs pooled within trials‡	Ratio of RRs Bayesian analyses§
Mortality	0.97 (0.87–1.08)	0.87 (0.75–1.02)	0.28	1.12 (0.92–1.35)	1.00 (0.53–1.88)	1.16 (0.09–13.79)
Myocardial infarction	0.86 (0.67–1.11)	0.72 (0.55–0.95)	0.36	1.19 (0.82–1.17)	1.02 (0.71–1.47)	1.06 (0.16–6.71)
Ischemic stroke	0.62 (0.31–1.24)	0.89 (0.41–1.94)	0.50	0.70 (0.25–1.97)	0.93 (0.37–2.34)	0.47 (<0.01–20.52)

*Random-effects model is used in all meta-analyses. Numbers in parentheses represent 95% CIs. †Ratios of RRs in this method are pooled across randomized controlled trials and subgroups of randomized controlled trials of patients with diabetes versus without diabetes; then a ratio of pooled estimates is estimated. Numbers in parentheses represent 95% CIs, which indicate a significant interaction if it excludes 1. ‡Ratios of RRs in this method are estimated within each randomized controlled trial and then pooled. CIs that exclude 1 indicate a significant interaction. Numbers in parentheses represent 95% CIs, which indicate a significant interaction if it excludes 1. §Analysis conducted using Bayesian random-effects logistic regression. Numbers in parentheses represent 95% credible intervals.

Sensitivity analysis

Our conclusions were not significantly altered by the exclusion of the APLASA ($P_{interaction}$ 0.28, 0.36, and 0.63 for mortality, myocardial infarction, and ischemic stroke, respectively) or ETDRS trials ($P_{interaction}$ 0.18, 0.62, and 0.48 for mortality, myocardial infarction, and ischemic stroke, respectively).

CONCLUSIONS — Consistent with prior studies (7,9,10), we found no significant benefit of aspirin therapy for the primary prevention of cardiovascular events among patients with diabetes. Even for the outcome of myocardial infarction, in which the overall risk reduction was statistically significant, our estimated risk reduction among patients with diabetes remained nonsignificant. However, our estimates were imprecise and unable to exclude a treatment benefit of 13, 33, and 69% for the outcomes of mortality, myocardial infarction, and ischemic stroke, respectively. Using a between-studies approach, a within-studies approach, and a Bayesian analysis, we found evidence that the effect of aspirin among patients with diabetes was not significantly different from patients without diabetes. Thus, the data we present here provide imprecise evidence of benefit from using aspirin in patients with diabetes without a history of cardiovascular events; this treatment effect does not differ significantly from that observed in patients without diabetes.

Limitations and strengths

The main limitation of our study relates to our use of published aggregate data and lack of statistical power. The possibility of publication bias cannot be adequately assessed and corrected given the small number of RCTs (20). Our comprehensive literature search minimized the risk of publication and reporting biases, although our author response rate was relatively low and resulted in less complete data. It is possible that other aspirin RCTs have examined diabetes subgroups but have not reported these results because of lack of a significant aspirin-diabetes interaction. If this were to be the case, their inclusion would likely strengthen our conclusions. The small number of included trials and the small number of events within these trials reduced the statistical power and therefore the precision of the estimates in our main analysis and in our tests for interaction between aspirin effect and diabetes status. Our analyses using multiple statistical methods to examine the diabetes-aspirin interaction and their consistent results strengthen our conclusions. While the use of composite end points would have increased our statistical power, we chose to pool individual end points because the composite end points in the included trials represent outcomes with large gradients in importance to patients and in potential magnitude of the effect of treatment across component end points (21). We did not examine the potential harm from aspirin therapy such as gastrointestinal bleeding, since these events in the small population of patients with diabetes included in RCTs are usually rare, leading to imprecise estimates. Hence, evidence about harm is better obtained from larger studies that include patients without diabetes.

Implications

Our inferences should be considered in the context of proposed criteria to evaluate the validity of a subgroup effect (22). Good evidence of a valid subgroup effect results from testing few a priori hypotheses based on strong biological rationale. The extent to which this is true for the diabetes subgroup analyses reported in the literature is unclear to us. Our analyses, however, do not support other criteria for a valid subgroup effect. We found that differences in aspirin treatment effect between patients with and without diabetes, both between and within RCTs, were inconsistent and of small magnitude. Thus, the current best evidence suggests that the efficacy of aspirin for the primary prevention of cardiovascular events in patients with diabetes is similar to that in patients without diabetes.

The decision to use aspirin for primary prevention in individual patients with diabetes remains a complex issue. Ultimately, the decision to use aspirin for an individual patient should consider the advantages and disadvantages of this preventive treatment given the patient's context and preferences. We suggest first estimating the 10-year risk of coronary heart disease (23,24). Multiplying this estimate by 0.88 (12% relative risk reduction with the use of aspirin based on data from the Antithrombotic Trialists' Collaborative [7]) would provide the revised 10-year risk estimate for a patient using aspirin. This should be presented alongside the risk of major gastrointestinal and extracranial bleeds with and without aspirin (7,25). A patient decision aid could present these data to help patients and clinicians consider the relative merits and downsides of aspirin use, as was done recently for use of statin therapy in patients with diabetes (26).

Summary

While there are insufficient data among patients with diabetes to conclusively

show a benefit of aspirin therapy for the primary prevention of cardiovascular events, our data suggest, but do not confirm, that the relative benefit of aspirin is similar in patients with and without diabetes. Additional evidence from RCTs and individual-patient-data meta-analyses may help to further clarify this issue.

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References

1. Fox CS, Coady S, Sorlie PD, D'Agostino RB Sr, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544–1550
2. American Diabetes Association. Standards of medical care in diabetes: 2007. Diabetes Care 2007;30:S4–S41
3. Colwell JA, for the American Diabetes Association. Aspirin therapy in diabetes. Diabetes Care 2004;27:S72–S73
4. Nicolucci A. Aspirin for primary prevention of cardiovascular events in diabetes: still an open question. JAMA 2008;300:2180–2181
5. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer M-J, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Other C, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc J-J, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Document R, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JRG, Graham I, Monteiro PF, Parhofer K, Pyorala K, Raz I, Schernthaner G, Volpe M, Wood D. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88–136
6. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2009;150:405–410
7. Antithrombotic Trialists' Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-1860
8. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. JAMA 1992;268:1929–1300
9. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–2141
10. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R; Prevention of Progression of Arterial Disease and Diabetes Study Group, Diabetes Registry Group; and Royal College of Physicians Edinburgh. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840
11. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet 1999;354:1896–1900
12. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560
13. Altman DG, Bland JM. Statistics notes: interaction revisited: the difference between two estimates. BMJ 2003;326:219
14. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. J Comput Graph Stat 1998;7:434–455
15. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004;23:1351–1375 [erratum in Stat Med 2006;25:2700]
16. Zabel-Langhennig R, Ruttmann B, Schiele I, Schäfer W, Aisch W. 5-year controlled therapy study on the prevention of diabetic angiopathy with the platelet-function inhibitor acetylsalicylic acid. Z Gesamte Inn Med 1982;37:661–665 [in German]
17. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304
18. Erkan D, Harrison M, Levy R, Peterson M, Petri M, Sammaritano L, Unalp-Arida A, Vilela V, Yazici Y, Lockshin M. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum 2007;56:2382–2391
19. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762
20. Lau J, Ioannidis JPA, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ 2006;333:597–600
21. Ferreira-Gonzalez I, Permanyer-Miralda G, Domingo-Salvany A, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, Alonso-Coello P, Alonso J, Worster A, Upadhye S, Jaeschke R, Schunemann HJ, Pacheco-Huergo V, Wu P, Mills EJ, Guyatt GH. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ 2007;334:786
22. Guyatt G, Wyer P, Ioannidis J: When to believe a subgroup analysis. In *Users' Guides to the Medical Literature*. 2nd ed. Guyatt G, Rennie D, Meade MO, Cook DJ, Eds. New York, McGraw-Hill, 2008, p. 571–593
23. Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679
24. UKPDS Risk Engine [version 2.01 online], 2009. Available from http://www.dtu.ox.ac.uk/index.php?maindoc=/riskengine. Accessed 7 August 2009
25. *Aspirin for the Prevention of Cardiovascular Disease*, Topic Page. March 2009. U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality, Rockville, MD. Available from http://www.ahrq.gov/clinic/uspstf/uspsasmi.htm
26. Weymiller AJ, Montori VM, Jones LA, Gafni A, Guyatt GH, Bryant SC, Christianson TJ, Mullan RJ, Smith SA. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice ran-

domized trial. Arch Intern Med 2007; 167:1076–1082
27. Zanchetti A. *Aspirin and Antiplatelet Drugs in the Prevention of Cardiovascular Complications of Diabetes*. New York, Springer Science, 2007
28. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129–135
29. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A, Group PPP Collaborative Group. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care 2003;26:3264–3272