Review
The benefit of aspirin therapy in type 2 diabetes: What is the evidence?

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Received 4 May 2007; received in revised form 11 October 2007; accepted 14 January 2008
Available online 20 May 2008

Abstract

Many clinical guidelines recommend aspirin therapy for the prevention of cardiovascular events in individuals with type 2 diabetes. However, it is unclear whether the level of evidence in guidelines is derived from studies carried out among individuals with diabetes. Medline and Embase databases were searched to retrieve studies published since 1990, evaluating the effect of aspirin on cardiovascular outcomes in subjects with type 2 diabetes. Four studies corresponded to the inclusion criteria. The three clinical trials retrieved could not prove from a statistical point of view, the benefits of aspirin therapy for subjects with type 2 diabetes. Reduction in cardiac mortality was found only in one observational study. Consequently, these findings suggest that the clinical guidelines have based their recommendations upon the expected benefit previously observed in other high-risk populations. Given the lack of hard evidence and the different well-known platelet physiology encountered in patients with diabetes, use of aspirin as a standard treatment at the highest level of evidence in guidelines for subjects with type 2 diabetes should be revisited.

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Keywords: Type 2 diabetes; Aspirin; Clinical guidelines; Cardiovascular diseases

1. Introduction

Cardiovascular complications are almost inevitable in subjects with type 2 diabetes. In fact, individuals with diabetes carry a 2- to 4-fold increased risk of suffering from such diseases than do subjects without diabetes [1]. Indeed, 80% of patients with diabetes will die from cardiovascular events [2]. Treatment of conventional risk factors is therefore essential in reducing the burden related to cardiovascular diseases (CVD) in this population. A part of such treatment may be the use of antiplatelet medication, namely aspirin. Given that subjects with type 2 diabetes present many alterations in platelet functions, such as alterations in platelet turnover [3], enhanced aggregation [4,5] or augmented thromboxane synthesis [6], this therapy could indeed turn out to be an essential one. On the other hand, the efficacy of antiplatelet agents in patients with diabetes also appears to be reduced, particularly in the setting of a poor metabolic control [7,8].

Many clinical guidelines suggest aspirin use, in either the primary or secondary prevention of cardiovascular events. Examples of these guidelines can be found in Table 1. The level of reference to aspirin recommendations is quite high. Nonetheless, two previous meta-analyses [9,10] could not prove a statistically significant benefit for antiplatelet therapy in the primary prevention of cardiovascular events in patients with type 2 diabetes. The Antithrombotic Trialists’ Collaboration [10] reported a meta-analysis of 195 randomized trials of antiplatelet therapy published up to 1997.
including 9 trials with almost 5000 patients with diabetes. Compared to a 22% reduction in the risk of major cardiovascular events among 135,000 high-risk subjects on antiplatelet therapy, patients with diabetes showed no significant benefit (7%±8% risk reduction). Also, it is unclear whether the evidence in clinical guidelines is derived from studies involving individuals with type 2 diabetes. This paper therefore aims to review studies published since 1990 that have been undertaken concerning aspirin use for primary or secondary prevention of cardiovascular events in populations with type 2 diabetes.

2. Methods

On July 11th, 2005 and on January 22nd, 2007 we identified articles in two databases, Medline and Embase. The terms used in Medline included: “Diabetes Mellitus, Type 2” (MeSH), while the search terms in Embase were: “Non-insulin dependent diabetes mellitus”, and “aspirin”. In both searches the following limits also applied: publication between January 1st 1990 and January 22nd 2007, and human study populations. To ensure a thorough search, there were no restrictions with regard to the type of publication.

Three inclusion criteria were developed. Articles had to: 1) report results of an evaluation of the efficacy of prolonged (>1 month) aspirin treatment against placebo, 2) include subjects with type 2 diabetes and, 3) assess cardiovascular morbidity or mortality, or total mortality. The selection process involved, first of all, an evaluation based on the title of the article. Then the abstracts of the remaining articles were similarly assessed. Next, review articles, letters or editorials not excluded in the first two rounds were eliminated if they did not report relevant primary data. It should be noted that the references of these papers were reviewed as a potential source of further articles as well; likewise the references from the included articles.

3. Results

Four studies were identified as meeting all the established criteria. For details of the search, see Fig. 1. Of these studies,
three were clinical trials and one an observational study. A summary of the studies is presented in Table 2 and a brief description of each study follows.

3.1. Early Treatment Diabetic Retinopathy Study (ETDRS)

The ETDRS was a randomized controlled trial that took place between 1980 and 1985 and involved 3711 subjects with type 1 and type 2 diabetes aged between 18 and 70 (with near half presenting CVD) [11]. Individuals were assigned either 650 mg of aspirin daily or a placebo, and followed for 5 years. A non-statistically significant relative risk reduction of 9% in total mortality was observed for aspirin users in the entire cohort (RR = 0.91; 99% CI, 0.75–1.11) and, myocardial infarctions were reduced by 17% (RR = 0.83; 99% CI, 0.66–1.04). However, in the subgroup with type 2 diabetes, aspirin, when compared to placebo, did not impact favorably cardiovascular outcomes, since the authors specified that all results were not statistically significant (Table 2). Moreover, 5-year life table rates and estimates of relative risk in subjects with type 2 diabetes showed that neither death (RR = 0.92; 99% CI, 0.69–1.23), nor myocardial infarction (RR = 0.83; 99% CI, 0.59–1.17), nor stroke (RR = 1.37; 99% CI, 0.77–2.43) were statistically significantly reduced by the use of 650 mg daily aspirin. Interestingly, the authors mentioned that a time-dependant analysis suggested that the ratio of the hazard rate for the aspirin group to the rate for the placebo group decreased with longer follow-up. Decreased adherence to study medication during the later years of follow-up, aspirin delaying rather than preventing myocardial infarction, or simple random variation, were some hypotheses the authors put forward to explain this phenomenon.

3.2. European Stroke Prevention Study (ESPS)

The ESPS was a randomized controlled trial examining secondary prevention of stroke or death in patients having suffered a recent ischemic cerebral attack. The combination of 75 mg of dipyridamole with 330 mg of aspirin three times daily was compared to placebo [12]. A secondary analysis of

![Fig. 1. Summary of search results and trials retrieval.](image-url)
| Study design | Study population | Medication | Cardiovascular outcomes | Mortality |
|-------------|------------------|------------|--------------------------|-----------|
| Study/year of publication | Type of study/analysis/follow-up | # patients with type 2 diabetes (%), Mean age (years) | # (%) of individuals experiencing cardiovascular disease RR (95% CI) | # (%) of individuals experiencing myocardial infarction RR (95% CI) | # (%) of individuals experiencing stroke RR (95% CI) | # (%) of individuals dead during the trial RR (95% CI) |
| ETDRS 1992 [11] | Randomized controlled trial/primary analysis/5 years follow-up | 1152 (50%), N/A (91.7% were >50 years) | Aspirin: 650 mg daily (587); Placebo: 565 | Aspirin:117 (19.9%); Placebo:124 (21.9%); RR: 0.91 (N/A) | Aspirin:107 (18.2%); Placebo:118 (20.9%); RR: 0.87 (N/A) | Aspirin:49 (8.3%); Placebo:34 (6.9%); RR: 0.95 (N/A) |
| ESPS 1992 [12] | Randomized controlled trial/secondary analysis/2 years follow-up | 216 (54%), 67 | Aspirin 330 mg+ dipyridamole 75 mg three times daily: (106); Placebo (110) | Aspirin: 65 (11.2%); Placebo: 56 (10.8%); RR: 0.90 (N/A) | Aspirin: 65 (11.2%); Placebo: 56 (10.8%); RR: 0.90 (N/A) | Aspirin: 9 (1.7%); Placebo: 4 (0.8%); RR: 0.48 (N/A) |
| PPP 2003 [13] | Open-label randomized trial/secondary analysis/3.7 years follow-up | 1031 (52%), 64 | Aspirin 100 mg daily (519); No aspirin (control) (512) | Aspirin: 5 (1.0%); Control: 10 (2.0%); RR: 0.49 (0.17–1.40) | Aspirin: 9 (1.7%); Control: 10 (2.0%); RR: 0.49 (0.17–1.40) | Aspirin: 9 (1.7%); Control: 10 (2.0%); RR: 0.49 (0.17–1.40) |
| Harpaz et al. 1998 [16] | Observational retrospective study/6 years follow-up | 2,368 (25%), 60.3 | Aspirin daily (1220); No aspirin (1148) | Aspirin: 18.4%; Placebo: 20.7% | Aspirin: 18.4%; Placebo: 20.7% | Aspirin: 18.4%; Placebo: 20.7% |

Harpaz et al. [16] reported the results of a retrospective observational study that included individuals first screened between 1990 and 1992 for participation in the Bezafibrate Infarction Prevention Study (BIP) [17], but who did not take part in it. Demographic characteristics, medical history, medication use, glucose and lipid levels had been recorded at the first screening visit and were thus available for analysis at the first screening visit and were thus available for analysis. Mortality information was obtained from the Israeli Population Registry 6 years later. A total of 2,368 individuals, all with coronary artery disease, were included. Approximately half of both the patients with and without diabetes reported aspirin use at baseline [1220 (52%)] of type 2 diabetes patients and 4801 (56%) of type 2 diabetes patients without diabetes reported aspirin use at baseline [1148 (25%)].

The PPP trial was a randomized, open-label, two-by-two factorial design study assessing the effect of aspirin and vitamin E on primary prevention of CVD in patients with and without type 2 diabetes. The study was stopped prematurely to be beneficial in grounds, aspirin having been proved to be beneficial in primary prevention of CVD in patients with type 2 diabetes (RR = 0.90; 95% CI, 0.85–0.96). The authors therefore concluded that although the antiplatelet therapy used appeared to be more effective in subjects without type 2 diabetes, the potential confounding factors was not carried out. The weak therapeutic response in patients with diabetes could, in part, be explained by the study population [12].
mortality was less frequent in individuals with type 2 diabetes treated with aspirin when compared to those not receiving the antiplatelet therapy (10.9% vs. 15.9% and 18.4% vs. 26.2% respectively). Adjustment for potential confounding factors did not influence conclusions; the use of aspirin was still independently associated with a reduction in cardiac mortality and all causes mortality [Hazard ratio (HR)=0.8; 95% CI, 0.6–1.0 and HR=0.8; 95% CI, 0.7–0.9 respectively]. Dosage, time of initiation or duration of treatment with aspirin were however unknown.

4. Discussion

Very few studies since 1990 have assessed the effect of aspirin use on cardiovascular events in subjects with type 2 diabetes, and most of them showed no statistically significant benefit. These results are in lines with the ones obtained in a previous article published in 1989, The Physicians’ Health Study [18]. This randomized controlled trial was performed among 22,071 healthy male individuals to determine whether aspirin (325 mg every other day) would decrease cardiovascular mortality, and whether beta carotene would decrease aspirin use on cardiovascular events in subjects with type 2 diabetes included in the study (11/275 in the aspirin group vs. 26/258 in the placebo group). These overall non-significant results are in agreement with the conclusions of the two prior meta-analyses carried out by the Antiplatelet Trialists’ Collaboration [9,10]. Designed to evaluate the effects of antiplatelet therapies on cardiovascular events in a wide range of patients, the first of these meta-analyses [9] included about 110,000 patients from 174 trials. Information on subjects with diabetes was scarce and although overall results appeared to favor treatment, the reduction of events in subjects with diabetes seen with antiplatelet therapy did not attain statistical significance. As previously mentioned, the proportional reduction of serious vascular events in the other meta-analysis [10] was again somewhat low for the subgroup with diabetes (7%, not statistically significant). The authors of this meta-analysis warned that their result did not mean individuals with diabetes do not benefit from aspirin therapy [10]. Rather, they emphasized that the reduction remained consistent with that of about 25% observed overall in the larger population included in the meta-analysis [10]. In fact, they suggested “that aspirin is likely to be effective for the primary prevention of vascular events among diabetic patients” [10], while at the same time suggesting that direct evidence from randomized controlled trials involving patients with diabetes would be helpful.

In fact, several hypotheses may explain why patients with diabetes do not appear to obtain benefits similar to those obtained by other high-risk populations. First, two of the studies retrieved in our search were subgroup analyses, and lacked the power to generate positive results. The PPP study [13], for example, was halted prematurely, and in this study, individuals with diabetes suffered less cardiovascular events (event rate of 1% per year) than had been predicted in the sample size calculation (event rate of 4% per year).

Furthermore, adherence to study medication could have an important impact on outcomes. For example, Glynn et al. [19] noted that, in the Physicians’ Health Study [18], individuals with excellent adherence to aspirin had increased benefits compared to those with poorer adherence. Two of the studies in this review did not include any information on adherence [12,16]; on the other hand, about one third of patients in the ETDRS [11] and the PPP [13] trials stopped therapy before the end of the trial, indicating that persistence with treatment might be problematic. The authors did not question this fact, so information concerning prevention of discontinuation is not available.

Another hypothesis to explore is whether low doses would be less effective for patients with diabetes. The authors of the PPP trial [13] suggested that individuals with diabetes might present a resistance to aspirin that is a “failure of aspirin therapy to prevent a major vascular event in an individual on aspirin therapy” [20]. It has been suggested that due to the increase in platelet turnover and thromboxane synthesis in diabetes, higher doses or multiple daily dosing of aspirin may be preferred in patients with diabetes [7]. However, the ETDRS study [11] used daily doses of 650 mg and obtained results very similar to the other studies using lower doses. Use of relatively high-dose aspirin therapy in patients with diabetes must also be weighted against the potential adverse effects, including both gastro-intestinal serious side effects and negative impacts on renal function and blood pressure control. On the other hand, there have been no clinical trials to study whether multiple daily dosing would improve cardiovascular outcomes.

Although the results of antiplatelet studies with type 2 diabetes do not appear significant when taken individually, one cannot conclude aspirin therapy is not effective in diabetes. Studies undertaken with subjects with type 2 diabetes are few, often refer to subgroup analyses that lack power and have several limits. One of those that could have added information on the subject is the Hypertension Optimal Trial (HOT) study [15]. However, since the authors did not present the specific results for the population with diabetes in the original publication, this particular study could not be included in the present review. The authors of the HOT study reported that the 1500 subjects with type 2 diabetes included in the trial obtained a similar relative benefit for major cardiovascular events and myocardial infarctions to the entire HOT population. Aspirin reduced major cardiovascular events by 15% in the entire study population (p=0.03). Use of 75 mg daily aspirin statistically reduced the rate of myocardial infarctions (RR =0.64; 95% CI, 0.49–0.85), but stroke (RR =0.98; 95% CI, 0.78–1.24), cardiovascular mortality (RR =0.95; 95% CI, 0.75–1.20) and total mortality (RR =0.93; 95% CI, 0.79–1.09) were not statistically lowered at a 5% level.
A statistically significant 20% reduction of total mortality was observed in the Harpaz et al. [16] study, resulting mostly from a reduction in cardiac mortality. However, further population-based research should be undertaken to verify whether these results can be reproduced. An improved definition of aspirin use (including time of initiation, dose used, adherence to therapy and side effects related to the medication) should be considered in order to improve our understanding of the effects of aspirin. Cardiovascular events and not only cardiac mortality should also be addressed in any future research.

New studies involving aspirin should draw the attention of both health care professionals and patients to the value of aspirin use, since it has been repeatedly reported as being underused in the population with diabetes [21–25]. This relative indifference to aspirin therapy also emerges in recent major clinical trials targeting cardiovascular events in patients with diabetes. For example, in 17 trials on treatment of hypertension or dyslipidemia in subjects with type 2 diabetes, published between 2000 and 2004, nine did not report aspirin use [26–35]. Six of the eight other trials did not specifically report the proportions of aspirin use for the subgroup population with diabetes, so the extent of aspirin use in this population was not clearly established [36–41]. In the two trials reporting specific aspirin use by patients with diabetes, proportions of usage were around 15 to 20% [42,43]. This situation reveals little adherence to clinical guidelines, which may possibly be partly related to the lack of sound clinical evidence. On the other hand, it raises ethical concerns: for if aspirin is believed to reduce cardiovascular events and is considered an essential treatment according to guidelines, one could assume all individuals with type 2 diabetes should receive it before they enroll in studies that evaluate new drugs or that explore new uses. If individuals with type 2 diabetes do not receive standard treatment, the not negligible issue is whether or not we can be assured afterwards that the results obtained in the trial would have been similar, had the standard treatment been given.

Few therapies in cardiovascular medicine have been studied so intently and adopted so widely into clinical practice as aspirin. However evidence of long-term benefit for people with diabetes in both primary and secondary prevention is still lacking. Yet aspirin was adopted as part of the standard therapy for patients with diabetes, suggesting a lower threshold of evidence for accepting a therapy that might be of benefit. Evidence-based medicine should not allow double standards but should use the same rules to judge interventions.

5. Conclusion

Our review revealed little information on the impact of aspirin therapy on cardiovascular outcomes in the population with type 2 diabetes. Our results suggest that, in accord with the new ECS/EASD guidelines [44] but contrary to that which is asserted in other numerous guidelines [45–49] the level of evidence may be rather faint. In fact, we found no clinical randomized trial where aspirin use was associated with robust positive cardiovascular outcomes in subjects with type 2 diabetes. The only evidence comes from one observational study [16]. This, therefore, leads one to suspect that clinical guidelines include aspirin in their recommendations for individuals with diabetes based upon an expected benefit outcome that has been seen in other high-risk populations. Nicolucci et al. [50] have also reached similar conclusions in a recent paper. Given the lack of clear evidence, the level of evidence for the use of aspirin as a standard treatment in subjects with type 2 diabetes should be revisited in current guidelines. In fact, a new focus on this relatively inexpensive and secure therapy could, if it were proven effective, assist in increasing the proportion of individuals with diabetes using aspirin. Meanwhile, reassessments of past randomized studies including subjects with diabetes and further well-conducted population-based observational studies would provide useful information respectively on the efficacy and effectiveness of this potentially important therapy.

Acknowledgment

We thank Joanne Vidal for assistance in editing the text.

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