



HAL
open science

Aspirin in people with diabetes: Time to clean up the prescription list?

Julien Vouillarmet, Victor Aboyans

► **To cite this version:**

Julien Vouillarmet, Victor Aboyans. Aspirin in people with diabetes: Time to clean up the prescription list?. *Diabetes Research and Clinical Practice*, 2019, 10.1016/j.diabres.2019.02.005 . hal-02043843

HAL Id: hal-02043843

<https://hal-unilim.archives-ouvertes.fr/hal-02043843>

Submitted on 22 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial| 4.0 International License

Aspirin in people with diabetes: time to clean up the prescription list?

Julien Vouillarmet¹, Victor Aboyans²

¹Hospices Civils de Lyon, Diabetes department, Centre Hospitalier Lyon-Sud, Pierre Bénite, France. ²Department of Cardiology, Dupuytren University Hospital, Limoges, France

Corresponding author: Julien Vouillarmet

Address: Service d'Endocrinologie, Diabète et Nutrition, pavillon médical, Centre Hospitalier Lyon-Sud, 69495 Pierre Bénite

Tel: +33-4-78-86-14-84

Fax: +33-4-78-86-45-73

ABSTRACT

The effect of aspirin in primary cardiovascular (CV) prevention in people with diabetes is still a matter of debate. Recent results of ASCEND trial suggest that the absolute benefit on CV events is largely counter-balanced by the bleeding risk. However, one crucial question is whether aspirin should be maintained or withdrawn from the prescription list of those who are already under this therapy since a while ago. Indeed, large epidemiological data reported that the aspirin discontinuation was associated to an increased risk of CV events. Moreover, besides the CV outcome, potential positive impact of aspirin on cancer is still under investigation. To conclude, there is no more systematic indication for aspirin in people with diabetes free of CV disease, especially when diabetes and all other CV risk factors are optimally controlled. For those already on aspirin, data are not conclusive enough for a systematic approach and benefit/risk balance must be discussed with patients to take a shared decision.

Keywords: aspirin; diabetes; cardiovascular

Abbreviations:

CV	Cardiovascular
RCT	Randomized control trial

The effect of aspirin in primary cardiovascular (CV) prevention in people with diabetes is still a matter of debate [1]. Recent European guidelines do not recommend the use of aspirin in primary CV prevention [2] whereas American Diabetes Association guidelines retain its use in people with diabetes over 50 years old with an additional CV risk factor but who are not at increased risk of bleeding [3].

Recently a large randomized double blind control trial (RCT) reported that in people with diabetes free of CV disease at baseline, aspirin lead to a 12% decrease of major CV events during 7.4 years of follow-up, but was also associated with a 29% increase risk of major bleeding [4]. The authors concluded that the absolute benefit is largely counter-balanced by the bleeding risk.

These results sound like the swan song for a regular prescription of aspirin in people with diabetes for primary prevention. One burning question is whether aspirin should be maintained or withdrawn from the prescription list of those who were under this therapy since a while ago, with apparently good tolerance up to now. In a Swedish nationwide population-based cohort study, among individuals taking aspirin for primary prevention, aspirin discontinuation was associated to a 28% increased risk of CV events [5]. This trend was also observed in the diabetic subgroup: the risk increased soon after aspirin discontinuation and appeared stable during 3 years of follow-up. The mechanisms involved are not clear and a rebound of the platelet function and loss of the protective effect of aspirin have been proposed [6]. These results are important to take into account to interpret the ASCEND study results [4]. Indeed, 35% of the ASCEND population were on aspirin before randomization and, it cannot be excluded that, the difference of CV events observed between the two groups was partly due to an increase risk of events in people who discontinued aspirin in the placebo group (as compared to aspirin continuation in the other arm of the study). In a subgroup analysis, patients who were already under aspirin had numerically a higher benefit of staying under aspirin over placebo with lower rates of CV events and major bleeding (respectively

HR: 0.83; 95%CI 0.71-0.96 and HR: 1.17; 95%CI 0.89-1.53), than those free of aspirin before enrolment (respectively HR: 0.92; 95%CI 0.82-1.04 and HR 1.36; 1.11-1.87), although no significant interaction was found (respectively $p=0.26$ and 0.38). This trend in ASCEND study added with epidemiological data did not permit to exclude for sure a negative effect of aspirin withdrawal.

Besides this questionable deleterious effect of aspirin cessation, the positive impact of aspirin on cancer must be kept in mind in the assessment of the risk/benefit balance to discontinue aspirin. Indeed, pooled analysis of RCTs underline that aspirin reduces incidence of cancer by 25% but also prevents distant metastasis and reduces the rate of cancer related-deaths by 40% [7-8]. Preliminary results from ASCEND are more mitigating with no difference in the incidence of cancer in people with diabetes [5]. Another study in the elderly people reports an increased rate of cancer related-deaths in those with aspirin compared to placebo mainly driven by colorectal cancer [9]. Different molecular expression, notably COX-2 expression, by tumours might explain the variability of response to aspirin [10,11].

To take the decision, the duration of aspirin treatment before re-assessment is important to take into account. Indeed, time to event analysis in RCT highlight that the beneficial effect of aspirin on major CV events but also the increase of major bleeding were mainly observed during the first 3 years after randomisation and were no more significant after this period [4-10]. At the opposite, the beneficial effect observed on cancer appears only after at least 3 years of treatment [10]. Long-term follow-up of ASCEND is ongoing to assess any long acting beneficial effect of aspirin on cancer incidence. Another consideration is the absence of pre-defined strategy in RCT to prevent gastro-intestinal bleeding. Indeed, people with a high risk of bleeding were excluded in the exclusion criteria as well as run-in period of the ASCEND trial but only a quarter of patients in both groups were on proton-pump inhibitors at the end of the study [4].

To conclude, there is no more systematic indication for aspirin in people with diabetes free of CV disease, especially when diabetes and all other CV risk factors are optimally controlled. For those already on aspirin, data are at that time not enough conclusive for a systematic approach. Also it seems reasonable, before further information, to discuss with the patient about the new findings, and to weigh up the deceiving results because of the bleeding risk with the good tolerance of that specific patient already under aspirin sometimes since many years. The current situation is a good example of the need to explain honestly the benefit/risk balance with patients and take a shared decision.

Declarations of interest: none.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

- [1] Kokoska LA, Wilhelm SM, Garwood CL, Berlie HD. Aspirin for primary prevention of cardiovascular disease in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract* 2016;120:31-39.
- [2] 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Atherosclerosis* 2016;252:207-274.
- [3] ADA. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018; 41: S86-S104.
- [4] ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018;379:1529-1539.

- [5] Sundström J, Hedberg J, Thuresson M, Aarskog P, Johannesen KM, Oldgren J. Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events: A Swedish Nationwide, Population-Based Cohort Study. *Circulation* 2017;136:1183-1192.
- [6] Oldgren J, Sundström J. Response by Oldgren and Sundström to Letter Regarding Article, "Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events: A Swedish Nationwide, Population-Based Cohort Study". *Circulation* 2018;137:2313.
- [7] Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012 ;379(9826):1591-601.
- [8] Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, Lee R, Belch JF, Wilson M, Mehta Z, Meade TW. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012;379(9826):1602-12.
- [9] McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, Kirpach B, Shah RC, Ives DG, Storey E, Ryan J, Tonkin AM, Newman AB, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Radziszewska B, Grimm R, Murray AM; ASPREE Investigator Group. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med* 2018;379(16):1519-1528.
- [10] Drew DA, Cao Y, Chan AT. Aspirin and colorectal cancer: the promise of precision chemoprevention. *Nat Rev Cancer* 2016;16(3):173-86.
- [11] Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007;356(21):2131-42.