Cor et Vasa

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Primární prevence | Primary prevention

Přehledový článek | Review article

Current opinion on aspirin in primary prevention of atherosclerotic cardiovascular diseases. Is there any difference between diabetic and non-diabetic patients?

Barbora Nussbaumerová, Hana Rosolová

II. interní klinika, Lékařská fakulta Plzeň, Univerzita Karlova v Praze a Fakultní nemocnice Plzeň, Plzeň, Česká republika

INFORMACE O ČLÁNKU

Historie článku:
Došel do redakce: 31. 10. 2012
Přepracován: 23. 11. 2012
Přijat: 24. 11. 2012
Dostupný online: 1. 12. 2012

Keywords:
Aspirin
Cardiovascular disease
Primary prevention
Type 2 diabetes

Klíčová slova:
Diabetes mellitus 2. typu
Kardiovaskulární onemocnění
Kyselina acetylsalicylová
Primární prevence

ABSTRACT

Aspirin reduces vascular death by approximately 15% and nonfatal vascular events by about 30% in secondary prevention. The evidence in primary prevention in non-diabetic subjects is not so powerful. The benefit of aspirin primary prevention in type 2 diabetes remains to be advocated definitely.

SOUHRN

Užívání kyseliny acetylsalicylové v sekundární prevenci aterosklerotických vaskulárních onemocnění snižuje kardiovaskulární mortalitu přibližně o 15 % a riziko nefatálních vaskulárních příhod přibližně o 30 %. Důkazy svědčící pro stejný prospěch z užívání kyseliny acetylsalicylové v primární prevenci u osob bez diabetu nejsou již tak přesvědčivé. Ani u osob s diabetes mellitus 2. typu nemáme zatím dostatek důkazů, z nichž by plynulo paušální doporučení podávat kyselinu acetylsalicylovou v primární prevenci.

Adresa: MUDr. Barbora Nussbaumerová, Ph.D., II. interní klinika, Lékařská fakulta Plzeň, Univerzita Karlova v Praze a Fakultní nemocnice Plzeň, Dr. E. Beneše 13, 305 99 Plzeň, e-mail: nussbaumerova@fnplzen.cz
DOI: 10.1016/j.crvasa.2012.11.019

Tento článek prosím citujte takto: B. Nussbaumerová, H. Rosolová, Current opinion on aspirin in primary prevention of atherosclerotic cardiovascular diseases. Is there any difference between diabetic and non-diabetic patients?, Cor et Vasa 55 (2013) e190–e195, jak vyšel v online verzi *Cor et Vasa* na http://www.sciencedirect.com/science/article/pii/S0010865012001373

Introduction

Aspirin (acetylsalicylic acid, ASA) is an effective, time-tested antithrombotic agent. Aspirin inhibits the production of thromboxane A_2, a potent platelet aggregation and vasoconstriction agent, by inhibiting the enzyme platelet cyclooxygenase (COX-1). Aspirin is usually administered in peroral doses of 75–325 mg daily. In secondary cardiovascular prevention, the indication is clear. Aspirin therapy was proven to reduce the risk of vascular death by about 15% and the risk of nonfatal myocardial infarction and stroke by about 30% in patients with unstable angina, suspected acute myocardial infarction, silent myocardial ischemia, or a past history of myocardial infarction, coronary angioplasty, aortocoronary bypass surgery, stroke, or a transient ischemic attack reliably [1–5]. There are also sufficient data supporting the use of aspirin in secondary prevention in diabetic subjects [6].

On the other hand, the administration of aspirin to asymptomatic subjects without any manifested cardiovascular diseases, i.e. primary prevention subjects, is not yet clear. There is also some evidence of preventing myocardial infarction in both males and females older than 50 years but not as strong as in secondary cardiovascular prevention. There is no powerful evidence of preventing vascular deaths by aspirin in primary prevention. The evidence is also not really consistent in diabetic subjects. Physicians prescribing aspirin to their patients should be aware of possible adverse events that can occur during the treatment; especially gastrointestinal bleeds, intracerebral hemorrhage and hypersensitivity/allergy to aspirin. Aspirin in primary prevention is definitely contraindicated in subjects with allergy to aspirin, with overall tendency to bleed, with personal history of recent gastrointestinal bleeding, with active liver disease and under 21 years of age.

Evidence on aspirin in primary prevention

In the past three decades, aspirin in primary prevention was handled as "the golden standard" for many subjects with some presence of cardiovascular risk and for subjects with type 2 diabetes. A known prothrombogenic and proinflamatory state in diabetes might advocate the use of aspirin in primary prevention because of the presence of high cardiovascular risk among these subjects [7,8]. Clinical guidelines recommended strictly the administration of aspirin for both primary and secondary cardiovascular prevention in diabetes; e.g. the ones in our country, the Czech "Guidelines on prevention of cardiovascular diseases in adults" (published in 2005) recommend the administration of aspirin or other antiaggregation drug to all subjects with manifest cardiovascular disease, type 2 diabetes, type 1 diabetes with microalbuminuria, cardiovascular risk according to SCORE risk model over 5% and hypertensive subjects with a moderately elevated creatinine level [9]. Nevertheless, clinical practice has changed in about the past 4 years because newer emerging surveys questioned the clinical benefit of such an approach. The evidence for the aspirin administration in primary prevention proceeds from larger and smaller surveys. The largest ones with about 85,000 subjects, with the dose of aspirin between 100 mg on alternate days and 500 mg daily are summarized in Table 1 [10–15], i.e. the Physicians' Health Study (PHS), British Doctors' Trial (BDT), Thrombosis Prevention Trial (TPT), Hypertension Optimal Treatment (HOT) trial, Primary Prevention Project (PPP) and Women's Health Study (WHS). The reduction of myocardial infarction was between 3% and 40% in the trials mentioned above. A metaanalysis of these surveys (without WHS) in 1998 also reported a statistically significant 15% risk reduction of any important vascular event associated with aspirin therapy (relative risk [RR] – 0.85, 95% CI [confidence interval] = 0.79–0.93), driven in large part by the statistically extreme finding of reduced myocardial infarction risk by 32% (RR 0.68, 95% CI = 0.59–0.79). No statistically significant decrease was shown in total stroke overall (RR = 1.02, 95% CI = 0.85–1.23), maybe due to a low number of strokes and an inexact definition of either ischemic or hemorrhagic stroke. For vascular deaths, there was no significant reduction in risk although the CIs were wide and included the plausible decrease seen in the trials of secondary prevention, as well as a small increase (RR = 0.98, 95% CI = 0.85–1.12) [16].

Table 1 – The most important trials on aspirin in primary prevention.

	PHS (1988)	BDT (1988)	TPT (1998)	HOT (1998)	PPP (2001)	WHS (2005)
Number of subjects	22,071	5139	5085	18,790	4495	39,876
Follow up (years)	5	5.8	6.8	3.8	3.6	10
Population	Healthy male physicians	Healthy male physicians	Males in high risk of CHD	Males and females with hypertension	Males and females with 1 CHD risk factor	Females
Age (years)	40–84	50–78	45–69	50–80	50 – over 80	> 40; aver. 54
Males : females (%)	100 : 0	100 : 0	100 : 0	53 : 47	42 : 58	0 : 100
Aspirin dose (mg)	325 OAD	500 D	75 D	75 D	100 D	100 OAD
Control	Placebo	No placebo	Placebo	Placebo	No placebo	Placebo

BDT – British Doctors' Trial; CHD – coronary heart disease; D – daily; HOT – Hypertension Optimal Treatment; OAD – on alternate days; PHS – Physicians' Health Study; PPP – Primary Prevention Project; TPT – Thrombosis Prevention Trial; WHS – Women's Health Study.

In 2005, the Women's Health Study was published [15]. The trial on 39,896 sole female participants looked at the use of aspirin in primary prevention of cardiovascular events. Aspirin (100 mg on alternate days) did not lower the risk either of myocardial infarction or cardiovascular death overall, but it significantly reduced the risk of stroke by 17% in the whole trial group (RR 0.83, 95% CI = 0.69–0.99, $p = 0.04$), owing to a 24% reduction of the risk of ischemic stroke (RR 0.76, 95% CI 0.63–0.93, $p = 0.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (RR 1.24, 95% CI 0.82–1.87, $p = 0.31$). In women aged over 65, there was a significant benefit of aspirin use compared to placebo. The risk of major cardiovascular events was reduced by 26% among those who were on aspirin (RR 0.74, 95% CI 0.59–0.92, $p = 0.008$). The risk of ischemic stroke was reduced by 30% (RR 0.70, 95% CI 0.49–1.00, $p = 0.05$). The risk of myocardial infarction was also reduced by 34% (RR 0.66, 95% CI 0.44–0.97, $p = 0.04$). On the other hand, aspirin failed to show any effect on cardiovascular events in women aged 45–65. The dose of aspirin may have been too low in this trial, as shown in the metaanalyses of other trials mentioned above where the doses lower than 75 mg daily were not effective.

In 2009, the Antithrombotic Trialists' Collaboration published an individual patient-level metaanalysis of six large trials on aspirin for primary prevention in the general population [17]. These trials enrolled over 95,000 participants, including almost 4000 with diabetes. Overall, this metaanalysis found that aspirin reduced the risk of vascular events by 12% (RR 0.88, 95% CI 0.82–0.94, $p = 0.0001$). The largest reduction was for nonfatal myocardial infarction (RR 0.77, 95% CI 0.67–0.89, $p < 0.0001$). The net effect on stroke was not significant (0.20% vs 0.21% per year, $p = 0.4$, hemorrhagic stroke 0.04% vs 0.03%, $p = 0.05$, other stroke 0.16% vs 0.18% per year, $p = 0.08$). Vascular mortality did not differ significantly (0.19% vs 0.19% per year, $p = 0.7$). The net effect on total stroke reflected a relative reduction in risk of ischemic stroke (14%) and a relative increased risk of hemorrhagic stroke (32%). In this trial, aspirin allocation increased major gastrointestinal and extracranial bleeds (0.10 % vs 0.07 % per year, $p < 0.0001$). Main risk factors were identical for coronary disease and for bleeding.

The newest metaanalyses on aspirin in primary prevention emerged in 2011 and 2012 [18,19]. The same fact was shown, i.e. aspirin had no effect on vascular and total mortality and had a protective effect on new onset of cardiovascular events driven mainly by myocardial infarction. Nontrivial bleeds were present significantly more often in the aspirin group than in the placebo group in the second metaanalysis (OR 1.31, 95% CI 1.14–1.50, number needed to harm 73).

Evidence on aspirin in diabetes in primary prevention

The proportion of patients with diabetes mellitus was small in each of the above mentioned primary preventive trials with aspirin (PPP: 17%; HOT: 8%; PHS: 2%; BDT: 2%; and TPT: 2%). Only in PHS, patients with diabetes derived greater benefit from aspirin than those without diabetes in 41% RR reduction of myocardial infarction in the 5 years follow up (RR 0.59, 95% CI 0.33–1.06) [20].

In the Early Treatment Diabetic Retinopathy Study (ETDRS) in which 3711 subjects with type 1 and 2 diabetes (majority of them without any history of myocardial infarction or stroke) were randomized to receive 650 mg aspirin daily or placebo was not shown any positive effect of aspirin regarding total mortality but some reduction in fatal and nonfatal myocardial infarctions (RR 0.83, 99% CI = 0.66–1.04) [21].

In a metaanalysis perfomed by the Antiplatelet Trialists' Collaboration 4961 patients with diabetes in nine trials were included. Antiplatelet therapy was associated with only a 7% proportional reduction in serious vascular events [6]. None of the trials reported major extracranial bleeding.

There was a need to design surveys focused on diabetic patients with no coronary heart disease separately. The first ones emerged in 2008. The trial Prevention of Progression of Arterial Disease and Diabetes (POPADAD) included quite high-risk patients, with type 1 or type 2 diabetes and peripheral artery disease (PAD). Secondary prevention could be considered in these patients. Asymptomatic PAD was determined by a lower-than-normal ankle-brachial pressure index of 0.99 or less, but no symptoms. The subjects (n = 1276) were older than 40 years and were randomized to receive either aspirin 100 mg daily or placebo, and followed over 9 years. It was investigated whether aspirin could reduce set primary endpoints: 1. death from coronary heart disease or stroke, nonfatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischemia; 2. and death from coronary heart disease or stroke. Overall, there was found no benefit from aspirin. Patients in both study groups experienced the same number (116 and 117) of primary events (hazard ratio [HR] 0.98, 95% CI = 0.76–1.26, $p = 0.86$). There were 43 deaths from coronary heart disease or stroke in the aspirin group compared with 35 in the placebo group (HR 1.23, 95% CI = 0.79–1.93, $p = 0.36$). There was found no evidence that aspirin was of any benefit in the primary prevention of cardiovascular events in diabetic patients with asymptomatic PAD [22]. Some say the study was underpowered with only 1276 patients.

The trial Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) randomized 2539 patients aged maximally 85 years with a good control of type 2 diabetes and arterial hypertension of an average of 4.4 years follow up [23]. They did not have any history of atherosclerotic disease (structural or arrythmic cardiovascular disease, stroke and other cerebrovascular diseases, peripheral vascular disease). The subjects received aspirin at either 81 mg daily or 100 mg daily or placebo on an open-label basis and did not receive either other antiplatelet or anticoagulation drugs. Atherosclerotic events were defined as sudden death; death from coronary, cerebrovascular, or aortic causes; nonfatal myocardial infarction, unstable angina, new exertional angina; nonfatal ischemic or hemorrhagic stroke; transient ischemic attack; or nonfatal aortic or peripheral vascular disease. After the median of 4.4 years follow up, there was no significant difference in the new atherosclero-

tic events. A total of 154 atherosclerotic events occurred with a nonsignificant difference: 68 in the aspirin group and 86 in the nonaspirin group (HR 0.80; 95% CI 0.58–1.10, p = 0.16). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR 0.90; 95% CI 0.57–1.14, p = 0.67). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and in 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR 0.10, 95% CI 0.01–0.79, p = 0.0037) which was the only one significant result in this study in fact. In a subgroup analysis (1363 patients aged ≥ 65 years), the group of 719 subjects on aspirin showed a significant aspirin-related decrease in risk of atherosclerotic events; younger patients showed no such difference. The composite of hemorrhagic stroke and serious gastrointestinal bleeding was not significantly different between the aspirin and placebo groups.

One could summarize, there is available evidence on aspirin in primary prevention of cardiovascular disease from three trials focused on diabetics separately and six other large trials including some number of diabetics up-to-date. None of these trials provides definitive results and solutions. Several metaanalyses of these trials provide different results according to the trials included into each metaanalysis. The most limiting fact is the low event rate in the control groups. One might conclude aspirin is effective in a modest-sized reduction in myocardial infarction and stroke in patients with diabetes, but current evidence is not definite. The differences in outcomes for males and females have to be further investigated. There have also been too small totals of events in the performed trials and we rely on analyses of subgroups within larger trials to be able to make any conclusion.

Recommendations in primary prevention in the "new era of aspirin" after 2010

After the results of POPADAD and JPAD trails and the Antithrombotic Trialists' Collaboration's metaanalysis on aspirin use in primary prevention following Czech guidelines were published. The Czech "Standards of Medical Care in Diabetes" from 2012 recommend to follow to administer aspirin (100 mg daily) in primary prevention to diabetic subjects with other risks and in secondary prevention, nevertheless, no exact definition of "other risks" is given [24]. The newest Czech "Diagnostic and therapeutic recommendations on arterial hypertension – version 2012" support the allocation of aspirin in primary prevention to those with arterial hypertension and a very high cardiovascular risk according to SCORE risk model or with renal impairment because of a doubtful ratio of risk and benefit of aspirin in hypertensive subjects at low cardiovascular risk. A routine admission of aspirin is not recommended in these subjects [25].

In 2010, a Position Statement of the American Diabetes Association (ADA), a Scientific Statement of the American Heart Association (AHA), and an Expert Consensus Document of the American College of Cardiology Foundation (ACCF) was published [26].

Low-dose (75–162 mg daily) aspirin use for primary prevention is reasonable for adults with diabetes who are at increased cardiovascular risk (10-year risk of cardiovascular events over 10% according to Framingham risk model) and who are not at increased risk of bleeding (based on a history of previous gastrointestinal bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as nonsteroidal anti-inflammatory drugs [NSAIDS] or warfarin). Those adults with diabetes at increased cardiovascular risk include most males over age 50 years and females over age 60 years who have one or more of the following additional major risk factors: smoking, arterial hypertension, dyslipidemia, family history of premature cardiovascular disease, and albuminuria (ACCF/AHA Class IIa, Level of Evidence: B) (ADA Level of Evidence: C).

Aspirin should not be recommended for cardiovascular prevention for adults with diabetes at low cardiovascular risk (men under age 50 years and women under 60 years with no major additional cardiovascular risk factors; 10-year cardiovascular risk under 5%) as the potential adverse effects from bleeding offset the potential benefits (ACCF/AHA Class III, Level of Evidence: C) (ADA Level of Evidence: C).

Low-dose (75–162 mg/day) aspirin use for prevention might be considered for those with diabetes at intermediate cardiovascular risk (younger patients with one or more risk factors, or older subjects with no risk factors, or patients with 10-year cardiovascular risk of 5–10%) until further research is available (ACCF/AHA Class IIb, Level of Evidence: C) (ADA Level of Evidence: E).

There is a need of a proper cardiovascular risk assessment, as a part of the decision-making process about aspirin allocation because not all subjects with diabetes are at high cardiovascular risk. We should consider the risk factors based on either a combination of age, sex, and other risk factors or on an estimate of absolute cardiovascular risk. The cardiovascular risk should be reassessed over time. It is possible to use several tools for cardiovascular risk estimation in diabetics [27–29].

The European Guidelines on cardiovascular disease prevention in clinical practice (version 2012), the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR) say simply aspirin cannot be recommended in primary prevention [30].

Results of our research

In our department, a group of 415 outpatients with type 2 diabetes has been followed in the frame of a clinical research project since 2005 [31,32]. In the beginning, these 219 males and 196 females were aged 66 ± 9 years and 95% were hypertensive; 28% (n = 116) had atherosclerotic complications, i.e. coronary heart disease, stroke, transient ischemic attack, symptomatic carotid stenosis or peripheral artery disease (these pathologies were also considered as endpoints in the follow-up); 55% of athe-

Table 2 – Basic characteristics of the sample of asymptomatic diabetics.

Parameter	Value (± SD)
N (males/females)	143/156
Age (years)	62 ± 9
Diabetes history (years)	8.4 ± 7.7
BMI (kg/m^2)	31 ± 6
Waist circumference (cm)	107 ± 13
Systolic blood pressure (mmHg)	144 ± 17
Diastolic blood pressure (mmHg)	80 ± 17
LDL-cholesterol (mmol/l)	3.26 ± 0.91
HDL-cholesterol (mmol/l)	1.16 ± 0.25
Triglycerides (mmol/l)	2.08 ± 1.73
Fasting glycemia (mmol/l)	9.32 ± 3.35
Hemoglobin A1c (mmol/mol, IFCC)	60 ± 17.6

IFCC – International Federation of Clinical Chemistry and Laboratory Medicine; SD – standard deviation.

rosclerotic complications were coronary heart disease, significantly more often in males, $p < 0.01$; 54% (n = 224) had microvascular complications, i.e. neuropathy, nephropathy, and retinopathy; 95% of microvascular complications were diabetic nephropathy, no difference between sexes; 40% (n = 167, no difference between sexes) had no vascular complications. The subjects with atherosclerotic complications had more often microvascular complications. The subjects with presence of any complications had a worse risk profile than the ones without any complications. The risk factors associated independently and significantly with atherosclerotic complications were male gender, age over 60 years, a higher level of high-sensitivity C-reactive protein (hs-CRP) > 1 mg/l, glycemia > 5.6 mmol/l, lower diastolic blood pressure and lower HDL-cholesterol. The risk factors associated independently and significantly with microvascular complications were age over 60 years, history of diabetes exceeding 8 years and hs-CRP > 1 mg/l.

Our research was not primarily focused on aspirin treatment. Nevertheless, we can provide some data on aspirin administration in primary prevention of any vascular complications in diabetics. The characteristics of the subgroup "asymptomatic" (n = 299), i.e. without any manifestation of atherosclerotic complications are given in Table 2. In such a sample of 143 males and 156 females aspirin was given to 29 males (20%) and 24 females (15%). After a 5-year follow up, there were 3 deaths from vascular causes in the aspirin group (1 male and 2 females, 5.6% of the aspirin group) and 12 deaths in the nonaspirin group (6 males and 6 females, 4.8% of the non-aspirin group). New endpoints (as mentioned above) developed in 15 subjects in the aspirin group (7 males and 8 females, 28% of the aspirin group) and 53 subjects in the nonaspirin group (21 males and 32 females, 22% of the nonaspirin group). From the group "asymptomatic" there were 94 males and 108 females left in 2012 (the difference in totals died from nonvascular causes or was lost), from which 13 males (14%) and 14 females (13%) were on aspirin. We are aware our observed cohort of patients was small, it does not allow statistically validated conclusions and serves only to information about the problem.

Final conclusion

According to the above mentioned information, we try to answer the question whether there is any difference between aspirin use in diabetic and non-diabetic subjects in primary prevention. In general, the difference is not very distinctive. We have to assess the global cardiovascular risk properly, follow the available evidence for every particular group of patients and then decide carefully whether to start or not the aspirin allocation. We have to consider the protective effects of aspirin treatment on one side and the bleeding risk on the other; i.e. individualized treatment is necessary for every patient in primary prevention of cardiovascular diseases. More data from randomized controlled trials are needed for the primary prevention of atherosclerotic vascular events, especially in subjects at high and moderate global cardiovascular risk.

References

[1] Antiplatelet Trialists' Collaboration, Secondary prevention of vascular events by prolonged antiplatelet therapy, British Medical Journal 296 (1988) 320–331.
[2] C. Hennekens, J.E. Buring, P. Sandercock, et al., Aspirin and other antiplatelet agents in the secondary and primary prevention of cardiovascular disease, Circulation 80 (1989) 749–756.
[3] V. Fuster, M.L. Dyken, P.S. Vokonas, C. Hennekens, Aspirin as a therapeutic agent in cardiovascular disease, Circulation 87 (1993) 659–675.
[4] Antiplatelet Trialists' Collaboration, Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients, British Medical Journal 308 (1994) 81–106.
[5] Antiplatelet Trialists' Collaboration, Collaborative overview of randomised trials of antiplatelet therapy – II: maintenance of vascular graft or arterial patency by antiplatelet therapy, British Medical Journal 308 (1994) 159–168.
[6] Antithrombotic Trialists' Collaboration, Collaborative metaanalysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients, British Medical Journal 324 (2002) 71–86.
[7] J.L. Ferreiro, J.A. Gomez-Hospital, D.J. Angiolillo, Platelet abnormalities in diabetes mellitus, Diabetes and Vascular Disease Research 7 (2010) 251–259.
[8] S.H. Alzahrani, R.A. Ajjan, Coagulation and fibrinolysis in diabetes, Diabetes and Vascular Disease Research 7 (2010) 260–273.
[9] R. Cífková, S. Býma, R. Češka, et al., Prevence kardiovaskulárních onemocnění v dospělém věku, Cor et Vasa 47 (Suppl) (2005) 3–14.
[10] Steering Committee of the Physicians' Health Study Research Group, Final report on the aspirin component of the ongoing Physicians' Health Study, The New England Journal of Medicine 321 (1989) 129–135.
[11] R. Peto, R. Gray, R. Collins, et al., Randomised trial of prophylactic daily aspirin in British male doctors, British Medical Journal 296 (1988) 313–316.
[12] Medical Research Council's General Practice Research Framework, Thrombosis Prevention Trial: randomised trial of

low-intensity oral anticoagulation with warfarin and low--dose aspirin in the primary prevention of ischemic heart disease in men at increased risk, Lancet 351 (1998) 233–241.
[13] L. Hansson, A. Zanchetti, S.G. Carruthers, et al., 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 351 (1998) 1755–1762.
[14] G. de Gaetano, Collaborative Group of the Primary Prevention Project, Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice, Collaborative Group of the Primary Prevention Project, Lancet 357 (2001) 89–95.
[15] P.M. Ridker, N.R. Cook, I.M. Lee, et al., A randomised trial of low-dose aspirin in the primary prevention of cardiovascular disease in women, The New England Journal of Medicine 352 (2005) 1293–1304.
[16] R.S. Eidelman, P.R. Hebert, S.M. Weisman, C.H. Hennekens, An update on aspirin in the primary prevention of cardiovascular disease, Archives of Internal Medicine 263 (2003) 2006–2010.
[17] Antithrombotic Trialists' (ATT) Collaboration, Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials, Lancet 373 (2009) 1849–1860.
[18] A.A. Bartolucci, M. Tendera, G. Howard, Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin, The American Journal of Cardiology 107 (2011) 1796–1801.
[19] S.R. Seshasai, S. Wijesuriya, R. Sivakumaran, et al., Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials, Archives of Internal Medicine 172 (2012) 209–216.
[20] M. Sacco, F. Pellegrini, M.C. Roncaglioni, et al., 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 26 (2003) 3264–3272.
[21] ETDRS Investigators, Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early treatment diabetic retinopathy study report, Journal of the American Medical Association 268 (1992) 1292–1300.
[22] J. Belch, A. MacCuish, I. Campbell I, et al., The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomized placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease, British Medical Journal 337 (2008) a1840.
[23] H. Ogawa, M. Nakayama, T. Morimoto, et al., Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial, Journal of the American Medical Association 300 (2008) 2180–2181.
[24] Doporučený postup péče o nemocné s diabetes mellitus 2. typu, Diabetologie, metabolismus, endokrinologie, výživa 15 (2012) 13–18.
[25] J. Filipovský, J. Widimský jr., J. Ceral, et al., Diagnostické a léčebné postupy u arteriální hypertenze – verze 2012. Doporučení České společnosti pro hypertenzi, Vnitřní lékařství 58 (2012) 785–801.
[26] M. Pignone, M.J. Alberts, J.A. Colwell, et al., Aspirin for primary prevention of cardiovascular events in people with diabetes, Journal of the American College of Cardiology 55 (2010) 2878–2886.
[27] UKPDS Risk Engine. http://www.dtu.ox.ac.uk/riskengine/index.php
[28] ARIC CHD Risk Calculator. http://www.aricnews.net/riskcalc/html/RC1.html
[29] American Diabetes Association Risk Assessment Tool, Diabetes PHD. http://www.diabetes.org/phd
[30] European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Heart Journal 33 (2012) 1635–1701. http://dx.doi.org/10.1093/eurheartj/ehs09.
[31] H. Rosolová, B. Nussbaumerová, F. Šefrna, et al., Kardiovaskulární profil, úroveň kontroly a vztah ke komplikacím u diabetiků 2. typu. Závěrečná zpráva projektu podpořeného IGA MZČR NR 8279-3/2005-2007.
[32] B. Petrlová (Nussbaumerová), H. Rosolová, J. Šimon, et al., Kontrola kardiovaskulárních rizikových faktorů u diabetiků 2. typu, Vnitřní lékařství 55 (2009) 812–818.