Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Low-dose Aspirin

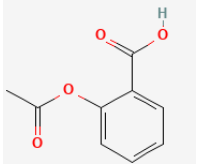
Evidence Summary

Low-dose aspirin may modestly reduce risks for cardiovascular events and cancer in some high-risk subgroups, but it does not reduce mortality risks. It carries a risk for bleeding that increases with age.

Neuroprotective Benefit: Aspirin use is not associated with primary prevention for dementia, though it may modestly reduce risk in some groups with cardiovascular disease with long term use.

Aging and related health concerns: Aspirin is beneficial as an antiplatelet medication in people with cardiovascular disease but does not show clear benefit for primary prevention of cardiovascular disease or cancer in healthy people.

Safety: Aspirin is associated with an increased risk for bleeding, particularly in the GI system, as well as in the brain. The bleeding risk increases with age.

Availability: OTC	**Dose**: Low dose aspirin is typically administered orally at a dose of 75-100 mg/day.	**Chemical formula:** $C_9H_8O_4$ **MW**: 180.16 g/mol  Soure: PubChem
Half-life: Plasma $T_{1/2}$ ~20 minutes but the platelet inhibition lasts for duration of platelet lifespan (~7 days)	**BBB**: Penetrant	
Clinical trials: Low-dose aspirin has been tested in hundreds of trials, including many trials with >10,000 participants, primarily for primary and secondary prevention of cardiovascular disease and cancer.	**Observational studies**: Some studies find that a long-term low-dose aspirin regimen may help reduce the risks for dementia, cardiovascular disease, and cancer, but only in particular high-risk subgroups.	

What is it?

Acetylsalicylic acid is aspirin, a salicylate type of Non-Steroidal Anti-Inflammatory Drug (NSAID), sometimes referred to as NSAIMs, that reduce pain, fever and inflammation. While traditional NSAIDs act by transiently inhibiting both COX-1 and COX-2, aspirin irreversibly inactivates COX-1 and COX-2, with much stronger inhibition of COX-1 [1]. This inhibition reduces the production of prostaglandins and thromboxane. The irreversible suppression of thromboxane A2 in platelets is responsible for aspirin's inhibition of platelet aggregation (i.e. clotting). The inhibition of prostaglandins underlies its use as a pain reliever, while its effects on platelets supports its role as an anti-clotting agent. Aspirin is widely used as part of an anti-thrombotic regimen in individuals with cardiovascular disease. It has also been widely used for the primary prevention of cardiovascular disease and cancer. However, updated guidelines no longer recommend the use of aspirin for primary prevention in the general population (USPSTF statement). This report will focus primarily on low-dose aspirin, which is typically defined as between 75-100 mg/day, though some studies classify it as doses less than 325 mg.

Neuroprotective Benefit: Aspirin use is not associated with primary prevention for dementia, though it may modestly reduce risk in some groups with cardiovascular disease with long term use.

Types of evidence:

- 1 Cochrane meta-analysis of 3 RCTs
- 3 meta-analyses of RCTs and cohort studies
- 1 meta-analysis of cohort studies with long follow-ups
- 2 meta-analyses of observational studies plus 7 subsequent cohort studies
- 3 RCTs assessing low-dose aspirin in dementia prevention
- 2 RCTs assessing low-dose aspirin for cerebrovascular disease

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

The epidemiology on aspirin and dementia prevention is mixed, as it is for the other NSAIDs (see non-ASA NSAID report). For the general population, aspirin use does not appear to impact cognitive trajectories and is not associated with a reduced incidence of dementia. However, similar to what has been observed with the use of low-dose aspirin for primary prevention in cardiovascular disease, there appear to be particular subgroups that may benefit from a regular low-dose aspirin regimen. These benefits are modest, and only apparent with long-term use of at least ten years. Since the population, dose, timing, and duration of administration all influence the potential for benefit, it is not surprising that aspirin does not show cognitive benefit in pooled analyses. Additionally, very few studies have had long enough follow-up periods to reliably detect an effect on dementia risk.

A meta-analysis including 126,740 participants from 19 cohort studies and three RCTs found that aspirin use was not significantly associated with all-cause dementia risk (Hazard ratio [HR]: 1.13, 95% Confidence Interval [CI] 0.89 to 1.43) or Alzheimer's disease (AD) risk (HR: 0.91, CI 0.80 to 1.04) in cohort studies, though there was high heterogeneity across studies [2]. All three RCTs tested low-dose aspirin and also found no significant effect on dementia risk (HR: 0.92, CI 0.84 to 1.01), though the follow-up period may not have been long enough. A meta-analysis including 36,196 participants from five longitudinal studies and 3 RCTs similarly found that the use of low dose aspirin (<300 mg/day) was not associated with cognition or dementia [3]. An analysis of the five longitudinal studies with a median follow-up of six years (n=26,159) found that aspirin use was not associated with the onset of dementia or cognitive impairment (Odds ratio [OR]: 0.82, 95% CI 0.55 to 1.22). The analysis of the three RCTs with a median follow-up of five years (n=10,037) did not observe an effect of aspirin on global cognition (Standardized mean difference [SMD]: 0.005, 95% CI −0.04 to 0.05). One of the studies (the Women's

Health Study), which included only women (n= 6,377), did observe a protective effect of low-dose aspirin on category fluency, a measure of semantic memory (Relative risk [RR]: 0.80, 95% CI 0.67 to 0.97)[4]. Another meta-analysis including a total of 100,909 participants from 12 cohort studies and three RCTs similarly found that aspirin use had no effect on dementia risk in the pooled analyses from cohort studies (RR: 0.75, 95% CI 0.63 to 0.9) or RCTs (RR: 0.94, 95% CI 0.84 to 1.05), but a protective effect on dementia risk (RR: 0.75, 95% CI 0.63 to 0.9) was observed in cohort studies using low-dose aspirin (75-100 mg/day) [5]. An analysis including 1,866 participants in the ADNI cohort found that there was no association between aspirin use and cognitive decline in those with normal cognition (n=509) [6]. The relationship between aspirin use and dementia was highly variable across studies in earlier analyses. A 2004 meta-analysis of five cohort and three case-control studies reported no significant association with Alzheimer's risk (RR: 0.87, CI 0.70 to 1.07, p=0.79) [7] but a 2008 meta-analysis of six cohorts reported a reduced risk (adjusted HR: 0.78, CI 0.66 to 0.92) [8]. Subsequent large prospective studies have reported either no effect [9; 10; 11; 12], increased risk [13; 14], or reduced risk [15] on various measures of cognitive health, dementia risk, or dementia pathology.
Due to the high heterogeneity in observational studies and relatively short duration of RCTs, these analyses generally conclude that there is insufficient evidence to determine the potential impact of aspirin on cognitive trajectories.

A meta-analysis of two large cohort studies assessing the impact of low-dose aspirin on dementia risk in community dwelling populations, the German ESTHER study (n= 5,258) with a median follow-up of 14.3 years and the UK Biobank (n=305,394) with a median follow-up of 11.6 years, found that cognitive benefits were only observed in a particular subset of participants [16]. While there was a weak association with aspirin use and dementia risk in the pooled cohorts (HR: 0.96, 95% CI 0.93 to 0.99), there were potentially meaningful reductions in dementia risk in participants with coronary heart disease (CHD). In this subgroup, aspirin use was associated with a 31% reduction (95% CI 41% to 20%) in hazard for AD, a 69% reduction (95% CI 73% to 65%) for vascular dementia, and 54% reduction (95% CI 58% to 50%) for all-cause dementia. This is consistent with the impact of low-dose aspirin on cardiovascular disease prevention, in that the benefits are limited to high-risk populations for primary prevention, while benefits are readily observed in the context of secondary prevention. Additionally, the reduction in dementia incidence was only significant when aspirin was used for at least ten years, which again would be more likely when used for secondary prevention in those with pre-existing cardiovascular disease. Relative to non-users, long-term (≥10 years) use of aspirin was associated with lower hazards of AD, vascular dementia, and all-cause dementia by 42%, 52%, and 49%, respectively.

Together these studies suggest that **aspirin does not meaningfully impact dementia risk in a general population without cardiovascular disease, but may mitigate dementia risk when taken for an extended period of time, in those with cardiovascular disease**, such as those taking it to prevent the recurrence of adverse cardiovascular events. There is some evidence to suggest that it may also benefit individuals at high risk for cardiovascular disease. The timing may also be an important aspect of potential benefit, but this has not been adequately addressed in the studies to date. Since the pathology underlying dementia generally takes decades to develop prior to the onset of symptoms, starting an aspirin regimen in middle age (50s) may have a protective effect, whereas starting it in late life (>age 65) may be too late to meaningfully impact cognitive outcomes.

While a variety of smaller studies have been conducted, there have been three large RCTs to date that have most shaped the current understanding of the relationship between low-dose aspirin and dementia prevention.

ASPREE: The ASPREE (aspirin in reducing events in the elderly) trial was designed to assess the impact of a low-dose aspirin regimen on disability-free survival in a cohort of 19,114 healthy older (≥65 or ≥70 years of age depending on ethnicity) from the United States and Australia [17]. All participants were free from cardiovascular disease, dementia, and disability at baseline. The study ended six months early due to futility on the primary endpoint, resulting in a median follow-up period of 4.7 years. Incident clinically probable and possible AD, and mild cognitive impairment (MCI), along with the rate of cognitive decline were prespecified secondary endpoints in the study [18]. The Modified Mini-Mental State Examination (MMSE), Hopkins verbal learning test–revised, symbol digit modalities test, and controlled oral word association tests were used to assess cognition. There were no differences in the rates of incident dementia (HR: 1.03; 95% CI 0.91 to 1.17), probable AD, or MCI between groups. There were also no changes in cognitive trajectories between the aspirin and placebo groups over the course of the study. The relatively short follow-up time may have impacted the ability to detect a difference. Due to the healthy bias of this study, participants may have had a lower burden of risk factors and been less likely to develop dementia relative to the general population. This study suggests that aspirin lacks utility in primary dementia prevention.

ASCEND: The ASCEND (a study of cardiovascular events in diabetes) trial assessed the risk of serious vascular events in individuals with diabetes but without established atherosclerotic cardiovascular disease [19]. An associated cognitive study including 15,427 ASCEND participants without recorded dementia at baseline assessed the impact of low-dose aspirin (100 mg/day) for a mean of 7.4 years on dementia [20]. The study utilized the 'Healthy Minds' cognitive function test developed by the UK Biobank. Overall, the dementia outcome occurred at similar rates between aspirin users and nonusers (RR: 0.91 95% CI 0.81 to 1.02). Cognitive function was also not significantly different between the groups

at the end of the study, though the reliability of this assessment is limited as the cognitive assessment could only be conducted on 58% of participants.

JPAD: The JPAD (Japanese primary prevention of atherosclerosis with aspirin for diabetes) trial had the longest follow-up period, with a median of 11.4 years, and was the only one to observe an effect of aspirin on cognitive outcomes [21]. However, unlike the other studies where dementia was a pre-specified outcome, this finding comes from a follow-up post-hoc analysis of dementia incidence from the randomized, open-label, standard care-controlled trial. The analysis included 2,536 participants from the JPAD trial with type 2 diabetes without a history of cardiovascular or cerebrovascular disease, but at high risk. There was no effect on dementia rates in the overall population (HR: 0.82, 95% CI 0.58 to 1.16), but there was a lower incidence in women taking low-dose aspirin (HR: 0.58, 95% CI 0.36 to 0.95). In addition to the longer follow-up period, the inclusion of participants at higher baseline risk for dementia due to cardiovascular risk factors may have contributed to the finding of a protective effect.

Infarct-related cognitive impairment: NO CLEAR BENEFIT

While low-dose aspirin has been associated with a reduced risk for stroke in some populations, it does not appear to protect against stroke/infarct-related cognitive decline. The double-blind CHALLENGE RCT compared the effect of low-dose aspirin (100 mg/day) versus the blood vessel relaxer cilostazol (200 mg/day) on the rate of white matter changes on MRI in 256 patients with moderate or severe white matter changes and at least one lacunar infarction detected on MRI [22]. There was no significant difference between the two therapies on the primary outcome, with the majority of participants experiencing an increase in white matter changes over two years. The incidence of ischemic vascular events was lower with cilostazol relative to aspirin (0.5 vs 4.5 cases per 100 person-years). Cognition declined over the two years in both groups, with MMSE scores worsening by about one point and Clinical Dementia Rating scale-Sum of Boxes scores worsening by about 0.5 points.

In the longitudinal, double blind Silence Study, the effect of low-dose aspirin (100 mg/day) on the prevention of new cerebrovascular events and cognitive impairment was assessed in 83 participants with silent brain infarcts [23]. Aspirin use was not associated with a significant reduction in cerebrovascular events or on cognitive trajectories over a four-year period based on assessments of psychomotor speed, memory performance, and global cognition.

Human research to suggest benefits to patients with dementia:

The available randomized trial data show no benefit from low-dose aspirin. In patients with dementia, aspirin does not slow disease progression based on three open-label clinical trials totaling 1,745 patients, treated with 50-150mg/day for six months to three years [24]. Trials on other NSAIDs have been similarly not promising (see non-ASA NSAIDs report).

An observational analysis including 1,899 participants from the ADNI cohort, with normal cognition, MCI, or AD, found that aspirin use only impacted the rate of cognitive decline on the MMSE over time in AD patients, such that aspirin use was associated with a slower rate of decline [6]. Aspirin use was more common in male participants, with an average dose of 130 ± 98 mg/day. The effect appeared to be modified by sex, such that only male AD patients exhibited a protective effect on cognition with aspirin use.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Several mechanisms by which aspirin may protect against dementia have been identified in preclinical studies.

Amyloid production: Platelets are a major systemic source of Aβ [5]. Upon crossing the BBB, the platelets may transfer this amyloid to the brain for deposition. Through its antiplatelet activity, aspirin may mitigate this process. Additionally, through the activation of PPARγ, aspirin may decrease the production of Aβ fragments via the downregulation of BACE1 [16].

Cerebral blood flow: The antiplatelet activity of aspirin may help limit white matter damage and enhance cognitive performance by enhancing cerebral blood flow [16].

Inflammation: The inhibition of COX-1 dampens the production of prostaglandins and can inhibit inflammation. These anti-inflammatory properties are more apparent at higher doses of aspirin, so it is unclear the extent to which low-dose aspirin may attenuate neuroinflammation.

APOE4 interactions*:* NSAIDs overall have been suggested to interact with Apo*E4* status, with NSAID use protecting Apo*E4* carriers but harming non-carriers (See the non-ASA NSAIDs report). Some studies suggest that the ability of an aspirin regimen to protect against dementia was dependent on ApoE4 status, however, other studies have not found a significant association with ApoE4 [6; 16].

Aging and related health concerns: Aspirin is beneficial as an antiplatelet medication in people with cardiovascular disease but does not show clear benefit for primary prevention of cardiovascular disease or cancer in healthy people.

Types of evidence:

- 8 meta-analyses of studies assessing aspirin for primary CVD prevention
- 5 meta-analyses of studies assessing aspirin for secondary CVD prevention
- 8 meta-analyses of studies assessing aspirin for cancer prevention

- 3 meta-analyses of trials assessing aspirin in covid-19 mortality
- 1 RCT testing aspirin in MASLD
- 9 Sub-studies or post-hoc analyses of the ASPREE trial
- 2 cohort studies assessing aspirin for primary CVD prevention
- 2 cohort studies assessing aspirin for cancer prevention
- Numerous preclinical studies

Aging biology and mortality: NO CLEAR BENEFIT

While low-dose aspirin use has been associated with reduced risk for adverse cardiovascular events in some high-risk populations, the impact on cardiovascular-related or all-cause mortality has generally been minor or absent across studies [25]. Some preclinical studies have suggested a potential benefit for lifespan, but these have not been apparent in human studies to date. For example, aspirin increased median survival but not maximum lifespan in male mice but not females in the Interventions Testing Program of the NIA [26] and, in *C. elegans*, aspirin has increased lifespan of *C. elegans* either through the DAF-16/FOXO and AMPK pathways [27] or protection from oxidative stress [28].

The ASPREE trial (NCT01038583) was designed to assess the impact of a low-dose aspirin regimen (100 mg/day) on disability-free survival in a cohort of 19,114 community dwelling older adults (≥70 years old or ≥65 years old if black or Hispanic) from the United States and Australia free from cardiovascular disease, dementia, or disability at baseline [17]. The trial was originally designed to last five years, but ended six months early due to a futility analysis. The trial did not achieve its primary endpoint of disability-free survival, as aspirin was associated with a slightly higher risk of death (HR: 1.14, 95% CI 1.01 to 1.29). The increased mortality was not related to bleeding risk, the primary adverse event associated with aspirin therapy, but rather cancer mortality, which was an unexpected finding inconsistent with other aspirin trials. It should be noted that the overall mortality rate in the trial population was 32% lower than the general population, likely stemming from the exclusion of participants with a physician-estimated life expectancy of less than five years at study entry. Additionally, the cancer-related death rates of 3.2% and 2.3% for the aspirin and placebo groups respectively, were collectively 49% lower than the rate of cancer-related mortality in the general population. These results suggest that low-dose aspirin does not promote healthspan or lifespan in an otherwise healthy population.

A prospective cohort study including 10,854 individuals from four cycles of the United States National Health and Nutrition Examination Survey (NHANES) also did not find evidence to support an impact of

low-dose aspirin on all-cause mortality (HR: 0.92, 95% CI 0.79 to 1.06), cardiovascular-related mortality, or cancer-related mortality over a median 4.8-year follow-up [25].

Cardiovascular disease prevention

Primary prevention: NO CLEAR BENEFIT UNLESS AT VERY HIGH RISK AT A YOUNG AGE
In 2022, the United States Preventive Services Task Force (USPSTF) updated their recommendation statement with respect to the use of low-dose aspirin for primary prevention of cardiovascular disease (CVD). In the prior (2016) iteration of the statement, low-dose aspirin had been recommended in adults aged 50-59 at a 10% or greater risk of CVD, with low bleeding risk, willing to take it for at least 10 years, with a B grade of evidence. **The updated (2022) statement no longer recommends low-dose aspirin for the primary prevention of CVD** due to a downgrading of the evidence to support the use of aspirin for this indication. The current recommendation states that the decision to initiate low-dose aspirin therapy for the primary prevention of CVD in adults aged 40-59 with a 10% or greater CVD risk should be an individual one based on the degree of CVD risk factors and bleeding risk, with a C grade of supportive evidence for potential benefit. The initiation of low-dose aspirin is not recommended in adults ≥60 years of age, based on a D grade of supportive evidence for benefit. The change in guidelines was influenced by the lack of cardiovascular benefit observed in the large ASPREE trial testing low-dose aspirin in a healthy elderly population. The task force commissioned a microsimulation model to estimate the magnitude of net benefit of low-dose aspirin use, as stratified by age, decade of aspirin initiation, sex, and baseline CVD risk (5 to 20%) [29]. The modeling data indicated that aspirin initiation in adults aged 40 to 59 years with a 10% or greater 10-year CVD risk generally provided a modest net benefit in both quality-adjusted life-years and life-years gained. Initiation between ages 60 to 69 led to mixed gains depending on the degree of CVD risk, while initiation at ages ≥70 years resulted in a net negative in terms of life-years irrespective of baseline risk. Since CVD risk is largely impacted by age, those at elevated CVD risk in their 40s and 50s have a higher cumulative lifetime risk and thus are most likely to experience benefit from initiating aspirin early and continuing into their 60s and 70s. Meanwhile, the benefit of aspirin usually takes many years to become apparent, thus those already in their 60s and 70s are more vulnerable to the bleeding risk and less likely to achieve benefit in their lifetimes when initiated so late in life.
Some experts have recommended taking a platelet-guided approach, in which individuals who may be good candidates for low-dose aspirin therapy could be identified based on a hyperactivated platelet profile [30].

The shifting guidance with respect to low-dose aspirin for CVD prevention comes alongside a shift in the landscape of therapies for primary CVD prevention, such as statins for high cholesterol and potent antihypertensives, such as ACE inhibitors and angiotensin II receptor blockers (ARBs). It appears that only those whose CVD risk is not well-managed on this background of cardioprotective therapies stand to benefit from the addition of low-dose aspirin. The ASCEND trial suggests that diabetics may derive benefit [19]. An analysis of individual participant data from three large RCTs examining the effect of a polypill containing a fixed dose statin and antihypertensives found that the five-year number needed to treat (NNT) to prevent one cardiovascular event was lower (NNT=37) in trials including aspirin relative to those without aspirin (NNT=66), though the combination with and without aspirin has not been compared in a head-to-head trial [31].

A variety of meta-analyses of trials assessing low-dose aspirin for primary CVD prevention have found that while aspirin shows modest benefit for the reduction of major adverse cardiovascular events (MACE), such as stroke and myocardial infarction, it does not significantly impact cardiovascular-related or all-cause mortality. The overall effects are modest, with the benefits generally limited to particular high-risk subgroups. These findings are consistent with the recommendations from a variety of medical-related organizations, such that the use of low-dose aspirin for primary prevention should be limited to those who are relatively young and in the highest risk category.
A meta-analysis commissioned by the task force including 11 RCTs (n=134, 470) along with one pilot trial (n=400) found that low-dose aspirin was associated with a decrease in MACE (OR: 0.90, 95% CI 0.85 to 0.95), though the absolute effect size was quite small (-2.5% to -0.1%), and there was no significant effect on mortality [29]. Aspirin use was also associated with a decreased incidence of total ischemic stroke (OR: 0.82, 95% CI 0.72 to 0.92; based on 79,334 participants) and nonfatal ischemic stroke (OR: 0.88, 95% CI 0.78 to 1.00; based on 54,947 participants). A meta-analysis of 10 RCTs including 135,557 participants testing low-dose aspirin (75-100 mg/day) for the primary prevention of CVD found that aspirin use was associated with reduced risk for MACE (RR: 0.89, 95% CI 0.84 to 0.93), myocardial infarction (RR: 0.86, 95% CI 0.78 to 0.95), and ischemic stroke (RR: 0.84, 95% CI 0.76 to 0.93), but had no significant effect on mortality [32]. In absolute terms, 1,269 people would need to be treated to prevent one MACE. Subgroup analysis indicated that the benefits were largely restricted to those with high CVD risk and those younger than age 70. A nationwide cohort study from South Korea in which 400 participants were selected from a sample of 1,106,580 individuals with a follow-up period of nine years found that a regular low-dose aspirin (≤100 mg) regimen did not impact the risk for myocardial infarction or stroke in a primary prevention population [33].

Asymptomatic carotid atherosclerosis: NO CLEAR BENEFIT
A meta-analysis of five RCTs including 841 participants with established asymptomatic carotid atherosclerosis, a risk factor for stroke and myocardial infarction, found that aspirin therapy did not attenuate the progression of carotid intima-media thickness, or influence the risk for adverse vascular events [34].

Diabetes: HIGH RISK SUBGROUP WITH PREFERENTIAL BENEFIT
Diabetes places one at increased risk for CVD, thus diabetics are considered a higher risk subgroup. Studies suggest that due to this heightened baseline risk, diabetics with additional CVD risk factors may be more likely to benefit from low-dose aspirin therapy in the context of primary prevention.
A meta-analysis of nine RCTs including 29,814 participants testing low-dose aspirin (≤100 mg) for at least 12 months for primary CVD prevention in adults with type 2 diabetes found a 9% reduction in risk of MACE (RR: 0.91, 95% CI 0.84 to 0.98) [35]. A reduction in the risk of stroke (RR: 0.84, 95% CI 0.73 to 0.97) was also observed, but there were no significant reductions in the risk for myocardial infarction, or mortality. The benefits were only observed in participants over age 60, which may be related to an increased burden of CVD risk factors in this subgroup. A meta-analysis of 10 RCTs including 34,069 participants testing low dose aspirin (75-100 mg/day) for primary CVD prevention in adults with type 2 diabetes found that the reduced risk for MACE was only observed in those with moderate to high CVD risk, and there was no effect on mortality in any subgroup [36]. A meta-analysis of 12 RCTs including 34,227 participants testing aspirin for a median of five years for primary CVD prevention in adults with diabetes similarly found an 11% reduction in the risk for MACE, with an NNT of 95 (95% CI 61 to 208) to prevent one MACE over 5 years [37]. Low-dose aspirin (≤ 100 mg/day) was also associated with a reduced risk for stroke in this analysis, but not in an analysis of individual participant data (n= 2,306) from three RCTs. In the latter analysis, a reduction in MACE was only observed in non-smokers, which is consistent with the reduced efficacy of aspirin in smokers.
The ***ASCEND*** (A Study of Cardiovascular Events in Diabetes) primary prevention trial assessed the impact of low-dose aspirin (100 mg/day) relative to placebo in 15,480 participants ≥40 years of age with diabetes but without CVD [19]. The study had a mean follow-up of 7.4 years, during which time participants taking aspirin experienced a lower number of serious vascular events relative to those in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; RR: 0.88, 95% CI 0.79 to 0.97). It should be noted that this trial assessed the impact of low-dose aspirin on the background of other cardioprotective therapies, as 75% of participants were taking a statin and 58% were taking an ACE inhibitor or ARB (antihypertensive).

Lp(a): HIGHER RISK SUBGROUP WITH POSSIBLE PREFERENTIAL BENEFIT
Elevated levels of lipoprotein(a) (Lp(a)), which generally stemming from a genetic predisposition, are associated with increased risk for CVD. It is estimated that 20 to 30% of the population may have elevated levels of Lp(a) [38]. Some studies suggest that Lp(a) may interact with platelets and have antifibrinolytic (i.e. pro-clotting) properties [38]. Post-hoc analyses of trials assessing the effect of low-dose aspirin for primary CVD prevention suggest that low-dose aspirin may preferentially benefit individuals with higher genetically determined Lp(a) [38]. The Women's Health Study, which included healthy women ≥45 years of age randomized to 100 mg aspirin every other day or placebo, found that individuals with the rs3798220-C allele of the LPA gene (3.7% of study population) had an elevated risk for CVD (HR: 2.24) relative to non-carriers [38]. Carriers of the risk allele experienced a significant reduction in CVD risk (HR: 0.44, 95% CI 0.20 to 0.94) following aspirin therapy) after median 9.9 years of follow-up. Aspirin therapy reduced the risk of the carriers to the baseline level of risk observed in the non-carriers. Meanwhile, aspirin therapy had no significant effect on CVD risk reduction in the non-carriers, suggesting that the protective effects in the Lp(a) risk allele carriers were related to the mitigation of Lp(a) associated risk. Similarly, an analysis including 12,815 genotyped individuals from the ASPREE study found that carriers of the rs3798220-C allele (3.2% of study population) in the placebo group experienced an increased risk for MACE (HR: 1.90, 95% CI 1.11 to 3.24), while carriers taking aspirin did not exhibit increased risk (HR: 0.54, 95% CI 0.17 to 1.70) [39]. A similar trend was observed when considering quintiles of a Lp(a) genomic risk score, with those at the highest genomic risk showing an increased risk for MACE in the placebo group, but not in the aspirin group, suggesting that aspirin therapy attenuated the Lp(a)-related risk. The generalizability of these studies is limited by the lack of information regarding Lp(a) levels in the participants.

ASPREE trial: The Aspirin in Reducing Events in the Elderly (ASPREE) primary prevention RCT (NCT01038583) included 19,114 community dwelling older adults (≥70 years of age or ≥65 years of age among blacks and Hispanics) from the United States and Australia without cardiovascular disease, dementia, or disability at baseline [17]. Participants received 100 mg enteric-coated aspirin or placebo daily for a median of 4.7 years. The trial did not achieve its primary endpoint of disability-free survival and ended six months early due to a futility analysis. The study also failed to find a benefit for low-dose aspirin on the secondary endpoint of cardiovascular disease, defined as fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure (HR: 0.95, 95% CI 0.83 to 1.08) [40]. However, the expected cardiovascular disease rate of 22.4 events per 1000 person-years was higher than the observed rates of 10.7 events per 1000 person-years in the aspirin group and 11.3 events per 1000 person-years in the placebo group, indicative of the good baseline health of the

trial population relative to the general population. As such, it is difficult to interpret the generalizability of these results for the general population, but does indicate that in a healthy elderly population, the risks of aspirin therapy outweigh any potential benefits.

A variety of post-hoc analyses have been conducted using data from the ASPREE trial.
Cancer history: One secondary analysis found that participants with a history of cancer had higher baseline CVD risk, however, aspirin was no better than placebo at mitigating CVD risk in this population [41].
Atrial fibrillation: A post-hoc analysis including 17,267 ASPREE participants without atrial fibrillation and 983 with incident probable atrial fibrillation found that there was no significant difference in the incidence of atrial fibrillation between the aspirin and placebo groups (HR: 0.96, 95% CI 0.85 to 1.09) [42].
Blood pressure: An analysis of longitudinal changes in blood pressure in the ASPREE trial participants found small (-0.03 to -0.05 mmHg) non-significant changes in blood pressure with aspirin therapy, irrespective of baseline antihypertensive therapy status [43]. A meta-analysis of 17 articles including 1,807 patients examining low-dose aspirin (100 mg) for primary or secondary prevention of CVD found that the effect of aspirin on blood pressure was influenced by the time of day of aspirin administration [44]. Participants who took aspirin before bedtime were more likely to experience reductions in blood pressure relative to those taking it in the morning.
Diabetes: A post-hoc analysis including 16,209 ASPREE participants without type 2 diabetes at baseline identified 995 cases of incident type 2 diabetes over a median of 4.7 years in trial participants. The incidence rate was 15% lower in participants treated with aspirin relative to placebo (HR: 0.85, 95% CI 0.75 to 0.97) [45]. Additionally, aspirin use was associated with a slower rate of increase in free plasma glucose concentration at year five (between-group difference estimate -0.048 mmol/L, 95% CI -0.079 to -0.018).

Secondary prevention: BENEFIT ESPECIALLY IN COMBINATION WITH RIVAROXABAN
In people with diagnosed cardiovascular disease or prior stroke, aspirin is clinically recommended to reduce the risk of myocardial infarction, stroke, and cardiovascular-related death [46]. Aspirin has been widely used as an antithrombotic therapy in this population. However, studies suggest that dual pathway inhibition is superior to aspirin alone. Rivaroxaban (Xarelto®) is a direct-acting oral anticoagulant that is an inhibitor of clotting Factor Xa [47]. It has been approved by the European Medicines Agency (EMA) for the prevention of recurrent adverse cardiovascular events in patients with coronary artery disease (CAD) and peripheral artery disease (PAD) [48]. Furthermore, the combination

of low-dose rivaroxaban with aspirin has been recommended as an antithrombotic regimen for high-risk patients with CAD by the European Cardiology Society [49].
A meta-analysis including four trials comparing low-dose aspirin and rivaroxaban with aspirin therapy in 43,859 patients with CAD or PAD found that dual pathway inhibition was superior to aspirin monotherapy in reducing MACE (HR: 0.77, 95% CI 0.69 to 0.87) and myocardial infarction (HR: 0.83, 95% CI 0.71 to 0.99) [47]. A meta-analysis sub-group including 30,193 patients with CAD or PAD found that treatment with low-dose rivaroxaban plus aspirin was associated with a reduced incidence of adverse cardiovascular events (HR: 0.86, 95%CI 0.78 to 0.94) and stroke (HR: 0.68, 95%CI 0.55 to 0.84) relative to aspirin alone [48]. A meta-analysis assessing 24 RCTs testing antithrombotic therapies in 48,759 patients with PAD concluded that long-term low-dose rivaroxaban plus aspirin was likely the best antithrombotic therapy to reduce rates of MACE and major ischemic limb events in the subgroup of patients who had undergone a peripheral vascular intervention [50]. A Bayesian network meta-analysis of 12 studies testing eight antithrombotic regimens in 122,190 patients with stable atherosclerotic cardiovascular disease identified rivaroxaban (2.5 mg 2x/day) plus low-dose aspirin as the preferred antithrombotic regimen in this population [51].

Cancer primary prevention: NO CLEAR BENEFIT
Aspirin does not appear to prevent cancer in the general population. Some analyses suggest that regular use could have a modestly protective effect in certain individuals at risk for particular types, such as digestive tract cancers, but there is a lack of clarity on the optimal dosage or duration. Consequently, formal guidelines do not recommend aspirin for this indication (USPSTF statement).
The main mechanism associated with aspirin's anti-cancer activity is the inhibition of the COX enzyme and downstream lipids, which are involved in cell signaling processes that can drive inflammation and tumor cell proliferation [52]. This may explain why some studies find that higher dose aspirin is more effective for cancer prevention relative to lower dose aspirin. However, there is evidence to suggest it may also have some COX-independent anticancer properties by influencing DNA repair pathways and epigenetic mechanisms.
A 20-year cohort study including 1,909,531 participants from Danish registries aged 40-70 years at baseline found that aspirin use was not associated with a reduction in overall cancer risk (HR: 1.04, 95% CI 1.03 to 1.06), however, continuous aspirin use for at least five years was associated with reduced incidence of some types of cancer [53]. The protective effects, typically around a 10% reduction, were primarily observed in gastrointestinal cancers, including colon, stomach, liver, pancreatic, and small intestine cancer, as well as some others, such as melanoma, meningioma, brain tumors, non-Hodgkin lymphoma, leukemia, and thyroid cancer. Higher dose aspirin (500 mg) use was associated with greater

benefit, as was initiation prior to 70 years of age. A higher incidence of lung cancer (HR: 1.21, 95% CI 1.18 to 1.24) and bladder cancer (HR: 1.16, 95% CI 1.11 to 1.20) was observed with aspirin use, but these associations could be confounded by smoking status. Smoking increases platelet aggregability and decreases the efficacy of aspirin, such that higher doses are needed in smokers. As a result, low-dose aspirin is unlikely to be effective in smokers, who are at elevated risk for various cancers, particularly lung cancer, which may confound associations in this population.

A meta-analysis including 88 cohort studies and seven RCTs assessing the effect of aspirin on common cancer risk similarly found that regular aspirin use was associated with reduced rates of some types of cancers, including a 15% reduction for colorectal cancer (based on 18 studies), a 33% reduction for gastric cancer (based on 10 studies), and a 7% reduction for breast cancer (based on 26 studies) [54]. A slightly increased risk for lung cancer was observed (RR:1.05, 95%CI 1.01 to 1.09), along with a dose-related risk for prostate cancer. Aspirin use was associated with a 7% reduction in the risk for prostate cancer across all (20) examined studies, but the protective effect only occurred with doses up to 325 mg. Studies assessing higher doses, such as 500 mg/day, found that aspirin use was associated with an increased risk for prostate cancer (HR: 1.85, 95% CI 1.04 to 3.32).

A meta-analysis including 16,654 participants from four cohort studies assessing the impact of prophylactic low-dose aspirin, and 65,768 patients from 13 cohort studies assessing the impact of low-dose aspirin use following a cancer diagnosis found that only post-diagnosis aspirin use was associated with reduced cancer mortality (OR: 0.84, 95% CI 0.75 to 0.93) [55]. This association was driven by digestive tract cancers, including colorectal, esophageal, and gastric cancer.

Colorectal cancer: The 2016 aspirin guidelines from the USPSTF included a recommendation for the use of low-dose aspirin in adults aged 50-59 for the prevention of colorectal cancer. However, this recommendation was removed from the 2022 USPSTF aspirin guidelines based on insufficient evidence of benefit for this indication. Protective effects have generally not been observed during trial periods, but only during open-label long-term follow-up [29]. Studies assessing low-dose aspirin for the prevention of cardiovascular disease with follow-up periods up to 10 years have not shown evidence of cancer prevention. Only the Women's Health Study (n = 39,876) identified a reduction in the incidence of colorectal cancer with a 17.5-year follow-up (Peto OR: 0.82, 95% CI 0.69 to 0.98), however, the effect was not maintained out to 26 years of follow-up (USPSTF). The impact on cancer mortality is highly variable across studies. Although some studies with long follow-up periods have shown evidence suggestive of benefit, they have not been properly powered for this endpoint, or adjusted for cancer risk [29].

A network meta-analysis assessing 278,694 participants from 32 trials testing 13 different interventions for the chemoprevention of colorectal cancer found that aspirin use was not associated with risk reduction in the general population [56]. In subgroup analyses, low-dose aspirin for ≥5 years was associated with reduced risk of colorectal adenoma, but the result was based on a single trial. Colorectal adenomas are precancerous neoplasms with the potential to become malignant if untreated. A network meta-analysis including 3,011 participants from eight RCTs found that low-dose aspirin (<300 mg/day) was more effective than high dose aspirin or placebo at reducing the recurrence rate of colorectal adenoma, with greater benefit for long-term use [57]. In contrast, a network meta-analysis of 11 RCTs including 92,550 participants assessing the relationship between aspirin dose and risk reduction for colorectal cancer found that high-dose aspirin (500–1200 mg/day) was likely the most effective [58]. Relative to placebo or non-use, high-dose aspirin was associated with reduced risk for colorectal cancer (OR: 0.69, 95 CI 0.50 to 0.96), whereas a similar effect was not observed for lower doses. However, there is high heterogeneity across studies, and the optimal dose may be population specific. Some studies have suggested that the effect of aspirin on colorectal cancer risk may be influenced by body weight. An analysis of ~200,000 new aspirin users and matched non-users from UK primary care datasets found that the protective effect of aspirin on colorectal cancer is not modified by body weight in the primary cardiovascular disease prevention population, but may be more apparent in those with lower body weight in the secondary prevention population [59].

Gastric cancer: A meta-analysis, including 11 case-control and 10 cohort studies, found that aspirin use was associated with a reduced risk for gastric cancer (OR: 0.64, 95%C 0.54 to 0.76) [60]. The protective effects are more apparent in studies using low-dose aspirin and with aspirin usage for longer than five years. However, the strength of results may be lessened by confounding and bias.

Ovarian cancer: An analysis including two nested case-control studies in Denmark and Sweden including 11,874 women with ovarian cancer and 473,960 matched controls found that low-dose aspirin use was not associated with ovarian cancer risk in the overall population [61]. However, it was associated with a reduced risk in women who had never given birth (OR: 0.80, 95%CI 0.70 to 0.92), which is a population with higher baseline risk for ovarian cancer stemming from a higher lifetime number of ovulation cycles.

Breast cancer: A population-based cohort study including 1,083,629 women ≥ 50 years of age in Norway assessed the association between low-dose aspirin use and breast cancer risk with a median follow-up of 11.6 years [62]. The study found that aspirin use was associated with a modestly reduced risk for estrogen receptor (ER+) breast cancer (HR: 0.96, 95% CI 0.92 to 1.00), but not for estrogen receptor

negative breast cancer. Additionally, the association was only significant in women aged ≥ 65 years, and became more prominent with longer term (≥ 4 years) use. The protective effect may be related to the inhibition of aromatase activity by blocking the COX-2/PGE-2 signaling axis, resulting in a reduction in estrogen production most relevant for postmenopausal women. A small RCT (n=55) found that six weeks of low-dose aspirin (100 mg/day) reduced estradiol levels to a greater degree than placebo (median change: − 3.5 pg/ml vs -1.5 pg/ml) in postmenopausal women [63].

The impact of a low-dose aspirin regimen in a healthy elderly population was evaluated as part of a series of sub-studies connected to the larger ASPREE trial. In general, none of these sub-studies identified a benefit for regular low-dose aspirin therapy on their primary outcomes of interest, and in some cases, aspirin was associated with worse outcomes.

Age-related macular degeneration (AMD): The ASPREE-AMD sub-study included 4,993 participants. Over a median follow-up of 3.1 years, the cumulative incidence of AMD did not differ significantly between the aspirin and placebo groups (RR: 1.02; 95% CI 0.85 to 1.22), nor did the rate of AMD progression [64].

Age-related hearing loss: A secondary analysis including 279 participants from the ASPREE trial found that aspirin use for three years was not associated with a change in the mean 4-frequency average hearing threshold from baseline to year three relative to placebo [65]. Aspirin was also not associated with a mean change in speech reception threshold over time.

Fracture risk: The ASPREE-FRACTURE sub-study included 16,703 participants. Over a median follow-up of 4.6 years, aspirin use was not significantly associated with fracture risk (HR: 0.97, 95% CI 0.87 to 1.06), but was associated with an increased risk for serious falls (total falls 884 vs 804; incidence rate ratio 1.17, 95% CI, 1.03 to 1.33) [66]. It is possible that the dose of aspirin (100 mg/day) was too low to modulate the pathways involved in bone remodeling observed in preclinical studies.

Depression: ASPREE-D was a sub-study including 1,879 ASPREE participants with depression at baseline [67]. Aspirin had been proposed to have an effect on depression through its anti-inflammatory properties, however, this study did not demonstrate a benefit for aspirin. Instead, aspirin use was associated with a significant increase in depressive scores relative to placebo. Although the level of baseline inflammation was not assessed, due to the general healthy nature of the population, systemic inflammation levels were likely to be lower than average, suggesting that the possible effect of aspirin on depressive symptoms could be modulated by baseline inflammatory status.

MASLD: POTENTIAL BENEFIT

Low-dose aspirin (81 mg/day) was tested in a Phase 2 double-blind, placebo-controlled RCT (NCT04031729) in 80 patients with metabolic dysfunction-associated steatotic liver disease (MASLD) without evidence of cirrhosis for six months [68]. The trial met its primary endpoint of the mean absolute change in hepatic fat content by magnetic resonance spectroscopy (MRS) at six months (−6.6% with aspirin vs 3.6% with placebo; difference, −10.2%, 95% CI, −27.7% to −2.6%). Those treated with aspirin also exhibited a greater reduction in relative hepatic fat content (−8.8 vs 30.0 percentage points; mean difference, −38.8 percentage points 95% CI −66.7 to −10.8), and a greater reduction in absolute hepatic fat content by MRI-PDFF (−2.7% vs 0.9%; mean difference, −3.7%, 95% CI −6.1% to −1.2%). Seventy-one participants completed the study, and similar results were observed in this per-protocol population. Significantly more participants in the aspirin group achieved a reduction in levels of the liver transaminase ALT of 17 IU/L or more (32.4% vs 8.8%), and a hepatic fat reduction of 50 percentage points or more (24.3% vs 5.9%). The protective effects are hypothesized to stem from the modulation of platelet and immune cell activation. Larger studies are needed to confirm these effects.

Covid-19: POTENTIAL BENEFIT FOR REDUCING COVID-RELATED MORTALITY
Meta-analyses of trials testing aspirin in patients hospitalized with covid-19 found that aspirin use was associated with a reduced risk for mortality. A meta-analysis of 14 studies including 164,539 hospitalized covid-19 patients found that aspirin use was associated with a reduced risk of in-hospital mortality, with a pooled effect size of 0.71 (95 % CI 0.59 to 0.85) [69]. The protective effect may be related to a reduction in coagulopathy and thromboembolic events, majors driver of mortality in patients with severe covid-19 [70]. Similarly, a meta-analysis of 17 studies including 49,041 patients hospitalized with covid-19 also found that aspirin use (adjusted RR: 0.69, 95% CI 0.50 to 0.95), particularly low-dose aspirin (adjusted RR: 0.64, 95% CI 0.48 to 0.85), was associated with a reduced risk of mortality [71]. A meta-analysis of six studies including 13,993 hospitalized covid-19 patients observed an association between low-dose aspirin use (75–325 mg/day) during or prior to hospitalization and reduced mortality (RR: 0.46, 95% CI 0.35 to 0.61) [70]. The optimal timing or dose was not established.

Safety: ***Rated B for potential and A for evidence*** Aspirin is associated with an increased risk for bleeding, particularly in the GI system, as well as in the brain. The bleeding risk increases with age.

Types of evidence:

- 15 meta-analyses of RCTs and/or observational studies assessing safety
- 2 studies assessing risk factors for aspirin-induced ulcers

Bleeding: The primary risk associated with aspirin is bleeding. Most of these bleeds occur in the gastrointestinal tract but bleeds can occur in the brain as well. Randomized trials may underestimate these risks due to the shorter timeframe and the highly selective participants of clinical trials. In one study of over 186,000 Italians, a low-dose aspirin taken for 5.7 years was associated with higher rates of hemorrhagic events (RR: 1.55, CI 1.48-1.63), with 20 more major bleeding events per 10,000 treated patients [72]. Numerous meta-analyses of clinical trials and observational studies indicate that aspirin use is associated with an increased risk for gastrointestinal bleeds, though some analyses find that the risk is only significant for higher dose aspirin. An analysis including 92,550 participants from 11 RCTs testing aspirin for chemoprevention found that low-dose aspirin was associated with a higher rate of gastrointestinal bleeding (OR: 1.24, 95% CI 1.08 to 1.44), but the risk was lower relative to high dose aspirin (OR: 0.47, 95 % CI 0.27 to 0.90) [58]. Another meta-analysis of trials testing aspirin for chemoprevention of colorectal cancer including 94,854 participants found that aspirin use was associated with an increased risk for bleeding (RR: 1.77, 95% CI 1.44 to 2.17), but the effect was not significant when limited to studies testing low-dose (≤100 mg) aspirin (RR: 1.56, 95% CI 0.98 to 2.49) [73]. A separate analysis found that the risk of upper gastrointestinal bleeding with aspirin was not modified by body weight [59]. A pooled analysis of 10 RCTs including 133,194 participants testing low-dose aspirin for the prevention of CVD or colorectal cancer found an increased incidence of total bleeding events with aspirin (OR: 1.44, 95% CI 1.32 to 1.57) [29]. Similarly, a meta-analysis including 29,814 participants with type 2 diabetes testing low-dose aspirin for primary CVD prevention found that aspirin was associated with an increased risk of major bleeding (RR: 1.24, 95% CI 1.03 to 1.48) [35]. A meta-analysis of 13 RCTs testing low-dose aspirin (≤100 mg/day) for primary CVD prevention including 134,446 participants assessed the risk of intracranial hemorrhage. The analysis found that aspirin was associated with an increased risk of intracranial hemorrhage (RR:1.37, 95% CI 1.13 to 1.66), particularly for subdural or extradural hemorrhage [74].

The risk of GI bleeding increases in elderly people and is twice as high in men than women [75]. It is also higher in patients with a history of ulcer disease or GERD/dyspepsia symptoms. The risk may also be increased by the concurrent use of drugs like corticosteroids, anticoagulants, antiplatelet therapies, SSRIs, and calcium- channel blockers [76]. Gastrointestinal bleeding risk or ulcer risk from aspirin may be somewhat decreased by proton pump inhibitors (PPIs) [77]. Aspirin that is enteric-coated or buffered is probably no safer than plain aspirin for GI bleeds [78]. The presence of the ulcer-causing bacteria *Helicobacter pylori* was associated with increased risk for low-dose aspirin-induced ulcers, relative to those without the bacteria (OR: 1.68, 95%CI 1.40 to 2.02) in a meta-analysis of 17 studies including 5,964

participants [79]. The risk was highest in those not taking antisecretory drugs (OR: 1.94, 95%CI 1.54 to 2.46), suggesting that PPIs have a protective effect. A genome-wide association study (GWAS) assessing genetic risk for aspirin-induced peptic ulcer disease identified the variant rs12678747, resulting in lower expression of EYA1 in the gastrointestinal epithelium, as a risk factor (OR: 2.03, 95% CI 1.65 to 2.50) [80].

Sensitivity: Some people have an aspirin sensitivity and cannot tolerate the drug, with possible resulting respiratory tract disease or urticarial/angioedema.

Drug interactions: According to Drugs.com, there are 347 drug interactions with aspirin, including 54 major interactions. These include other blood thinners, such as warfarin and heparin, other NSAIDs, corticosteroids, and SSRI antidepressants (NHS). Aspirin also has interactions with some herbal medications with antiplatelet properties such as gingko, ginger, and ginseng. Aspirin has a minor interaction with caffeine and a moderate interaction with alcohol. Consuming alcohol while taking aspirin can increase the risk of stomach bleeding. An analysis of potential drug interactions between aspirin and ACE inhibitors based on electronic health records from CVD patients found that the safety and tolerability of aspirin with enalapril or lisinopril was potentially superior to the combinations of aspirin with fosinopril, perindopril, and ramipril [81].

Dosing and Sources:
Low-dose aspirin is typically defined as between 75-100 mg/day. Most clinical trials tested doses of 100 mg/day, however, the most common OTC formulation is 81 mg oral tablets.
USPSTF recommendation: The decision to start a low-dose aspirin regimen in adults aged 40-59 with high CVD risk and low bleeding risk is an individual one. It is not recommended for CVD or cancer primary prevention for the general population.
American Heart Association: Low-dose aspirin may be considered for the primary prevention of atherosclerotic CVD in adults aged 40-70 with high CVD risk but low bleeding risk. It is not recommended for primary CVD prevention in adults over age 70 or those with elevated bleeding risk [82].
American Diabetes Association: Low-dose aspirin is recommended for primary CVD prevention in adults (≥50) with diabetes and elevated CVD risk and at least one additional CVD risk factor [83].
European guidelines: Low-dose aspirin is not recommended for primary CVD prevention due to increased risk of bleeding. It is not recommended for healthy people >70 years old. It can be considered in patients with diabetes at high CVD risk (International Aspirin Foundation).

Research underway:

According to Clinicaltrials.gov, there are currently around 500 active trials involving aspirin. Some trials of interest include several trials assessing the impact of aspirin on colon cancer survival, aspirin use for the prevention of gastric cancer (NCT04214990), COLchicine and Non-enteric Coated Aspirin in the Cardiovascular Outcomes Trial of patients with Type 2 Diabetes (COLCOT-T2D) (NCT05633810), Efficacy and Safety of Aspirin in Patients with Chronic Coronary Syndromes without Revascularization (ASA-IN) (NCT05347069), Chronotherapy with Low-dose Aspirin for Primary Prevention of Cardiovascular Events in Subjects with Impaired Fasting Glucose or Diabetes (CARING Study) (NCT00725127), ASPIrin in Reducing Events in Dialysis (ASPIRED) (NCT04381143), and Aspirin to Target Arterial Events in Chronic Kidney Disease (ATTACK) (NCT03796156).

Search terms:

Pubmed, Google: low dose aspirin +

- Cognitive, dementia, Alzheimer's vascular dementia, stroke-related dementia, mortality, lifespan, cardiovascular, cancer, clinical trial, meta-analysis, safety

Websites visited for Low-dose aspirin:

- Clinicaltrials.gov
- Examine.com
- DrugAge
- Drugs.com
- Drugbank.ca
- PubChem

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