

# Medicines Management Programme

## Guidance on the use of aspirin in the primary prevention of cardiovascular disease



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## Abbreviations

AAA	Aspirin for asymptomatic atherosclerosis
ABI	Ankle brachial index
ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
AHT	Anti-hypertensive treatment
ARI	Absolute rate increase
ARRIVE	Aspirin to Reduce Risk of Initial Vascular Events
ASCEND	A Study of Cardiovascular Events in Diabetes
ASCVD	Atherosclerotic cardiovascular disease
ASPREE	Aspirin in Reducing Events in the Elderly
ATT	Antithrombotic Trialists
BIHS	British and Irish Hypertension Society
BMD	British Male Doctors
CABG	Coronary artery bypass grafting

CCS	Canadian Cardiovascular Society
CDS	Community drug schemes
CHD	Coronary heart disease
CKD	Chronic kidney disease
COX-1	Cyclooxygenase-1
CV	Cardiovascular
CVD	Cardiovascular disease
DP	Drug Payment
ED	Erectile dysfunction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ETDRS	Early Treatment of Diabetic Retinopathy Study
GI	Gastrointestinal
GMS	General Medical Services
HDL-C	High-density lipoprotein cholesterol
HOT	Hypertension Optimal Trial
HSE	Health Service Executive
HTA	Health technology assessment
ICH	Intracranial haemorrhage
IHD	Ischemic heart disease
IPD	Individual patient data
ITFPCMD	International Task Force for the Prevention of Cardio Metabolic Disease
JBS3	Joint British Societies 3rd consensus statement
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
JPPP	Japanese Primary Prevention Project
LDL-C	Low-density lipoprotein cholesterol
LTI	Long Term Illness
MI	Myocardial infarction
MMP	Medicines Management Programme
NICE	National Institute of Health and Care Excellence
PAD	Peripheral arterial disease
PHS	Physician's Health Study
POPADAD	Prevention of Progression of Arterial Disease and Diabetes

PPP	Primary Prevention Project
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
SBP	Systolic blood pressure
SCORE	Systematic coronary risk evaluation
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic lupus erythematosus
SmPC	Summary of product characteristics
TIA	Transient ischemic attack
TC	Total cholesterol
TPT	Thrombosis Prevention Trial
USPSTF	United States Preventative Services Task Force
WHS	Women's Health Study

## Glossary

- For the purpose of this document, the use of **significant** or **non-significant** refers to the statistical rather than clinical significance of a result.
- **Relative risk** refers to the odds of an event occurring when the odds of two groups are compared with each other, e.g. a group taking aspirin versus a group taking placebo.
- **Absolute risk** refers to the ratio of people who have an event, compared to all of the people who could have an event and is expressed as a percentage.

## **1. Purpose**

The use of aspirin in the secondary prevention of cardiovascular disease (CVD) is well established and strongly supported by an unequivocal net benefit.<sup>1,2,3,4</sup> However, its use in primary prevention is off-label, and uncertainty remains as to whether aspirin provides a favourable balance of benefit to harm in this context.<sup>5,6</sup> This is reflected in the contradictory positions of international bodies in their guidance on the use of aspirin in the primary prevention of CVD (see Appendix A).

## **2. Scope**

The aim of this document is to review clinical evidence and guidelines and to provide a recommendation on the use of aspirin in the primary prevention of CVD. This guidance will only consider the use of aspirin in the primary prevention of CVD (an off-label use).

This guidance should be used in conjunction with clinical judgement. Full prescribing information for licensed indications is available in the summary of product characteristics (SmPC) for aspirin for individual medicinal products.

## **3. Cardiovascular disease**

### **3.1 Definition**

CVD encompasses a group of disorders of the heart and blood vessels including:<sup>7</sup>

- coronary heart disease
- cerebrovascular disease
- peripheral arterial disease
- congenital heart disease
- rheumatic heart disease
- deep vein thrombosis
- pulmonary embolism

Such diseases can cause the occurrence of acute events such as a myocardial infarction (MI), ischemic stroke or transient ischemic attack (TIA). Despite a dramatic reduction in rates of CVD in the past 30 years, circulatory diseases were the second most common cause of death in Ireland in 2017, accounting for 29% of all deaths.<sup>8,9</sup>

### **3.2 Prevention**

CVD prevention is defined by the European Society of Cardiology (ESC) as a coordinated set of actions, at the population level or targeted at an individual, that are aimed at eliminating or minimising the

impact of CVD and their related disabilities. This can be achieved by tackling unhealthy lifestyles (e.g. poor-quality diet, physical inactivity and smoking) and by optimising risk factors, such as hypertension and dyslipidemia.<sup>10</sup> Implementing these actions from an early age is strongly associated with low CVD risk profiles as an individual gets older.<sup>11</sup>

Primary prevention involves avoiding the onset of CVD in patients who have not yet developed clinically manifested CVD, while secondary prevention is the prevention of the recurrence of cardiovascular (CV) events or complications of CVD in patients with established CVD.<sup>7</sup> Risk assessment tools are widely recommended by clinical bodies such as the ESC for the primary prevention of CVD (see table 1).<sup>10</sup>

### **3.3 CVD risk estimation tools**

Estimating an individual's CV risk is a key component of the prevention of CVD in adults and can be obtained using a global risk score.<sup>12-14</sup> A range of risk scores are recommended by different clinical bodies internationally (see table 1). The ESC recommend a systematic CV risk assessment at least every five years using the Systematic Coronary Risk Evaluation tool (SCORE) or other locally validated risk scores. This is recommended in individuals at increased CV risk, and in men >40 years and in women >50 years of age with no known CV risk factors. Individuals automatically categorised as high- or very-high CV risk, such as individuals with documented CVD or chronic kidney disease (CKD), do not need the use of a risk score but rather require immediate attention to risk factors (see Appendix B).<sup>10</sup> The National Institute of Health and Care Excellence (NICE) also recommend estimating an individual's risk of CVD on an ongoing basis using the QRISK2 tool in adults >40 years of age (soon to be updated to the QRISK3). This tool is not recommended in patients with type 1 diabetes, pre-existing CVD or an estimated glomerular filtration rate (eGFR) less than 60ml/min/1.73m<sup>2</sup> and/or albuminuria.<sup>15</sup>

**Table 1.** Examples of 10-year cardiovascular disease global risk scores

Name of global risk score	What the risk score calculates	Low chance of an event occurring	Moderate chance of an event occurring	High chance of an event occurring	Age range (years)	Recommended by	Factors used to determine an individual's CV risk
ASSIGN-SCORE <sup>13</sup>	10-year risk of CVD events	Not defined	Not defined	≥20%	30-74	SIGN	Age, Sex, TC, HDL-C, SBP, Smoking status, Diabetes status, Deprivation, Family history
Framingham <sup>13</sup>	10-year risk of CVD events	<10%	10% - <20%	≥20%	30-75	CCS, NVDPA	Age, Sex, AHT, Diabetes status, Smoking status, SBP, TC, HDL-C
Pooled Cohort Studies Equations <sup>16</sup>	10-year risk of 1 <sup>st</sup> ASCVD event	<10%	10% - <20%	≥20%	20-79	AHA, ACC, USPSTF	Age, Sex, Ethnicity, TC, HDL-C, SBP, AHT, Diabetes status, Smoking status
PROCAM <sup>13</sup>	10-year risk of major coronary and cerebral ischemic events	<10%	10% - <20%	≥20%	20-75	ITFPCMD	Age, Sex, LDL-C, HDL-C, Diabetes status, Smoking status, SBP
SCORE <sup>13</sup>	10-year risk of CVD mortality	<1%	≥1% - <5%	≥5% - <10%	40-65	ESC	Age, Sex, TC or HDL-C ratio, SBP, Smoking status.
QRISK2 <sup>*17</sup>	10-year risk of CVD events	<10%	10% - <20%	≥20%	35-74	NICE and JBS3	Age, AF, AHT, BMI, CKD (stages 4- 5), Diabetes status, Deprivation, Ethnicity, Family history, RA, SBP, TC:HDL-C, Smoking Status, Sex
QRISK3 <sup>18</sup>	10-year risk of CVD events	<10%	10% - <20%	≥20%	25-84	n/a	Age, AF, AHT, Atypical AP, BMI, CKD (stages 3-5), Diabetes status, Deprivation, ED diagnosis or treatment, Ethnicity, Family history, Migraine, RA, Regular steroid tablets, SBP, SBP variable, Sex, Severe mental illness, Smoking status, SLE, TC:HDL-C

**Name of global risk score:** PROCAM: prospective cardiovascular Münster study; SCORE: systematic coronary risk evaluation

**What the risk score calculates:** ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease

**Low/moderate/high risk:** categories of CV risk depending on the score used

**Recommended by:** ACC: American College of Cardiology; AHA: American Heart Association; CCS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; ITFPCMD: International Task Force for the Prevention of Cardio Metabolic Disease; JSB3: Joint British Societies third consensus statement; NICE: National Institute of Health and Care Excellence; NVDPA: National Vascular Disease Prevention Alliance; SIGN: Scottish Intercollegiate Guidelines Network; USPSTF: United States Preventative Services Task Force

**Factors:** AF: atrial fibrillation; AHT: antihypertensive treatment; AP: antipsychotic; BMI: body mass index; CKD: chronic kidney disease; ED: erectile dysfunction; HDL-C: high density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; RA: rheumatoid arthritis; SBP: systolic blood pressure; SLE: systemic lupus erythematosus; TC: total cholesterol; TG: triglycerides

\*Both the QRISK2 and updated QRISK3 risk scores are included to reflect the use of QRISK3 in practice and the current NICE guidelines recommending QRISK2



Table 1 includes examples of some 10-year CVD global risk scores used by various international bodies. For example, the SCORE tool recommended by the ESC gives a measure of a person's 10-year risk of CVD mortality, i.e. fatal CVD. Those with a score of <1% are defined as having a low risk of CVD mortality, those with a score of 1% - <5% are defined as having a moderate risk of CVD mortality and those with a score of ≥5- <10% are categorised as high risk. Individuals whose risk is >10% have a very high risk of CVD mortality.<sup>10</sup>

**The European Society of Cardiology and the National Institute of Health and Care Excellence recommend carrying out a systematic CV risk assessment in adults at increased risk of CVD or those over 40 or 50 years (males and females respectively). This should be done on an ongoing basis using validated global risk scores such as SCORE or QRISK2.**

### **3.4 Management of modifiable risk factors**

All current guidelines on the primary prevention of CVD in clinical practice recommend the assessment of total CVD risk before management decisions are made. Modifiable risk factors identified from this estimation which contribute to a person's individual risk of CVD can then be appropriately managed, e.g. dyslipidemia, smoking, hypertension.<sup>10</sup> While guidelines are consistent in their recommendation for the estimation of an individual's risk of CVD, they differ substantially in their recommendations on the use of aspirin for the primary prevention of CVD (see Appendix A).<sup>5,6</sup>

## **4. Aspirin**

### **4.1 Mode of action**

Aspirin, or acetylsalicylic acid, has analgesic, anti-inflammatory, anti-pyretic and anti-thrombotic actions.<sup>19</sup> Its anti-thrombotic action is mediated through the inhibition of platelet activation by an irreversible acetylation of the cyclooxygenase-1 (COX-1) enzyme and subsequent inhibition of platelet-generated thromboxane A<sub>2</sub>. It is this anti-thrombotic action which is utilised in the primary and secondary prevention of CV events.<sup>20</sup>

### **4.2 Licensed indications**

Aspirin is currently licensed in Ireland for the following therapeutic indications:

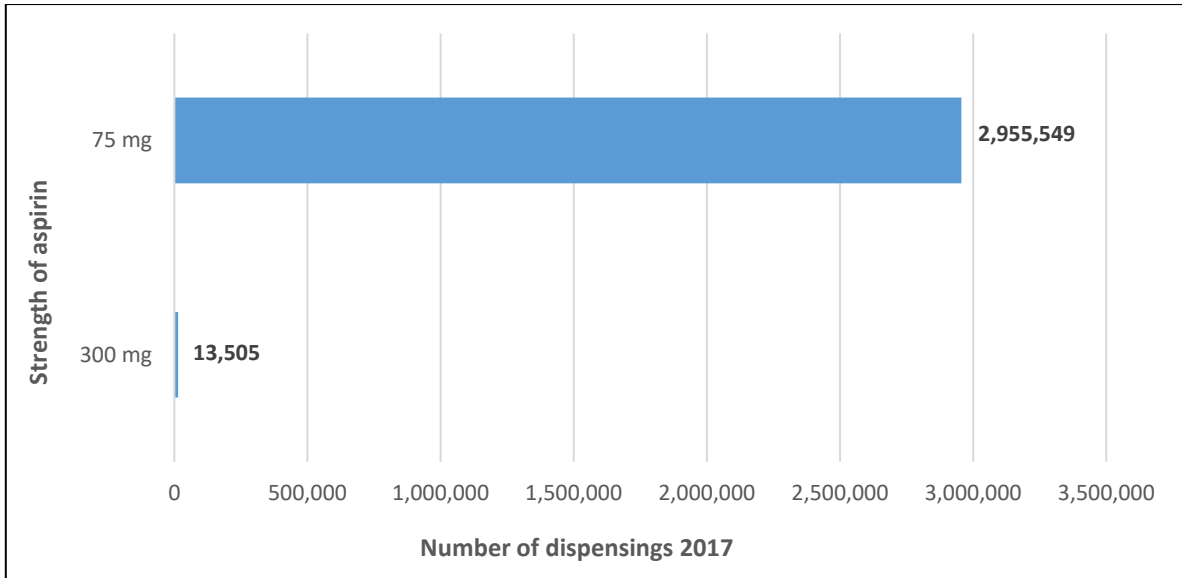
1. Secondary prevention of MI<sup>21</sup>
2. Prevention of CV morbidity in patients suffering from stable angina pectoris<sup>21</sup>
3. Patients with a history of unstable angina pectoris, except during the acute phase<sup>21</sup>
4. Prevention of graft occlusion after coronary artery bypass grafting<sup>21</sup>
5. Coronary angioplasty, except during the acute phase<sup>21</sup>
6. Secondary prevention of TIA and ischaemic cerebrovascular accidents, provided intracerebral haemorrhages have been ruled out<sup>21</sup>
7. Reduction of the risk of occlusive stroke and recurrent cerebral TIA in patients with a history of such thrombotic events<sup>12</sup>
8. As an analgesic, anti-pyretic and anti-inflammatory agent.<sup>22</sup>

The recommended dose of aspirin varies depending on the indication, ranging from 75 mg daily for the secondary prevention of MI to a maximum dose of 8 g daily when used as an analgesic and anti-inflammatory agent in acute rheumatic disorders.<sup>21,22</sup> Aspirin is not licensed for the primary prevention of CVD and therefore its use in this context represents an off-label use of this medicine.

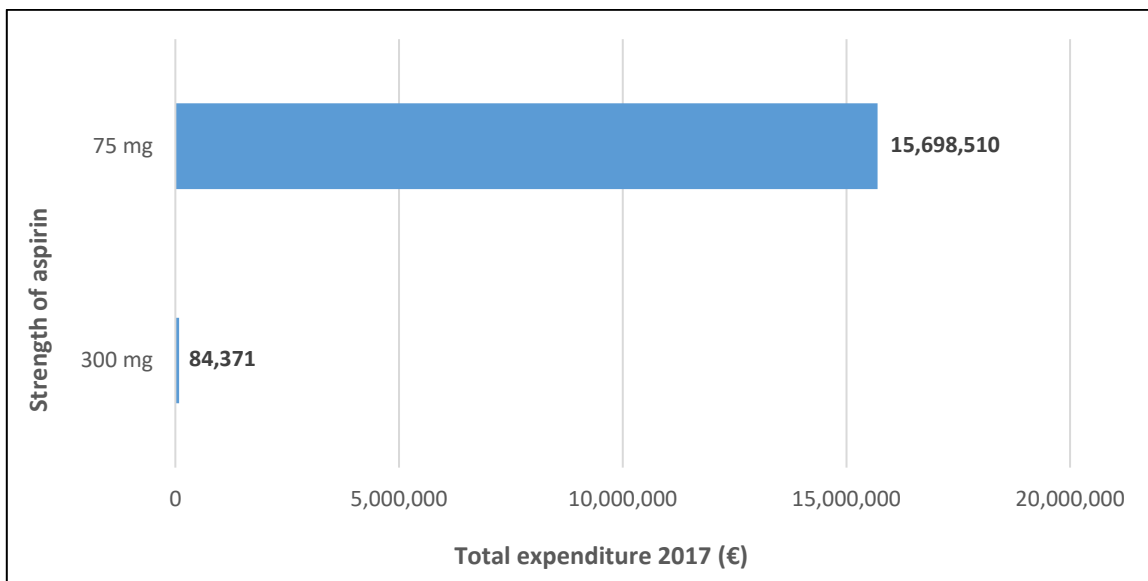
**Aspirin is not licensed for the primary prevention of CVD in Ireland.**

#### **4.3 Utilisation and expenditure**

Aspirin was the most frequently dispensed medicine under the Community Drug Schemes (CDS) in 2017.<sup>23</sup> Medicinal products containing aspirin 75 mg and aspirin 300 mg are currently reimbursed in Ireland, with the lower strength accounting for 99% of aspirin dispensings.<sup>24</sup> In 2017, over 2.95 million prescriptions were issued for aspirin 75 mg on the CDS, accounting for a total expenditure (including ingredient cost, dispensing fees and VAT where applicable) of €15.6 million under the Drug Payment (DP), General Medical Services (GMS) and Long Term Illness (LTI) schemes combined.<sup>25</sup>



**Figure 1.** Prescription frequency for aspirin 300 mg and aspirin 75 mg in 2017 under the Drug Payment, General Medical Services and Long Term Illness schemes combined<sup>25</sup>



**Figure 2.** Total expenditure for aspirin 300 mg and aspirin 75 mg in 2017 under the Drug Payment, General Medical Services and Long Term Illness schemes combined<sup>25</sup>

**Aspirin is the most frequently dispensed medicine under the Community Drug Schemes with over 2.95 million dispensings and a total expenditure of €15.6 million for the 75 mg strength in 2017.**

## **5. Clinical evidence for the use of aspirin in the primary prevention of CVD**

The majority of studies included in this review use an aspirin dose of 100mg, which is higher than the 75mg dose most frequently dispensed in Ireland. Studies have demonstrated similar benefits and harms of aspirin at both these doses.<sup>5</sup>

An initial body of evidence, comprising of trials published between 1988 and 2016, have to date formed the basis of recommendations surrounding the use of aspirin in the primary prevention of CVD (see table 2 overleaf).<sup>26-36</sup> Three large-scale primary prevention trials were published in 2018, which provided further data on the use of aspirin in this context (table 3).<sup>37-39</sup>

### **5.1 Initial trials**

Table 2 provides information on the 11 trials published between 1988 and 2016, which assessed the use of aspirin in the primary prevention of CVD.<sup>26-36</sup>

**Table 2.** Initial trials of aspirin for the primary prevention of cardiovascular disease (1988-2016)

<i>Trial</i>	<i>Year</i>	<i>Patient Population</i>	<i>Age Range (years)</i>	<i>Number of Participants</i>	<i>Follow-up (years)</i>	<i>Aspirin Dose (mg/day)</i>	<i>Placebo Control</i>	<i>Primary Endpoint</i>	<i>Change in Primary Endpoint</i>
JPAD <sup>26</sup>	2016	Patients with type 2 diabetes	30-85	2,539	10.3	100	No	Incidence of any atherosclerotic event (composite of sudden death, death from coronary, cerebrovascular and aortic causes, non-fatal acute MI, unstable angina, newly developed exertional angina, non-fatal ischemic and haemorrhagic stroke, TIA, non-fatal aortic and peripheral vascular disease)	Non-significant
JPPP <sup>27</sup>	2014	Patients with $\geq 1$ risk factor for CVD	60-85	14,464	6.5	100	No	Incidence of a composite of CV death, non-fatal stroke (ischemic, haemorrhagic or undefined) and non-fatal MI	Non-significant
AAA <sup>28</sup>	2010	Patients with ABI $\leq 0.95$	50-75	28,980	8.2	100	Yes	Incidence of a composite of initial fatal or non-fatal coronary event or stroke or revascularisation	Non-significant
POPADAD <sup>29</sup>	2008	Patients with diabetes and ABI $\leq 0.99$	$\geq 40$	1,276	6.7	100	Yes	Two primary endpoints: (1) incidence of death from CHD or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia, (2) death from CHD or stroke	Non-significant
WHS <sup>30</sup>	2005	Female Health Professionals	$\geq 45$	39,876	10.1	100 every 2nd day	Yes	Incidence of a combination of first major CV events (non-fatal MI, non-fatal stroke and CV death)	Non-significant
PPP <sup>31</sup>	2001	Patients with $\geq 1$ risk factor for CVD	45-94	4,495	3.6	100	No	Incidence of CV death, stroke (ischemic, haemorrhagic, unknown) or MI	Non-significant
TPT <sup>32</sup>	1998	Men at high risk for IHD	45-69	2,540	6.8	75	Yes	Incidence of IHD events	Significant reduction (20%)
HOT <sup>33</sup>	1998	Patients with hypertension	50-80	18,790	3.8	75	Yes	Incidence of fatal and non-fatal MI, fatal and non-fatal stroke (ischemic, haemorrhagic, unknown) and all other CV deaths	Significant reduction (15%)
ETDRS <sup>34</sup>	1992	Patients with diabetes and diabetic retinopathy	18-70	3,711	5	650	Yes	Incidence of all-cause mortality (sum of coronary death and fatal and non-fatal MI)	Non-significant
PHS <sup>35</sup>	1989	Male physicians	40-84	22,071	5	162.5	Yes	Incidence of CV mortality, MI and stroke	Non-significant
BMD <sup>36</sup>	1988	Male physicians	19-90	5,139	6	500	No	Incidence of MI, stroke (ischemic, haemorrhagic, unknown), vascular death (including sudden death, pulmonary embolism and haemorrhage)	Non-significant

AAA: Aspirin for Asymptomatic Atherosclerosis; ABI: ankle brachial index; BMD: British Male Doctors; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; ETDRS: Early Treatment Diabetic Retinopathy Study; HOT: Hypertension Optimal Treatment; IHD: ischemic heart disease; JPAD: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP: Japanese Primary Prevention Project; MI: myocardial infarction; PAD: peripheral arterial disease; PHS: Physicians Health Study; POPADAD: Prevention of Progression of Arterial Disease and Diabetes; PPP: Primary Prevention Project; TPT: Thrombosis Prevention Trial; WHS: Women's Health Study

## Key findings

- Two out of the eleven major primary prevention trials included in table 2 reported significant reductions in their primary endpoints. The HOT study reported a 15% reduction in the relative risk of fatal and non-fatal MI, fatal and non-fatal stroke (ischemic, haemorrhagic, unknown) and all other CV deaths. The TPT reported a 20% reduction in the relative risk of all ischemic heart disease (sum of coronary death and fatal and non-fatal MI).<sup>32,33</sup>
- No trial reported a significant reduction in all-cause mortality.<sup>26-36</sup>
- Three trials found significant reductions in the relative risk of non-fatal MI of 35%, 41% and 47%.<sup>27,32,35</sup>
- One trial (WHS), consisting of an all-female study population, reported a significant reduction of 19% in non-fatal stroke.<sup>30</sup>

## 5.2 Trials published in 2018

Three trials published in 2018 have provided further evidence on the use of aspirin in the primary prevention of CVD (see table 3 overleaf).<sup>37-41</sup>

**Table 3.** Trials of aspirin in the primary prevention of cardiovascular disease (2018)

<i>Trial Name</i>	<i>Patient Population</i>	<i>Age (years)</i>	<i>Number of Participants</i>	<i>Follow-up (years)</i>	<i>Aspirin dose (mg/day)</i>	<i>Placebo Control</i>	<i>Primary endpoint</i>	<i>Change in Primary Endpoint</i>
<i>ARRIVE</i> <sup>37</sup>	Patients at estimated moderate risk of CVD (10-<20% risk over 10 years)	≥55/60 (male/female)	12,546	5	100 mg	Yes	Time to first occurrence of CV death, MI, unstable angina, stroke or TIA	Non-significant
<i>ASCEND</i> <sup>38</sup>	Patients with diabetes mellitus without known CVD	≥40	15,480	7.4	100 mg	Yes	<b>Efficacy:</b> First serious vascular event (MI, stroke, TIA or death from any vascular cause excluding ICH)  <b>Safety:</b> First major bleeding event (ICH, sight-threatening bleeding in eye, GI bleed or other serious bleed)	12% ↓ risk in primary efficacy endpoint  29% ↑ risk in primary safety endpoint versus placebo
<i>ASPREE</i> <sup>39,40,41</sup>	Healthy older adults	≥65/70 (depending on ethnicity)	19,114	4.7	100 mg	Yes	First occurrence of death, dementia or persistent physical disability	Non-significant

*ARRIVE: Aspirin to Reduce Risk of Initial Vascular Events; ASCEND: A Study of Cardiovascular Events in Diabetes; ASPREE: Aspirin in Reducing Events in the Elderly; CV: cardiovascular; CVD: cardiovascular disease; GI: gastrointestinal; ICH: intracranial haemorrhage; MI: myocardial infarction; TIA: transient ischemic attack; ↓: reduced; ↑: increased*

## Key findings

- In ARRIVE and ASPREE, aspirin did not reduce the primary CV endpoints.<sup>37,39</sup>
- In ASCEND, which was carried out in patients with diabetes, a 12% reduction in the primary efficacy outcome - first serious vascular event (MI, stroke, TIA or death from any vascular cause excluding ICH)- was reported in the group taking aspirin. A 29% increase was also reported with aspirin in the trial's primary safety endpoint - first major bleeding event (ICH, sight-threatening bleeding in eye, gastrointestinal (GI) bleed or other serious bleed).<sup>38</sup>
- In ASPREE, a significant 14% increase in all-cause mortality was reported as a secondary outcome.<sup>40</sup>
- Increases in the risk of bleeding were consistently significant in the aspirin groups across the three trials, at 29% and 38% for major bleeds in the ASCEND and ASPREE trials respectively<sup>38,41</sup>, while GI bleeds increased more than two fold in the ARRIVE study.<sup>37</sup>

## 5.3 Systematic reviews and meta-analyses

Table 4 overleaf details systematic reviews and meta-analyses published since 2013, which assess the effect of aspirin in the primary prevention of CVD.<sup>5,20,42,43,44,45</sup> The 2009 Antithrombotic Trialists' (ATT) Collaboration individual patient-level data meta-analysis was also included due to its significance and use in informing international guidelines.<sup>1</sup>



**Table 4.** Systematic reviews and meta-analyses of aspirin in the primary prevention of cardiovascular disease (2009-2019)

<i>Systematic review/Meta-analysis</i>	<i>Year</i>	<i>Studies included</i>	<i>Pooled relative risk outcomes in aspirin groups</i>
<b>Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events A Systematic Review and Meta-analysis<sup>42</sup></b>	2019	ARRIVE, ASCEND, ASPREE, JPAD, JPPP, AAA, POPADAD, WHS, PPP, TPT, HOT, PHS, BMD	<ul style="list-style-type: none"> <li>• 11% ↓ in primary CV outcome (composite of CV mortality, non-fatal MI and non-fatal stroke)</li> <li>• 43% ↑ in primary bleeding outcome (any major bleeding, as defined by the individual studies)</li> <li>• No significant ↓ on all-cause or CV mortality</li> </ul>
<b>Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of RCTs<sup>5</sup></b>	2018	ARRIVE, ASCEND, ASPREE, JPAD, JPPP, WHS, PPP, TPT, HOT, PHS, BMD	<ul style="list-style-type: none"> <li>• No significant ↓ all-cause mortality</li> <li>• 47% ↑ major bleeding</li> </ul>
<b>Aspirin for the primary prevention of cardiovascular events: a systematic review for the U.S Preventative Services Task Force<sup>20</sup></b>	2016	JPAD, JPPP, AAA, POPADAD, WHS, PPP, TPT, HOT, ETDRS, PHS, BMD	In trials with aspirin dose of ≤100 mg per day: <ul style="list-style-type: none"> <li>• No significant ↓ in all-cause mortality or CV mortality</li> <li>• 14% ↓ non-fatal stroke</li> <li>• 17% ↓ non-fatal MI</li> </ul>
<b>Bleeding risks with aspirin use for primary prevention in adults: A systematic review for the U.S. Preventive Services Task Force<sup>43</sup></b>	2016	10 RCTs, 2 IPD meta-analyses, 4 cohort studies	In trials with aspirin dose of ≤100 mg per day: <ul style="list-style-type: none"> <li>• 58% ↑ GI bleeding</li> <li>• Non-significant 27% ↑ haemorrhagic stroke</li> </ul>
<b>Bleeding risk with long-term low-dose aspirin: A systematic review of observational studies<sup>44</sup></b>	2016	39 observational studies	<ul style="list-style-type: none"> <li>• 40% ↑ GI bleeding</li> <li>• 40% ↑ ICH</li> </ul>
<b>Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews<sup>45</sup></b>	2013	22 systematic reviews and 5 RCTs	<ul style="list-style-type: none"> <li>• 10% ↓ Major CV events</li> <li>• 37% ↑ GI bleeding</li> <li>• 54-62% ↑ major bleeds</li> </ul>
<b>Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials<sup>1</sup></b>	2009	WHS, PPP, HOT, TPT, PHS, BMD	<ul style="list-style-type: none"> <li>• 12% ↓ serious vascular events (did not depend on age, sex, estimated risk of CHD or history of diabetes)</li> <li>• 23% ↓ non-fatal MI</li> <li>• 50% ↑ major GI and extra cranial bleeds</li> </ul>

AAA: Aspirin for Asymptomatic Atherosclerosis; ARRIVE: Aspirin to Reduce Risk of Initial Vascular Events; ASCEND: A Study of Cardiovascular Events in Diabetes; ASPREE: Aspirin in Reducing Events in the Elderly; BMD: British Male Doctors; CI: confidence intervals; CV: cardiovascular; CVD: cardiovascular disease; ETDRS: Early Treatment of Diabetic Retinopathy Study; GI: gastrointestinal; HOT: Hypertension Optimal Treatment; ICH: intracranial haemorrhage; IPD: individual patient data; JPAD: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP: Japanese Primary Prevention Project; MI: myocardial infarction; PHS: Physicians Health Study; POPADAD: Prevention Of Progression of Arterial Disease and Diabetes; PPP: Primary Prevention Project; RCTs: randomised controlled trials; RR: relative risk; TPT: Thrombosis Prevention Trial; WHS: Women's Health Study. ↓: reduction; ↑: increase

This table is not exhaustive.

## Key findings

- Aspirin is not associated with a significant reduction in all-cause or CV mortality, in primary prevention.<sup>5,20,42</sup>
- In a 2019 systematic review and meta-analysis by Zheng *et al*, aspirin was associated with a 11% reduction in the primary CV outcome (composite of CV mortality, non-fatal MI and non-fatal stroke) and a 43% increase in the primary bleeding outcome (major bleeds).<sup>42</sup>
- In a 2018 meta-analysis by Mahmoud *et al*, aspirin was associated with an increased incidence of major bleeding (47%) and ICH (33%). The previously reported reduction in risk of MI with aspirin was not sustained when analysis was limited to more recent trials (after 2000).<sup>5</sup>
- The absolute benefits and risks of aspirin in the primary prevention of CVD are small (<1%), especially when compared to the overall burden of disease. They are also an order of magnitude smaller than those seen in the secondary prevention context.<sup>1,5,42,45</sup>
- Risks associated with aspirin use occur at a higher frequency in the primary prevention setting and are supported by statistically stronger evidence than the reported benefits.<sup>44</sup>

## 6. Factors affecting treatment effect

Factors which affect the risk/benefit of aspirin in the primary prevention of CVD include diabetes, gender, age, and baseline risk of bleeding.

### 6.1 Diabetes

Despite the two-to-four fold increased risk of CVD among patients with diabetes, the evidence to support the use of aspirin in the primary prevention of CVD in this population remains weak.<sup>46-48</sup> No difference in outcomes based on diabetes status was reported in the 2009 ATT Collaboration meta-analysis, however it did find that people with diabetes had a higher risk of major extra-cranial bleeds.<sup>1</sup> Other analyses of primary prevention trials yielded similar results for a lack of effect modification based on diabetes status and increased risks for serious bleeding.<sup>20,43,45</sup> The more recent ASCEND trial found the absolute percentage reduction in the rate of first occurrence of a serious vascular event to be 1.1%, but the absolute percentage increase in the rate of major bleeds was 0.9%.<sup>38</sup>

Guidance on the use of aspirin in primary prevention amongst patients with diabetes is conflicting. The ESC maintain that the bleeding risk exceeds the benefit of therapy, and NICE guidelines recommend against aspirin use in the primary prevention of CVD in patients with type 1 and 2 diabetes.<sup>10,49,50</sup> The American Diabetes Association state that low-dose aspirin may be considered in patients with diabetes who are at an increased risk of CVD (10-year risk >10%) and after a discussion with the patient on the risk/benefit of its use, while the American College of Chest Physicians and the US Preventative Services Task Force report no difference in aspirin effect between those with diabetes and those without.<sup>51-53</sup>

An ongoing study investigating the use of aspirin for the primary prevention of CVD in a cohort of patients with diabetes who are also taking simvastatin, will provide more evidence (ACCEPT-D trial).<sup>54</sup>

**Although patients with diabetes have a two-to-four fold increased risk of CVD, they also have an increased risk of bleeds and there is no evidence that a modification in effect exists based on diabetic status. Current guidelines from the European Society of Cardiology and the National Institute of Health and Care Excellence do not recommend the use of aspirin to patients with type 1 or type 2 diabetes without CVD.**

## 6.2 Gender

Gender affects an individual's risk of CVD and as such is featured in the calculation of all global risk scores outlined in table 1. Although some evidence from primary prevention trials exists that suggests gender alters the outcomes of aspirin in the primary prevention of CVD, systematic reviews and meta-analyses fail to support this hypothesis.<sup>1,5,20,35,42,45, 55</sup> Furthermore, this gender effect has not been demonstrated in secondary prevention trials.<sup>1</sup>

Effects on combined CVD outcomes, although similar amongst men and women, are largely driven by reductions in different individual CV events; in men a reduction in MI is seen and in women a reduction in ischemic stroke drives the overall reductions observed.<sup>1</sup> This is reflected in the separate guidelines for women published by the American Heart Association, and in the ESC recommendations on the age at which to start systematic CV risk assessments, which differ depending on gender.<sup>55</sup>

It is also widely accepted that the risk of CVD in women is deferred by 10 years when compared to men.<sup>10,55,56</sup> Although males have a higher risk of CVD than women at a given age, they also have a lower risk of mortality and better clinical outcomes after CV events such as MI.<sup>57,58</sup> The age at which systematic CV risk assessment is recommended by the ESC differs between males and females to reflect this.<sup>10</sup>

**Although gender impacts on an individual's baseline risk of CVD, there is no evidence to support the hypothesis that gender modifies the effect of aspirin on the overall risk of CVD.**

## 6.3 Age

Age is an independent risk factor for developing CVD, and as such features in all CVD risk scores mentioned in table 1.<sup>59</sup> Although not a modifiable risk factor, it is the dominant driver of CV risk, with risk approximately doubling with each advancing decade of age.<sup>1,10</sup> The majority of individuals are already at high or very-high risk of CVD at the age of 65 years, although it has been argued that risk should not be treated when it is age-driven alone.<sup>10</sup>

A number of guidelines stratify their recommendations based on age, despite older patients historically being under-represented in primary prevention trials.<sup>10,52,53,56,60</sup> Given the higher baseline risk of CVD in older people, the absolute benefits expected from taking aspirin are greater.<sup>44</sup> However, data published in 2018 on the use of aspirin in the elderly did not support this, as it did not find aspirin

to be beneficial in improving disability-free survival in a cohort of 19,114 patients aged over 70 years (65 years for Blacks and Hispanics in the United States).<sup>39</sup>

**As a patient gets older their baseline risk of CVD increases. Although traditionally under-represented in primary prevention trials, data published in 2018 on the use of aspirin in healthy elderly patients over 65 years of age reported a lack of benefit for its use in this age group.**

#### **6.4 Baseline risk of bleeds**

Aspirin significantly increases the risk of major bleeding events by 43%, even in trials mainly representing a younger age group.<sup>42</sup> Older age also plays a major role in an individual's baseline bleeding risk, with risk increasing as a person gets older, independent of aspirin.<sup>44,60</sup> A population-based study in patients aged  $\geq 75$  years found that major upper GI bleeds were at least as likely to be disabling or fatal as recurrent ischemic stroke.<sup>60</sup> This is of importance as aspirin increases the risk of upper GI bleeds in this age group by 87%, further reducing the likelihood of a net benefit.<sup>41</sup>

Perhaps the most serious side-effect related to the use of aspirin is the 33-34% increased risk of ICH, however absolute rate increases are very low (0.1%).<sup>5,42</sup>

Although no formal validated tool is available to estimate a person's risk of bleeding taking aspirin, the patient's comorbidities, medications, age and gender will inform the predictions of risk.<sup>6</sup>

**Aspirin increases the risk of major bleeding by 43%. This is particularly important in older patients who have a higher baseline risk for bleeding. The European Society of Cardiology do not recommend the use of aspirin for the primary prevention of aspirin in any age group because of this increased risk of bleeding.**

## 7. Discussion

The use of aspirin in the secondary prevention of CVD is well established.<sup>42</sup> As such, international guidelines for secondary prevention are more consistent in their recommendations in comparison to guidelines for primary prevention.<sup>6,42</sup> A number of initial trials, which were used to inform guidelines, pointed towards a net benefit for aspirin use in primary prevention, mainly driven by its apparent reduction in MI.<sup>1</sup> However, on assessing recent trials more relevant to modern-day practice, this effect on MI becomes non-significant, with a smaller reduction in total stroke reported in its place.<sup>5,42</sup>

Improved management of CVD risk factors such as smoking status, blood pressure and dyslipidemia come with clearer benefits than aspirin use, without the same level of risk.<sup>10,42,61</sup> Although analyses of primary prevention trials with aspirin suggest a 10-12% reduction in the risk of major CV events, this does not translate into a reduction in all-cause or CV mortality.<sup>4,5,42,45</sup> Combine this with the most consistent side-effect of aspirin, the increased risk of major bleeding, and the net benefit of aspirin becomes questionable.<sup>4,5,42,44,45</sup>

**Relative** risk reductions and increases are not hugely different from those seen in secondary prevention. However, when the **absolute** rate differences are reviewed, a large difference exists.<sup>1</sup> Both CV and bleeding events occur in a population without clinically manifested CVD at a very low rate, and so the benefits and risks of aspirin are small and, furthermore, closely aligned (see Appendix C).<sup>1,42</sup>

The ESC does not recommend the prescription of aspirin for the primary prevention of CVD due to the increased risk of major bleeding.<sup>10</sup> NICE do not include a general recommendation on aspirin in its guidelines on the primary prevention of CVD, except to recommend against its use in patients with diabetes.<sup>49,50</sup> Instead these clinical bodies recommend alternative strategies to reduce an individual's risk of CVD, supported by much stronger evidence and less associated risk. These strategies include lifestyle changes, lowering of low-density lipoprotein cholesterol and the management of hypertension.<sup>10</sup>

Given the knowledge that atherosclerotic processes begin long before the occurrence of an event, screening for and advice on modifying an individual's risk factors from an early age are key steps in the primary prevention of CVD.<sup>10,15,59</sup> However, the addition of a therapeutic agent to an individual's treatment regimen with firstly, modest to non-significant benefits and secondly, modest risks, does not follow a contemporary evidence-based approach, particularly given the burden of medicines on many patients already.<sup>62</sup>

## **8. Conclusion**

The Medicines Management Programme (MMP) acknowledge the need for early and continued minimisation of modifiable risk factors for CVD given the long-term benefits.<sup>10,59,63</sup> There is accumulating evidence against the use of aspirin in primary prevention; and there is a body of evidence supporting widespread implementation of other strategies that work more effectively to reduce the risk of first occurrence of CV events.<sup>10</sup>

**Initiation of low-dose aspirin in adults for primary prevention of CVD is not recommended by the MMP.**

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## Appendix A: Guidance on the use of aspirin in the primary prevention of cardiovascular disease

International Body	Year of Guidance	Risk Score Used	Recommendation
World Health Organisation <sup>64</sup>	2007	WHO/ISH risk prediction chart	<ul style="list-style-type: none"> <li>• Low Risk (&lt;10%): Aspirin should not be given.</li> <li>• Moderate Risk (10-&lt;20%): Aspirin should not be given.</li> <li>• High Risk (20-&lt;30%): Aspirin should probably not be given.</li> <li>• Very High Risk (≥30%): Low-dose aspirin should be given.</li> </ul>
National Institute of Clinical Excellence <sup>49,50</sup>	2016 2017	QRISK2	<ul style="list-style-type: none"> <li>• Do not offer aspirin for the primary prevention of CVD to adults with type 1 diabetes.</li> <li>• Do not offer antiplatelet therapy for adults with type 2 diabetes without CVD.</li> </ul>
Scottish Intercollegiate Guidelines Network <sup>65</sup>	2017	ASSIGN-SCORE	<ul style="list-style-type: none"> <li>• Aspirin is not recommended for primary prevention of CVD.</li> <li>• Aspirin is not routinely recommended in people with diabetes who do not have a diagnosis of CVD.</li> <li>• Aspirin is not recommended for primary prevention of CVD in patients with hypertension.</li> <li>• There is insufficient evidence to form a recommendation on the use of aspirin for primary prevention of CVD in individuals with CKD.</li> </ul>
Joint British Societies <sup>66</sup>	2014	JBS3 risk calculator	<ul style="list-style-type: none"> <li>• There is no role for aspirin in primary prevention of CVD in type 1 diabetes.</li> <li>• Low dose aspirin is not recommended for primary prevention of CVD in patients with type 2 diabetes.</li> <li>• Routine use of aspirin is not recommended for primary prevention of CVD in CKD.</li> </ul>
British and Irish Hypertension Society <sup>14</sup>	2017	JBS3 risk calculator	<ul style="list-style-type: none"> <li>• Daily aspirin is not generally advised.</li> <li>• Aspirin may be considered beneficial if an individual's future risk of stroke or heart attack is higher than average, however aspirin should only be considered after an accurate assessment of that individual's risk by his or her doctor and after blood pressure has been controlled to target, if hypertensive.</li> </ul>

European Society of Cardiology <sup>10</sup>	2016	SCORE	<ul style="list-style-type: none"> <li>• Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.</li> <li>• Antiplatelet therapy is not recommended for people with diabetes mellitus who do not have CVD.</li> </ul>
European Society of Cardiology Working Group on Thrombosis <sup>13</sup>	2014	Risk of major CV event per 100 patient years (based on country-specific risk factor estimates)	<ul style="list-style-type: none"> <li>• Consider aspirin in the primary prevention of CVD in both sexes at a level of risk of major CV events (death, MI and stroke) &gt;2 per 100 subject-years, provided they have no clear evidence of increased risk of bleeding.</li> </ul>
American Heart Association <sup>55</sup>	2011	ACC/AHA ASCVD risk calculator	<ul style="list-style-type: none"> <li>• Aspirin therapy can be useful in women ≥65 years of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of GI bleeding and haemorrhagic stroke.</li> <li>• Aspirin may be reasonable for women &lt;65 years of age for ischemic stroke prevention.</li> <li>• Routine use of aspirin in healthy women &lt;65 years of age is not recommended to prevent MI.</li> <li>• Aspirin therapy (75-325mg) is reasonable in women with diabetes unless contraindicated.</li> </ul>
American Heart Association/American Stroke Association <sup>67</sup>	2011	ACC/AHA ASCVD risk calculator	<ul style="list-style-type: none"> <li>• The benefit of aspirin for reduction of stroke risk has not been satisfactorily demonstrated for patients with diabetes; however, administration of aspirin may be reasonable in those at high CVD risk.</li> <li>• Aspirin is not useful for preventing a first stroke in persons with diabetes or diabetes plus asymptomatic peripheral artery disease (defined as an ankle brachial pressure index ≤0.99) in the absence of other established CVD.</li> <li>• The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6 to 10%).</li> </ul>

			<ul style="list-style-type: none"> <li>Aspirin (81 mg daily or 100 mg every other day) can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment.</li> <li>Aspirin is not useful for preventing a first stroke in persons at low risk.</li> </ul>
American College of Chest Physicians <sup>53</sup>	2012	Modified Framingham risk score	<ul style="list-style-type: none"> <li>Suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy for persons aged 50 years or older without symptomatic CVD.</li> </ul>
United States Preventative Services Task Force <sup>20</sup>	2016	ACC/AHA ASCVD risk calculator	<ul style="list-style-type: none"> <li>Initiate low-dose aspirin use for the primary prevention of CVD and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.</li> <li>The decision to initiate low-dose aspirin for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one.</li> <li>The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.</li> <li>The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.</li> </ul>
American Diabetes Association <sup>51</sup>	2019	ACC/AHA ASCVD risk calculator	<ul style="list-style-type: none"> <li>Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased CV risk, after a discussion with the patients on the benefits versus increased risk of bleeding. For patients &gt;70 years of age (with or without diabetes) the balance appears to have greater risk than benefit, therefore aspirin may be considered in the context of high CV risk with low bleeding risk, but generally not in older adults.</li> <li>Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged &lt;50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding.</li> <li>Clinical judgment should be used for those at intermediate risk. Patients' willingness to undergo long-term aspirin therapy should also be considered.</li> </ul>

American Association of Clinical Endocrinologists <sup>68</sup>	2015	-	<ul style="list-style-type: none"> <li>• For primary prevention of CVD, the use of aspirin (75-162mg) may be considered for those at high risk (10- year risk &gt;10%).</li> </ul>
Canadian Cardiovascular Society <sup>46</sup>	2011	Framingham Risk Score	<ul style="list-style-type: none"> <li>• For men and women without evidence of manifest vascular disease, the use of aspirin at any dose is not recommended for routine use to prevent ischemic vascular events.</li> <li>• In special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk is low, aspirin 75-162 mg daily may be considered.</li> <li>• There is currently no evidence to recommend routine use of aspirin at any dose for the primary prevention of vascular ischemic events in patients with diabetes.</li> <li>• For patients with diabetes and aged &gt;40 years and at low risk for major bleeding, low-dose aspirin (75-162 mg daily) may be considered for primary prevention in patients with other cardiovascular risk factors for which its benefits are established.</li> </ul>
National Heart Foundation of Australia, Kidney Health Australia and the National Stroke Foundation <sup>69</sup>	2012	Framingham Risk Equation	<ul style="list-style-type: none"> <li>• Aspirin or other antiplatelet therapy is not routinely recommended for primary prevention of CVD even for those at high risk (15% absolute risk of CVD events over 5 years).</li> </ul>

ACC: American College of Cardiology; AHA: American Heart Association; ASCVD: Atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CRC: colorectal cancer; CV: cardiovascular; CVD: cardiovascular disease; GI: gastrointestinal; ISH: International Society for Hypertension; JBS3: Joint British Societies 3rd consensus statement; MI: myocardial infarction; WHO: World Health Organisation



**Appendix B: Cardiovascular risk scores from the European guidelines on cardiovascular disease prevention**

<b>Very high-risk</b>	<p>Subjects with any of the following:</p> <ul style="list-style-type: none"> <li>• Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery.</li> <li>• DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.</li> <li>• Severe CKD (GFR &lt;30 mL/min/1.73 m<sup>2</sup>).</li> <li>• A calculated SCORE ≥10%.</li> </ul>
<b>High-risk</b>	<p>Subjects with:</p> <ul style="list-style-type: none"> <li>• Markedly elevated single risk factors, in particular cholesterol &gt;8 mmol/L (&gt;310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.</li> <li>• Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).</li> <li>• Moderate CKD (GFR 30–59 mL/min/1.73 m<sup>2</sup>).</li> <li>• A calculated SCORE ≥5% and &lt;10%.</li> </ul>
<b>Moderate-risk</b>	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
<b>Low-risk</b>	SCORE <1%.

ACS: acute coronary syndrome, AMI: acute myocardial infarction, BP: blood pressure, CKD: chronic kidney disease, DM: diabetes mellitus, GFR: glomerular filtration rate, PAD: peripheral artery disease, SCORE: systematic coronary risk estimation, TIA: transient ischemic attack<sup>10</sup>

(Taken from Piepoli et al.)<sup>10</sup>

## Appendix C: Association of aspirin use for primary prevention with cardiovascular events and bleeding events

Efficacy	All patients		Low Risk		High Risk		Diabetes	
	ARD	NNT	ARD	NNT	ARD	NNT	ARD	NNT
Composite outcome	-0.38 (-0.55 to -0.20)	265	-0.34 (-0.52 to -0.14)	297	-0.51 (-0.93 to -0.06)	196	-0.65 (-1.16 to -0.10)	153
All-cause mortality	-0.13 (-0.32 to 0.07)		-0.01 (-0.27 to 0.27)		-0.43 (-0.84 to 0.02)		-0.24 (-0.91 to 0.49)	
Cardiovascular mortality	-0.07 (-0.17 to 0.04)		-0.07 (-0.16 to 0.03)		-0.04 (-0.32 to 0.27)		-0.05 (-0.94 to 1.27)	
All myocardial infarction	-0.28 (-0.47 to -0.05)	361	-0.27 (-0.49 to 0.00)	366	-0.32 (-0.74 to 0.16)		-0.26 (-0.88 to 0.47)	
All stroke	-0.09 (-0.20 to 0.04)		-0.04 (-0.21 to 0.14)		-0.19 (-0.49 to 0.16)		-0.77 (-1.48 to 0.16)	
Ischemic stroke	-0.19 (-0.30 to -0.06)	540	-0.16 (-0.29 to -0.02)	623	-0.28 (-0.63 to 0.12)		-0.83 (-1.70 to 0.50)	
Incident Cancer	0.03 (-0.37 to 0.46)		0.41 (-0.13 to 1.01)		-0.30 (-0.76 to 0.19)		-0.68 (-2.09 to 0.95)	
Cancer Mortality	0.05 (-0.11 to 0.23)		0.16 (-0.06 to 0.42)		-0.13 (-0.41 to 0.17)		0.16 (-0.56 to 1.02)	

Safety	All patients		Low Risk		High Risk		Diabetes	
	ARD	NNH	ARD	NNH	ARD	NNH	ARD	NNH
Major Bleeding	0.48 (0.34 to 0.63)	210	0.40 (0.25 to 0.57)	249	0.66 (0.36 to 1.00)	152	0.83 (0.31 to 1.43)	121
Intracranial Bleeding	0.11 (0.04 to 0.18)	927	0.13 (0.05 to 0.22)	796	0.07 (-0.04 to 0.21)		0.12 (-0.09 to 0.43)	
Major GI Bleeding	0.30 (0.20 to 0.41)	334	0.27 (0.15 to 0.40)	376	0.39 (0.16 to 0.69)	255	0.41 (0.06 to 0.86)	243

Absolute risk differences (ARDs), Number Needed to Treat (NNT) and Number Needed to Harm (NNH) for included outcomes. Negative ARD values indicate favoring aspirin, positive ARD values indicate favoring no aspirin. NNT and NNH values are reported only for outcomes with a statistically significant ARD.

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Absolute risk differences and numbers needed to treat from a 2019 systematic review assessing the use of aspirin in the primary prevention of cardiovascular disease<sup>42</sup>

(Taken from Zheng *et al.*)<sup>42</sup>