Low-Dose Aspirin Therapy for Cardiovascular Prevention
Quantification and Consequences of Poor Compliance or Discontinuation

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Abstract

Long-term therapy with low-dose aspirin (acetylsalicylic acid; ASA), 75–325 mg, is highly effective for the secondary prevention of cardiovascular (CV) events. For high-CV-risk patients to attain the full benefits of this therapy, it is important that treatment is continuous and that good compliance is maintained over the long term. We aimed to quantify the level of, and investigate the reasons for, patient-driven non-compliance and treatment discontinuation among patients taking low-dose ASA for the prevention of CV events. We therefore performed a systematic search of the PubMed, Embase, and Cochrane databases using the terms ‘aspirin’ AND ‘patient compliance’ OR ‘withdrawal’, with no restrictions on the start date and up to July 2008. A total of 32 studies, summarizing >144 800 patients, were selected from over 400 results for inclusion. Poor compliance (defined differently among the studies included) with low-dose ASA therapy ranged from approximately 10% to over 50%, and patient-initiated discontinuation of therapy occurred in up to 30% of patients. Common predictors of both non-compliance and treatment discontinuation were lower education level, female sex, or a history of depression, diabetes mellitus, or cigarette smoking. Adverse events were cited as the reason for low-dose ASA discontinuation in almost 50% of patients. The findings of this review suggest that poor compliance is common among patients receiving low-dose ASA therapy, placing them at substantial risk of CV events. By addressing barriers to compliance with low-dose ASA therapy, healthcare professionals can improve CV risk management for such patients.

Once-daily treatment with low-dose aspirin (acetylsalicylic acid; ASA), 75–325 mg, is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. Indeed, low-dose ASA is protective in most types of patients at increased risk of vascular events, including those with an acute myocardial infarction (MI) or ischemic stroke, unstable or stable angina pectoris, previous MI, cerebral ischemia, peripheral arterial disease, or atrial fibrillation. In
the primary prevention setting, in patients who are at high cardiovascular (CV) risk, treatment with low-dose ASA is recommended to be based on a 5- to 10-year CV risk profile assessment.\[1,3-5\] In an analysis conducted by the Antiplatelet Trialists’ Collaboration, antiplatelet therapy administered for 27 months as secondary prevention in approximately 20,000 patients gave a significant reduction of around 36 per 1000 at-risk patients (p<0.00001 vs controls) in the risk of a recurrent vascular event.\[6\] A significant reduction in vascular death (13 per 1000 at-risk patients; p<0.005) was also shown in these patients. In the Antithrombotic Trialists’ Collaboration analysis of low-dose ASA for prevention of serious vascular events in high-risk patients, the combined outcome of any serious vascular event was reduced by approximately one-quarter; non-fatal MI and non-fatal stroke were reduced by one-third and one-quarter, respectively.\[2\] However, the optimal dose of ASA to be used in CV prevention is currently the subject of some debate.\[7\]

The established clinical benefits of low-dose ASA therefore explain the widespread use of such therapy for secondary cardioprotection, and its use continues to increase. Data from the 2003 US Behavioral Risk Factor Surveillance System, for example, indicated that 36% of the adult population and 83% of those with CV disease (CVD) were taking regular low-dose ASA (i.e. every day or every other day); a relative increase of 12% in the use of prophylactic ASA therapy was observed from 1999 to 2003 among patients with CVD.\[8\]

Given the established clinical benefits, keeping high-CV-risk patients on low-dose ASA therapy is an important part of CV risk management. Indeed, poor compliance may increase the risk of adverse CV outcomes, including MI, stroke, and even death, as highlighted among patients with ASA ‘resistance’,\[9,10\] for which poor compliance may be a contributing factor.\[11\] Discontinuation of low-dose ASA was significantly associated with adverse clinical outcomes, such as death, MI, stroke, and major adverse CV events, in a meta-analysis of six prospective studies, comprising more than 50,000 patients at risk of coronary artery disease.\[12\] The extent of non-compliance, and the reasons for this and inappropriate discontinuation of low-dose ASA therapy, are not completely understood. In particular, the reasons for patients choosing to not adhere to therapy remain to be more fully elucidated and characterized.

We performed a systematic review of the medical literature primarily to quantify the level of non-compliance and treatment discontinuation among patients taking low-dose ASA for CV protection. Secondary objectives were to assess the evidence for predictors of non-compliance, evaluate the consequences of poor compliance in order to demonstrate the risks of patient-driven non-compliance, and to highlight the risks associated with physician-advised temporary discontinuation (e.g. in relation to planned surgery). In the context of this paper, ‘non-compliance’ or ‘poor compliance’ are defined as the failure of a patient to fully comply with a low-dose ASA treatment regimen, for any reason. The term ‘compliance’ is considered synonymous with ‘adherence’. ‘Discontinuation’ refers to complete cessation of treatment, either by the patient’s or prescribing physician’s decision, and is considered to be synonymous with ‘treatment withdrawal’. Finally, we discuss strategies that may help to improve compliance with low-dose ASA therapy.

1. Literature Search

To identify papers relevant to this review, we performed a systematic search of the PubMed, Embase, and Cochrane databases using the MeSH terms ‘aspirin’ AND ‘patient compliance’ OR ‘withdrawal’ (free-text term), with no restrictions on the start date and up to July 2008. The MeSH term ‘patient compliance’ included entry terms such as ‘non-compliance’ and ‘non-adherence’, and the MeSH term ‘aspirin’ included ‘acetylsalicylic acid’. Results were limited to full papers (clinical studies, review articles, and case reports) published in English. Following removal of duplications, an initial critique of the abstracts was undertaken to remove meta-analyses and review articles, single case study reports, studies that did not report CV-specific indications, those that did not utilize low-dose ASA, and those that did not report measurement of low-dose ASA compliance. The remaining papers were included in the review. A review of the bibliographies of selected papers was not undertaken.

Fig. 1. Geographical distribution of patients recruited to the studies. ROW = rest of world.
Compliance with Low-Dose Aspirin Therapy

The initial searches yielded over 400 publications, of which the majority (>90%) were excluded based on the criteria described above. A total of 32 studies (summarizing a total of more than 144,800 patients) were selected for inclusion. Several studies (n = 13) were included with the assumption that ‘low-dose’ ASA was used in view of the indication for CV protection.[13-25] In these instances, the authors of the publications were contacted and asked to provide ASA dosage information, where possible. In three instances, the authors were able to confirm that the doses of ASA used in their respective studies were within the low-dose range.[15,23,24] No information on doses was available for the remaining ten studies included.

Over half of the patients were from the US, with Canada and the UK contributing a further fifth of the total (figure 1). The majority of studies (n = 26) assessed patients taking low-dose ASA for secondary CV prevention; two studies were conducted in patients taking low-dose ASA for primary prevention, and the CV risk status for patients in the remaining four studies was not clearly stated (figure 2).

2. Compliance with Low-Dose ASA Therapy

The design and results (rates of discontinuation and non-compliance with low-dose ASA therapy) reported in the studies included in this analysis are summarized in table I. Studies used various methods of measuring treatment compliance. These included prescription monitoring, dosage counting, patient reporting, electronic monitoring of medication access, and biochemical testing to assess pharmacodynamic responses. Overall, the extent of non-compliance in the studies included in this systematic review ranged from approximately 10%[29,31,34] to over 50% of patients.[26,33] Compliance rates were particularly low in patients who displayed symptoms associated with depression.[26,34]

Some of the studies included in our analysis reported the rates of treatment discontinuation, rather than patient compliance rates over a period of treatment. Generally, up to 20% of patients withdrew from low-dose ASA therapy prematurely during the observed study periods.[13-15,17,18,28,30,32,36,40,44] Among 1521 patients discharged from hospital following MI with triple medication of low-dose ASA, β-adrenergic receptor antagonists (β-blockers), and HMG-CoA reductase inhibitors (statins), more than 20% discontinued the use of at least one medication, and 12.5% discontinued all three medications within 1 month.[24] Among those patients who discontinued ASA only, 1-year mortality was greater than in those continuing the medication (9.0 vs 3.0% respectively; p < 0.001); those patients who discontinued the use of all three medications had a significantly greater 1-year mortality (11.5%) than patients who continued with one, two, or all three medications (3.6%, 2.2%, and 2.2%, respectively; log-rank p < 0.001).[24] In a pharmacoeconomic analysis of over 17,000 patients who were newly prescribed low-dose ASA, 1.18 years of ASA exposure per patient was recorded during an observation period of 2.53 years; thus, patients were using low-dose ASA for only 46.6% of the study period.[33]

2.1 Predictors of Poor Compliance

2.1.1 Patient Characteristics

A number of patient characteristics found to be significant predictors of compliance and/or discontinuation in patients receiving low-dose ASA are listed in table II. Two studies examined the effect of depressive illness on compliance with low-dose ASA therapy. Among patients with major depression (defined according to the National Institute of Mental Health Standard Diagnostic Interview Schedule),[26] non-compliance with low-dose ASA therapy occurred, on average, more frequently (55% of study days) than among non-depressed patients (31%) during a 3-week treatment period. Similar results were seen in a study of patients with depressive symptoms, defined as a score of ≥10 on the Beck Depression Score.[34] In those with persistent symptoms of depression, the mean percentage of days of non-compliance during a 3-month period was 24%, compared with 11% in those who were non-depressed. Percutaneous coronary intervention performed during the study period was associated with greater consistent use of low-dose ASA and β-blocker therapy (odds ratio [OR] 2.27; 95% CI 2.01, 2.57), in a multivariable analysis of long-term compliance with evidence-based therapies in patients with...
### Table I. Summary of the design details and relevant results of the 32 studies included in this review

<table>
<thead>
<tr>
<th>Study</th>
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<th>ASA dosage</th>
<th>Major endpoint(s)</th>
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<td>Carney et al. 1995[26]</td>
<td>Prospective cohort study lasting 3 weeks in the US</td>
<td>55 patients aged ≥65 years with CVD (10 of whom [18%] had major depression)</td>
<td>81 mg bid</td>
<td>Compliance with low-dose ASA therapy (assessed by an electronic medication monitor)</td>
<td>Non-depressed patients adhered to therapy on 69% of the study days compared with 45% for depressed patients (p &lt; 0.02)</td>
</tr>
<tr>
<td>Carney et al. 1998[27]</td>
<td>Prospective non-randomized study in the US. Patients were given 3 weeks’ supply of low-dose ASA</td>
<td>65 patients ≤75 years with ischemic heart disease (28 with and 37 without angina symptoms)</td>
<td>81 mg bid</td>
<td>Compliance (assessed using electronic medication monitor)</td>
<td>Symptomatic patients were 62.4% compliant, while patients with silent ischemia were 77.4% compliant (p &lt; 0.03). Compared with asymptomatic patients, symptomatic patients had significantly higher scores on the Beck Depression Inventory (p = 0.01) and Autonomic Perception Questionnaire (p = 0.007)</td>
</tr>
<tr>
<td>De Schryver et al. 2005[28]</td>
<td>Retrospective, secondary analysis of two prospective trials (DTT[29] [Netherlands] and SPIRIT[26] [Australia, Netherlands, Portugal, UK])</td>
<td>3796 patients with a TIA or minor ischemic stroke</td>
<td>DTT: 30 or 283 mg od SPIRIT: 30 mg od</td>
<td>Treatment continuation</td>
<td>Eight percent of patients were not continuing with low-dose ASA therapy after a mean of 2.1 years without a clear medical reason. Older age (≥65 years) was associated with premature treatment withdrawal (HR 1.31; 95% CI 1.04, 1.64), as was higher dosage of ASA (HR 1.31; 95% CI 1.05, 1.65)</td>
</tr>
<tr>
<td>Eagle et al. 2004[13]</td>
<td>Prospective, observational study, investigating continuation of low-dose ASA, β-blockers, statins, or ACE inhibitors (Argentina, Australia, Belgium Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, UK, US)</td>
<td>13 830 evaluable patients discharged for MI or unstable angina</td>
<td>Not established</td>
<td>Treatment continuation</td>
<td>Of the 12 463 patients taking low-dose ASA, 92% were still receiving it at a median follow-up of 6 months. Younger patients, those treated by a cardiologist, and those who did not have heart failure were significantly more likely to continue with treatment</td>
</tr>
<tr>
<td>Hamann et al. 2003[30]</td>
<td>Prospective observational study in Germany</td>
<td>2640 patients with acute stroke or TIA followed up for 1 year</td>
<td>80–325 mg</td>
<td>Treatment continuation (self-reported during telephone questionnaire)</td>
<td>Of patients prescribed low-dose ASA therapy at discharge, 93% were still taking it at the 3-month follow-up. At 1 year, 84% were still receiving low-dose ASA, with 13% having changed to other medication, and only 4.5% taking no secondary preventative medication</td>
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<td>Komiya et al. 1994</td>
<td>Prospective observational study (location not stated)</td>
<td>238 patients (128 taking low-dose ASA and 110 receiving ticlopidine) for TIA or cerebral infarction</td>
<td>81 mg</td>
<td>Compliance with therapy assessed by platelet aggregation</td>
<td>15% of the 87 outpatients prescribed low-dose ASA therapy had high platelet aggregation levels (implicating non-compliance and/or resistance). During interview of 19 patients non-responsive to either treatment, 17 patients (7%) admitted non-compliance; of these, 11 were aspirin recipients</td>
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<tr>
<td>Kulkarni et al. 2006</td>
<td>Prospective observational study (location not stated)</td>
<td>1326 patients following cardiac catheterization for CVD taking an average of six medications at discharge (95% were prescribed low-dose ASA)</td>
<td>Not established</td>
<td>Treatment continuation and compliance (assessed by telephone questionnaire at 1 year)</td>
<td>Of patients prescribed low-dose ASA at discharge, 83% were still continuing with therapy at 1 year. Compliance with low-dose ASA therapy (78%) was higher than for β-blockers, ACE inhibitors, or statins (40–67%). Significantly more adherent patients were men, married, and better educated than patients who had discontinued therapy. The more medications patients were prescribed, the less likely they were to be treatment-compliant (p &lt; 0.05)</td>
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<tr>
<td>Mant et al. 2007</td>
<td>Prospective, randomized, controlled trial (BAFTA) of warfarin vs low-dose ASA lasting 2.7 years (mean follow-up) in the UK</td>
<td>973 patients aged ≥75 years with atrial fibrillation or atrial flutter</td>
<td>75 mg</td>
<td>Serious cerebrovascular events (also assessed treatment continuation)</td>
<td>Warfarin was more effective than low-dose ASA for preventing cerebrovascular events. Continuation of therapy for the duration of the study was 67% for warfarin and 76% for low-dose ASA. However, of the patients who discontinued low-dose ASA therapy, 70% either switched to or remained on warfarin</td>
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<tr>
<td>Morant et al. 2004</td>
<td>Retrospective, case-controlled, cohort study in the UK</td>
<td>17,244 newly prescribed low-dose ASA users (each with 10 matched comparators)</td>
<td>≤325 mg</td>
<td>Cost analysis of low-dose ASA use (including renal and GI complications)</td>
<td>Following a mean of 2.53 years of observation, newly prescribed users of low-dose ASA took the medication for only 46.6% of the time</td>
</tr>
<tr>
<td>Rieckmann et al. 2006</td>
<td>Prospective cohort study lasting 90 days in the US</td>
<td>165 patients with ACS taking low-dose ASA</td>
<td>81 or 325 mg</td>
<td>Compliance (≥75% of medication, assessed using MEMS)</td>
<td>Non-compliance rates were 10.5% in non-depressed patients, 9.8% in remittently depressed patients, and 42.1% in persistently depressed patients (p &lt; 0.001)</td>
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<tr>
<td>Sappok et al. 2001</td>
<td>Prospective cohort study lasting 1 year in Germany</td>
<td>386 evaluable patients with ischemic stroke or TIA</td>
<td>250 mg</td>
<td>Treatment continuation (assessed by telephone questionnaire)</td>
<td>86% of the patients discharged on low-dose ASA were still receiving it at follow-up. Higher age, non-smoking status, and more severe neurological deficit were associated with high treatment continuation rates</td>
</tr>
<tr>
<td>Silagy et al. 1994</td>
<td>Prospective, randomized, placebo-controlled trial (PACE) in Australia</td>
<td>400 subjects aged ≥70 years without previous CVD</td>
<td>100 mg</td>
<td>Compliance (assessed by pill count throughout 12 months)</td>
<td>87% of patients were compliant with therapy. Of a subset of 13 low-dose ASA-treated subjects who reported being compliant, one had no inhibition of platelet aggregation</td>
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<tr>
<td>Simpson et al. 2003</td>
<td>Retrospective cohort study, using data from a drug claims database in Quebec, Canada to monitor completed prescriptions over 1 year</td>
<td>14 057 patients with first-time acute MI aged ≥65 years (9134 of whom were prescribed low-dose ASA)</td>
<td>Not established</td>
<td>Compliance (collected prescribed drug in days 305–365 after discharge). Treatment continuation (collected prescriptions covering at least 80% of the year after discharge)</td>
<td>One-year compliance with low-dose ASA therapy was 74.4%. The low-dose ASA continuation rate during 1 year was 71.4%. Prescriptions of low-dose ASA at discharge were suboptimal, with only 65% of patients being prescribed long-term low-dose ASA therapy</td>
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<td>Sud et al. 2005</td>
<td>Prospective cohort study using data from telephone questionnaire in the US</td>
<td>208 patients with ACS</td>
<td>Not established</td>
<td>Treatment continuation and compliance (over the mean 10-month follow-up)</td>
<td>Use of ASA therapy decreased from 94.7% at discharge to 87.3% at the follow-up survey. The most commonly cited reason for treatment withdrawal was physician recommendation (62.5%). Also, 46% of patients prescribed low-dose ASA had some degree of non-compliance with therapy</td>
</tr>
<tr>
<td>Waeger et al. 1999</td>
<td>Prospective substudy of a randomized, double-blind, placebo-controlled trial (HOT) in patients from Germany, Italy, Switzerland, and the UK</td>
<td>501 hypertensive patients</td>
<td>75 mg od</td>
<td>Compliance (assessed using MEMS during 1 year)</td>
<td>Overall, 78.3% of patients were compliant with low-dose ASA or placebo. Compliance was significantly better during the first 6 months of treatment than thereafter (p &lt; 0.001)</td>
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<tr>
<td>Wald et al. 2007</td>
<td>Prospective cohort study in the UK lasting 2 years (undergoing PCI)</td>
<td>242 patients with CVD</td>
<td>Not established</td>
<td>Continuation</td>
<td>At discharge, 98% of patients were prescribed low-dose ASA as part of their cardioprotective regimen; 82% were still taking low-dose ASA at 2 years (p &lt; 0.001)</td>
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### Table 1. Continued

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| retrospective, telephone-survey-based study | 1358 patients hospitalized due to ACS taking or not taking oral antiplatelet agents | 75–250 mg | Therapeutic changes over time. | Outcomes associated with bleeding or ischemic events at 30 days. 

Both patients had an ischemic MI (one fatal, one 3 days and one 4 days following cessation of low-dose ASA therapy) |

Of 449 patients who had a previous history of CVD, only 65% had been receiving long-term antiplatelet therapy (97% of these were receiving low-dose ASA). Recent withdrawal of antiplatelet therapy also increased the risk of bleeding events (OR: 2.58; *p* = 0.0096) and death (OR: 2.05; *p* = 0.03) at 30 days. |

Recent withdrawal of antiplatelet therapy significantly increased the risk of death (p0.017) and MI death (p < 0.001) than those who regularly took low-dose ASA. |

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<td>Matsuzaki et al.</td>
<td>Case reports (Japan)</td>
<td>331mg (both patients)</td>
<td>Outcome following withdrawal</td>
<td>Two patients due to undergo CABG</td>
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<td>Collet et al.</td>
<td>Prospective, cohort study in France</td>
<td>11 CVD patients who had discontinued low-dose ASA therapy ≤15 days before admission for acute MI</td>
<td>Time to MI after low-dose ASA withdrawal</td>
<td>MI occurred within a mean of 9.4 days following cessation of low-dose ASA therapy</td>
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<td>Bachman et al.</td>
<td>Case reports (US)</td>
<td>13 patients who had discontinued low-dose ASA therapy</td>
<td>Cerebrovascular events</td>
<td>12 patients had a cerebrovascular event within 3 weeks of cessation of low-dose ASA therapy, and one within 6–8 weeks</td>
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<td>Califf et al.</td>
<td>Prospective, questionnaire-based study in the US</td>
<td>25,049 patients with CVD</td>
<td>Therapy changes over time. Effect of low-dose ASA use on long-term outcomes</td>
<td>Use of low-dose ASA increased over time from 59.2% in 1995 to 80.5% in 1999. Patients never taking low-dose ASA had a 1.85 times greater risk of death (p &lt; 0.0001) and 1.49 times greater risk of MI/death (p &lt; 0.0001) than those who regularly took low-dose ASA.</td>
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<td>Wang et al.</td>
<td>Retrospective, telephone-survey-based study in China</td>
<td>472 evaluable patients (434 on low-dose ASA) with ischemic stroke or TIA</td>
<td>At discharge, 2.3% (n = 10) were prescribed £40 mg/day and the remainder &gt;50 mg/day</td>
<td>Continuation (over 1 year of follow-up)</td>
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Of the 434 patients prescribed low-dose ASA at discharge, 70.5% were at least partially compliant with their discharge prescription at 1-year follow-up. Of these, 54.2% were taking low-dose ASA at the same or similar (variance within 80–120 mg per day) discharge dose. However, 29.5% were not receiving any antithrombotic treatment. |
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<td>McFadden et al. 2004[21]</td>
<td>Case reports (US)</td>
<td>Four patients who had sirolimus-eluting or paclitaxel-eluting stents implanted and who had discontinued antiplatelet therapy</td>
<td>Not established</td>
<td>Incidence of late-stent thrombosis</td>
<td>Thrombosis can arise very late after implantation of a single drug-eluting stent in a large vessel, when antiplatelet therapy is discontinued</td>
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<tr>
<td>Mitchell and Sethia 1999[22]</td>
<td>Case reports (UK)</td>
<td>Five patients discontinuing low-dose ASA therapy prior to transurethral prostatectomy</td>
<td>Not established</td>
<td>Outcome following ASA withdrawal</td>
<td>After discontinuation of low-dose ASA therapy, the following events occurred: TIA (within 8 days); brachial thrombus (within 11 days [1 day post-operation]); dense right hemiplegia (within 17 days [7 days post-operation]); fatal MI during operation (time since discontinuation not stated); fatal stroke (within 9 days)</td>
</tr>
<tr>
<td>Newby et al. 2003[40]</td>
<td><em>Post-hoc</em> analysis of two randomized, controlled trials (SYMPHONY [33 countries] and 2nd SYMPHONY [35 countries]) lasting median 94 days</td>
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<td></td>
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<td>5337 patients prescribed low-dose ASA following ACS</td>
<td>80 mg bid</td>
<td>Discontinuation of low-dose ASA therapy (with decision taken in conjunction with physician)</td>
<td>Of the patients randomized to receive low-dose ASA, 17.5% discontinued treatment early; 52% of these, representing &gt;9% of all high-risk post-ACS patients, did not maintain chronic low-dose ASA therapy Patients who discontinued low-dose ASA therapy were older, and more likely to be black and female, and have diabetes, hypertension, and prior MI, PCI, and bypass surgery</td>
</tr>
<tr>
<td>Sibon and Orgogozo 2004[41]</td>
<td>Prospective, cohort study in France</td>
<td>320 patients with TIA, or ischemic or hemorrhagic stroke</td>
<td>75–250 mg</td>
<td>Antiplatelet drug discontinuation prior to the event</td>
<td>13 patients (4.5%) had an ischemic stroke within 6–10 days following discontinuation of antiplatelet therapy &lt;1 month previously (11 of whom [85%] had been taking low-dose ASA). The mean delay between discontinuation and ischemic stroke was 7.4 days</td>
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<tr>
<td>Cotter et al. 2004[42]</td>
<td>Prospective, cohort assessed for 12 months in Israel</td>
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<td></td>
<td></td>
<td>73 patients post-MI</td>
<td>100 mg</td>
<td>Death, reinfarction or rehospitalization for unstable angina. Admission for any CV cause. Compliance (assessed by platelet thromboxane B2 production and interview)</td>
<td>Overall, 29% of patients displayed insufficient inhibition of platelet aggregation, including 16% of the cohort who admitted non-compliance and 12% who claimed consistent low-dose ASA use. Patients who admitted non-compliance were 6.3 times more likely to suffer serious ischemic events (95% CI 2.4, 7.7, ( p = 0.0005 )) and 4.1 times more likely to be readmitted (95% CI 3.0, 5.2, ( p = 0.0001 )) vs those compliant with or non-responsive to low-dose ASA</td>
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Table I. Contd

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>ASA dosage</th>
<th>Major endpoint(s)</th>
<th>Relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrari et al. 2005[23]</td>
<td>Prospective cohort preceding low-dose ASA use (France)</td>
<td>383 patients with known CVD from 1236 ACS admissions</td>
<td>100–160 mg (personal communication)</td>
<td>Coronary events</td>
<td>A total of 51 coronary events occurred within 1 month of discontinuing low-dose ASA therapy, representing 13.3% of patients with known CVD; the mean delay between low-dose ASA withdrawal and coronary event was 10 days. Twenty of the 51 patients discontinuing low-dose ASA therapy did so due to non-compliance. Patients stopping aspirin therapy were more likely to have ST-segment elevation ACS than those continuing low-dose ASA therapy (39% vs 18%, p &lt; 0.001)</td>
</tr>
<tr>
<td>Glynn et al. 1994[43]</td>
<td>Retrospective subset analysis of a randomized, placebo-controlled trial (Physicians’ Health Study), lasting 60 months (US)</td>
<td>22 071 male physicians free of MI and cerebrovascular disease</td>
<td>325 mg every 2 days</td>
<td>Association between compliance and cardiovascular outcomes</td>
<td>After 60 months, the mean adherence rate was 79.6% in low-dose ASA recipients. Multivariate analyses showed that non-compliant subjects were more likely to be cigarette smokers (p &lt; 0.001), overweight (p = 0.012), have angina (p = 0.006) and not exercise regularly (p &lt; 0.001) compared with participants with good compliance. In the low-dose ASA group, ≥95% compliance led to a 41% (95% CI 1, 65) reduction in MI risk, relative to those with &lt;50% compliance. The corresponding reduction in the risk of stroke was 29% (not statistically significant), while the risk of death increased approximately 4-fold in non-compliant patients (p &lt; 0.0001 vs those with good compliance)</td>
</tr>
<tr>
<td>Ho et al. 2006[24]</td>
<td>Prospective, cohort study (PREMIER) in the US</td>
<td>1521 evaluable patients prescribed combination therapy of low-dose ASA, β-blockers, and statins following MI hospitalization</td>
<td>325 mg (68% of patients), 162 mg (4%) or 81 mg (28%) (personal communication)</td>
<td>Continuation with therapy at 1, 6, and 12 months; 12-month mortality</td>
<td>Overall, 66.3% of patients were still taking all three medications at 1 month, with older patients (particularly women), those who did not graduate from high school, and those who were not White or married being significantly more likely to discontinue therapy (all p &lt; 0.001).</td>
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<table>
<thead>
<tr>
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<th>ASA dosage</th>
<th>Major endpoint(s)</th>
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</tr>
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<tbody>
<tr>
<td>Maulaz et al. 2005</td>
<td>Retrospective, case-controlled study in Switzerland</td>
<td>309 patients receiving low-dose ASA who suffered an ischemic stroke or TIA in the previous 6 months</td>
<td>100–300 mg</td>
<td>Association of ischemic stroke or TIA with discontinuation of low-dose ASA therapy</td>
<td>Discontinuation of combination therapy was associated with an increased risk of death (HR: 3.81; 95% CI 1.88, 7.72). The corresponding HR for discontinuation of low-dose ASA therapy was 1.82 (95% CI 1.09, 3.03). A total of 4.2% of low-dose ASA recipients discontinued therapy within 4 weeks of a cerebrovascular event. Significantly more patients discontinuing low-dose ASA therapy were men (p = 0.05 vs controls). Multivariate analysis showed that low-dose ASA discontinuation led to a 3.4-fold increase in the risk of ischemic stroke/TIA (95% CI 1.08, 10.63); the mean interval between low-dose ASA discontinuation and cerebral infarction was 9.5 days.</td>
</tr>
<tr>
<td>Newby et al. 2006</td>
<td>Retrospective analysis of patients with CVD in the US</td>
<td>31,750 patients with or without HF receiving low-dose ASA, and/or β-blockers, and/or lipid-lowering agents</td>
<td>Not established</td>
<td>Prevalence and consistency of self-reported medication use and its association with mortality</td>
<td>The use of each agent increased over the surveyed time period, reaching peak rates in 2002. At this time, 83% of patients were using low-dose ASA, and 39% were using all three agents. Overall, 71% of patients were using low-dose ASA consistently. A history of diabetes and smoking, as well as female sex, were associated with lower consistent use of low-dose ASA, while revascularization performed during or prior to the observation period was associated with greater consistent use. In multivariate modeling, consistent use of low-dose ASA was associated with greater long-term survival rates in patients with HF.</td>
</tr>
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</table>

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ASA = acetylsalicylic acid (aspirin); BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged Study; bid = twice daily; CABG = coronary artery bypass grafting; CI = confidence interval; CVD = cardiovascular disease; DTT = Dutch TIA Trial; HF = heart failure; HOT = Hypertension Optimal Treatment; HR = hazard ratio; MEMS = Medication Event Monitoring System; MI = myocardial infarction; od = once daily; OR = odds ratio; PACE = Prevention with low-dose Aspirin of Cardiovascular disease in the Elderly; PCI = percutaneous coronary intervention; PREMIER = Prospective Registry Evaluating Myocardial Infarction: Event and Recovery; SPIRIT = Stroke Prevention in Reversible Ischemia Trial; SYMPHONY = Sibrafiban vs aspirin to Yield Maximum Protection from ischemic Heart events post-acute cOroNary sYndromes; TIA = transient ischemic attack.
coronary artery disease.\[25\] In the GRACE (Global Registry of Acute Coronary Events) study, which included patients who had been discharged from hospital for an acute coronary syndrome, those who received treatment from a cardiologist were more likely to be compliant with low-dose ASA therapy (assessed using registry records) than those treated by a non-cardiologist (OR 1.45; 95% CI 1.19, 1.75; p < 0.001).\[13\] Indeed, in another study that explored the use of low-dose ASA (81–325 mg) over time, and characterized the patients who were likely to use low-dose ASA, an analysis of over 25 000 patients with documented coronary artery disease determined that low-dose ASA use was more likely when patients were under the care of a cardiologist during follow-up, or under the care of physicians who frequently referred patients for coronary angiography.\[37\] Contrasting data were found for age, with some studies indicating that older age was associated with higher continuation rates,\[15\] while others found that younger patients were more likely to persist with therapy.\[13,24,28,40\] Surprisingly, one of the most common reasons patients cited for stopping low-dose ASA therapy was recommendation from their physician, often because of an impending surgical procedure, but sometimes because the physician decided that there was no clinical indication for low-dose ASA therapy. Two studies investigated whether the discontinuation of low-dose ASA therapy was a risk factor for ischemic stroke or transient ischemic attack (TIA). In the first, which assessed 309 patients with TIA or ischemic stroke and 309 matched controls, a total of 17 subjects (13 patients and four controls) had withdrawn from low-dose ASA therapy within 4 weeks; of these, seven had done so on physician advice – six because of impending surgery and one because treatment was not considered to be clinically relevant.\[44\] In the second study, 11 of 289 patients hospitalized due to an ischemic stroke had discontinued low-dose ASA therapy within 1 month; six of these patients were advised to discontinue low-dose ASA therapy due to surgery.\[41\] A third study surveyed patient compliance with CV medications after discharge from hospital following acute coronary syndromes in a total of 208 evaluable patients; of 16 subjects who had stopped taking ASA, 11 (62.5%) had done so because their physicians did not think that it was necessary.\[17\]

### 2.1.2 Adverse Events

Gastrointestinal adverse events associated with ASA usage, such as dyspepsia and gastroesophageal reflux, and GI complications including bleeding, have been well documented even at the low doses used for primary and secondary CV prevention.\[45-48\] One of the mechanisms by which ASA damages the upper GI mucosa is related to its selectivity for cyclo-oxygenase (COX)-1 versus COX-2.\[49\] Prior reviews of the literature indicate that COX-1 is responsible for prostaglandin-mediated maintenance of the gastric mucus-bicarbonate barrier, and it is by inhibition of prostaglandin production that oral administration of ASA damages the GI mucosa.\[50\]

In a pharmacoeconomic analysis of patients who were newly prescribed low-dose ASA, 0.96 hospitalizations with upper GI diagnoses occurred per 1000 patient-years, compared with 0.45 events per 1000 patient-years among matched controls.\[33\] Once the differing risk factors for each group were taken into account, the risk of occurrence of an upper GI event in the cohort taking low-dose ASA was estimated to be 2.02 times greater than that in the comparator cohort. Of 13 hospitalizations that occurred during 13 thousand patient years of low-dose ASA exposure, 46% of the events were attributable to ASA therapy.

Overall, there is a paucity of data regarding the reasons for poor compliance with or withdrawal of low-dose ASA in patients being treated for cardioprotection. In those studies that did attempt to classify patients’ reasons for treatment discontinuation, there was a lack of specificity. For example, in their 2006 report, Newby et al.\[25\] reported that 1% of patients discontinued low-dose ASA therapy due to bleeding, but the cause and location of bleeding were not reported. This study did, however, report that a further 2.6% of patients discontinued low-dose ASA due to dyspepsia/GI upset, but it is not clear whether these symptoms were considered to be related to treatment with low-dose ASA. In the trials included in our current analysis, adverse events were reported as the reason for discontinuation of low-dose ASA in 7.4% (40 or 50 mg/day),\[36\] 18.7% (30 or 283 mg/day),\[28\] and 47.5% (250 mg/day)\[15\] of

### Table II. Patient factors predictive of non-compliance and treatment discontinuation among patients requiring cardiovascular protection with low-dose aspirin (acetylsalicylic acid; ASA)

<table>
<thead>
<tr>
<th>Predictors of low-dose ASA non-compliance</th>
<th>Predictors of low-dose ASA discontinuation</th>
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<tbody>
<tr>
<td>Depression[28,34]</td>
<td>Female sex[25]</td>
</tr>
<tr>
<td>Diabetes mellitus[25]</td>
<td>History of cigarette smoking[25,43]</td>
</tr>
<tr>
<td>Symptomatic angina pectoris[43]</td>
<td>Single marital status[14,24]</td>
</tr>
<tr>
<td>Cigarette smoking[25,43]</td>
<td>Lower level of education[14,24]</td>
</tr>
<tr>
<td>Overweight[43]</td>
<td>Less severe neurological impairment among patients who experienced ischemic stroke or TIA[15]</td>
</tr>
<tr>
<td>Female sex[25]</td>
<td>Failure to exercise regularly[43]</td>
</tr>
<tr>
<td>High pill burden and polypharmacy[14]</td>
<td>Treatment by a non-cardiologist[15]</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack.
all those patients who discontinued, but the nature of the adverse events was not defined by organ system or relation to treatment. Notably, a trend towards a positive relationship between increasing ASA dosage and withdrawal due to adverse events can be observed here. Elsewhere, discontinuation of low-dose ASA therapy was attributed to reasons other than adverse effects.\(^{[17]}\) In the report by De Schryver et al.,\(^{[28]}\) 6.5% of patients discontinued low-dose ASA therapy due to bleeding, but bleeding was defined as any major bleeding and did not report the proportion of bleeding episodes that were gastric or duodenal.

A similar figure was reported by Ferrari et al.,\(^{[23]}\) who found that 5.9% of patients who withdrew from low-dose ASA therapy did so due to bleeding (not otherwise specified). This was also the case for the study by Maulaz et al.\(^{[44]}\) who reported that over a 4-week period, among 17 patients who discontinued low-dose ASA, 29% had stopped due to bleeding complications, although the specific nature of these events was not reported.

Similarly, the reasons for non-compliance with low-dose ASA therapy were also poorly reported. The report from Komiya et al.\(^{[31]}\) was the only one to differentiate reasons for non-compliance; 29% of patients who were non-compliant quoted GI symptoms as the cause.

### 2.2 Consequences of Poor Compliance with or Discontinuation of Low-Dose ASA Therapy

Poor compliance with low-dose ASA therapy can lead to an increased risk of major CV events. In an assessment of compliance with low-dose ASA in relation to primary prevention of MI in over 22,000 male patients (The Physicians’ Health Study), those participants with excellent compliance (taking ≥95% of doses) had a 41% reduction in the risk of MI, compared with those with poor adherence (taking <50% of doses).\(^{[43]}\) In another study of patients admitted to hospital with suspected acute coronary syndrome, recent discontinuation of low-dose ASA therapy (n = 73) was associated with a higher 30-day rate of death or MI than continuous (within 3 weeks of admission) use (n = 355; 21.9% vs 12.4%; p < 0.017).\(^{[38]}\) Overall, discontinuation of low-dose ASA therapy (including in relation to planned surgery) was associated with: an increased risk of MI,\(^{[20,22,27-39,43]}\) stroke,\(^{[22]}\) or death,\(^{[24,37,38]}\) and increased 30-day death and bleeding rates;\(^{[38]}\) an increased risk of ST-segment elevation coronary syndrome,\(^{[23]}\) ischemic stroke,\(^{[41,44]}\) or TIA;\(^{[44]}\) and an increased risk of a CV event within weeks of discontinuing therapy.\(^{[19,42]}\) It might be expected that discontinuation following a history of poor compliance would further increase a patient’s CV risk; however, this was not evaluated in the studies reporting discontinuation. Discontinuation of low-dose ASA was also associated with late in-stent thrombosis in a case series of four patients who had received drug-eluting stents >1 year previously.\(^{[21]}\)

### 3. Overview of Compliance Issues

Overall, the published data included in this analysis indicate that poor compliance and treatment discontinuation are common among patients prescribed low-dose ASA therapy for primary or secondary cardioprotection, placing these patients at substantially increased risk of CV events including MI, ischemic stroke, and death. Non-compliance with preventive agents is common; previous studies have found similar non-compliance rates of approximately one-quarter to one-third in patients receiving calcium and vitamin D supplements as secondary fracture prevention;\(^{[51]}\) remitted patients with depression;\(^{[52]}\) patients with type 2 diabetes\(^{[53]}\) and those at high risk of developing type 2 diabetes;\(^{[54]}\) and patients infected with human immunodeficiency virus treated with antiretroviral agents.\(^{[55]}\) Indeed, non-compliance rates as high as 79% were reported in a medical-ward population receiving prophylaxis for venous thromboembolism\(^{[56]}\) and 76% in adolescent liver transplant recipients.\(^{[57]}\) Comparison of treatment compliance between studies is difficult, however, as there are various methods of measurement, with varying reliability. For example, in the two aforementioned studies,\(^{[56,57]}\) compliance was determined by patient record review and multiple methods (including biochemical testing). Other methods to measure compliance include assessment of prescription records and patient recall. Such variation in methodology may account for similar variation in results, and inaccurate reporting of compliance, particularly in association with patient reports.

Among the studies included in this analysis, the reported non-compliance rates varied, ranging from approximately 10% to over 50%, and as many as one-quarter of patients chose to discontinue taking low-dose ASA therapy following prescription, without physician direction. In turn, such patients are at risk of CV events, including death from cardiovascular causes, which can occur within weeks of withdrawal of low-dose ASA therapy.\(^{[19,20,22,23,39,41,58]}\) Withdrawal of treatment appears to represent a particular concern among patients with drug-eluting stents, who are at high risk for late in-stent thrombosis, especially during the first year following stent placement.

A number of previously published studies have noted a rebound effect following withdrawal of low-dose ASA,\(^{[59,60]}\) in that abnormally high levels of arachidonic acid metabolites are detected up to 2 weeks following rapid discontinuation of low-dose ASA in patients with CVD. It is possible that the
associated recovery of platelet function is responsible for the increase in the risk of major CV events.\(^{[61,62]}\) There is also evidence to suggest that this apparent rebound effect may also have an inflammatory component, additional to that mediated by prostaglandins, as ASA doses as low as 81 mg have been demonstrated to increase serum levels of ASA-triggered 15-epi-lipoxin A\(_4\), an anti-inflammatory epimer of lipoxin A\(_4\).\(^{[63]}\) However, the mechanisms of this apparent rebound effect are poorly understood.\(^{[64]}\)

In the studies included in this review, a number of patient-related characteristics were identified as possible risk factors for poor compliance with and withdrawal of low-dose ASA therapy, primarily including depression, a history of diabetes, obesity, lack of exercise, cigarette smoking, lower education level, and female sex. Some of these factors, such as obesity, lack of exercise, and cigarette smoking, are related to an increased risk of GI symptoms. As many patients who are prescribed low-dose ASA for CV protection tend to be older, there is the possibility that co-morbid disease with associated polypharmacy\(^{[65]}\) and age-related memory impairment may contribute towards poor compliance and continuation rates. Unfortunately, in the studies included in this review, such patient characteristics were either not captured or inconsistently reported. With regard to drug-related factors that influence compliance, it is important to note that upper GI symptoms were reported by 18% of patients receiving low-dose ASA in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study,\(^{[66]}\) and by more than 60% of low-dose ASA users in a study by Laheij et al.\(^{[67]}\) In this study, patients using low-dose ASA were 1.79 times (95% CI 1.1, 2.9) more likely to experience GI symptoms than those not using low-dose ASA. Continuous low-dose ASA treatment is associated with a risk of GI problems, including peptic ulcers and their complications such as bleeding and perforation.\(^{[48,66,68,69]}\) It is possible that awareness of, or previous experience with, such events could also impact patient compliance and continuation of low-dose ASA therapy. Indeed, adverse events including bleeding were reported as the reason for poor compliance or discontinuation in up to half of the patients who were poorly compliant or who withdrew from treatment prematurely in the studies included in this systematic review.\(^{[15,28,31,36,40,44]}\)

4. How Can We Improve Compliance with Low-Dose ASA Therapy?

The identification of these reasons and risk factors allows us to understand how the barriers to compliance with low-dose ASA might be addressed, and recent publications indicate support for a multi-modal approach.\(^{[70,71]}\) Recent research has shown that better education of patients can be very helpful in improving treatment adherence, as patients who receive information in a range of formats and become informed about their disease and treatments are most likely to comply with their treatment,\(^{[72-74]}\) even when taking preventative treatment (as is the case with low-dose ASA). When informed, patients feel in control and have a better understanding of the impact of their actions. It is important that physicians understand the reasons for poor compliance and patient-initiated withdrawal of low-dose ASA therapy, especially in those groups that are more likely to be non-compliant or discontinue treatment (e.g. patients with a lower level of education completion, and those with a history of depression, diabetes, and cigarette smoking).

It appears that despite a number of publications detailing the clinical benefits of low-dose ASA therapy and the importance of continued, long-term treatment,\(^{[1-4,75]}\) there are still physicians who do not believe such treatment to be necessary and recommend cessation of secondary low-dose ASA cardioprotection to their patients.\(^{[17,44]}\) To attain the best possible benefits of this treatment for high-CV-risk patients, it is vital that all physicians treating such patients are targeted with appropriate educational initiatives.

The use of practical tools such as traditional/‘smart’ pill boxes and reminder aids, which provide patients with a practical means of helping with compliance, should also be considered in patients considered to be at high risk of non-compliance or treatment discontinuation. There is also the possibility of using electronic pill boxes, a number of which are currently available on the market, to monitor compliance.

Another strategy that addresses the issue of drug-related adverse effects, and may also substantially improve patient compliance and continuation with long-term therapy, is acid-suppression co-therapy to treat and/or prevent upper GI symptoms and complications attributable to ASA in patients at high risk of such complications. A number of studies have shown that concomitant therapy with proton pump inhibitors (PPIs) has a gastroprotective effect, in that this strategy is effective in the prevention and treatment of gastroduodenal ulcers and other upper GI adverse events associated with long-term, low-dose ASA cardioprotection.\(^{[76,77]}\) Another possibility for the treatment and prevention of upper GI symptoms and complications in users of low-dose ASA is the use of histamine\(_2\)-receptor antagonists (H\(_2\)RAs); however, PPIs have been repeatedly shown to be significantly more effective than other therapies, such as H\(_2\)RAs and antacids.\(^{[78]}\) Many patients who take low-dose ASA also take the antiplatelet agent...
clopidogrel. The existence of a clinically significant interaction between clopidogrel and PPIs has been the subject of recent debate, and conflicting data from epidemiological studies and from pharmacokinetic and pharmacodynamic studies have been published.[79-86] However, clinical data from the TRITON-TIMI 38 trial, in which one-third of the 13,608 patients randomized to prasugrel or clopidogrel were taking a PPI, showed no association between PPI use and the risk of the primary endpoint of CV death, non-fatal MI, or non-fatal stroke. Thus, these findings did not support the avoidance of concomitant PPI use in patients taking dual antiplatelet therapy.[87] The interpretation of the findings of the TRITON-TIMI 38 trial have nevertheless been the subject of some debate regarding the concomitant use of PPIs and thienopyridines in terms of possible effects on clinical outcomes.[88,89]

Combining drug therapies into a single pill or capsule has previously been shown to be successful in the management of other chronic diseases such as hypertension.[90,91] Indeed, reducing pill counts through combination formulations is highly correlated with increased compliance.[92] These benefits may, in turn, facilitate an improvement in compliance with low-dose ASA and treatment continuation rates, thereby allowing patients at high risk of GI complications to continue to manage their CV risk with low-dose ASA therapy. A combination product would be particularly valuable for patients who need continuous low-dose ASA therapy and who are also at risk of GI problems. As every ASA dose would be accompanied by a gastroprotective PPI dose, the risk of low-dose ASA therapy being interrupted by GI problems might be expected to be reduced.

Because medication compliance can be measured directly, indirectly, and subjectively (self reports), and choice of method generally depends on study setting, duration, cost, and availability of necessary resources, there is a need for the development of reliable, validated compliance measurement tools. Future research should continue to refine the means by which medication compliance and interventions to improve compliance can be measured.

This systematic review has a number of limitations that are inherent to the methods used to assess compliance in the studies included. For example, a number of the included publications reported data generated by self-reporting during telephone interviews.[13-15,17,18,30,36,37] As such, levels of compliance may have been overestimated in some studies. Another factor that may lead to overestimation of patient compliance rates is the nature of patient adherence in randomized, controlled trials; it is entirely possible that the clinical picture of patient adherence with low-dose ASA therapy in the ‘real-world’ environment is worse than the rates described in the current systematic review. Also, compliance was defined differently in the various studies included in this systematic review. For example, Rieckmann et al.[154] defined ‘good compliance’ as patients taking ≥75% of their medication as prescribed, whereas in the study by Simpson et al.[116] compliance was estimated by assessments of the number of patients (from those who obtained a discharge prescription for low-dose ASA following hospital admission for acute MI, and were still alive at 1 year post-discharge) who were still obtaining prescriptions in the days 305–365 after discharge. Another limitation of this analysis lies in the lack of specific ASA dose information available for some studies. We aimed to rectify this limitation by undertaking personal communications with the authors of these studies to establish the specific ASA dose used, where possible. There is also the possibility that patients who are poorly compliant with, or voluntarily withdraw from, low-dose ASA are also poorly compliant with other medications prescribed for CV risk management. This factor may confound the association between compliance with low-dose ASA alone and CV outcomes.

5. Conclusions

Low-dose ASA therapy is highly effective for the secondary prevention of CV events in high-CV-risk patients and, therefore, continuation of therapy is desirable in such individuals. However, the findings of this review suggest that poor compliance and discontinuation are common among patients receiving low-dose ASA therapy, and this places them at substantially increased risk of CV events including MI, ischemic stroke, and death. By taking steps to address barriers to good compliance with low-dose ASA therapy, cardiologists and allied healthcare professionals can optimize CV risk management for such patients.

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