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REVIEW

Are evidence-based cardiovascular prevention therapies being used? A review of aspirin and statin therapies

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Abstract Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States and other developed countries. While therapeutic lifestyle changes are integral to general risk reduction, drug therapy proves necessary for patients whose cardiovascular risk is above critical thresholds. Among proven medical treatments, antiplatelet therapy (mainly aspirin) and cholesterol-lowering therapy (mainly statins) are unequivocally recommended for the reduction of cardiovascular risk. Therapeutic indications for both therapies share great similarities, while critical differences are identifiable. Despite the compelling evidence, the gap between recommended practice and actualized practice is large. Between the two therapies, aspirin tends to be more underused than statins despite its more favorable cost-effectiveness. Admittedly, barriers to optimal translation and implementation of science to practice are considerable, but they are not insurmountable and effective interventions are available to overcome a variety of commonly cited barriers. This article reviews current practice guidelines regarding antiplatelet therapy and cholesterol-lowering treatment for cardiovascular prevention, available data of treatment gaps, documented barriers to guideline adherence, and promising interventions for practice improvement.

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Contents

Cardiovascular diseases (CVD), including ischemic coronary heart disease (CHD), stroke, and peripheral vascular disease, are the leading cause of morbidity and mortality in the United States [1] and other developed countries [2]. In the United States alone, over 70 million people have one or more types of CVD, and CVD causes as many deaths as the next four leading causes of death combined [1]. The estimated direct and indirect costs of CVD were about $400 billion in 2005 [1]. Because CVD events, including a high proportion of first events, are often fatal or disabling and associated with tremendous personal and societal burdens, [1] prevention is imperative. Evidence is clear that major causes of CVD are lifestyles and modifiable physiological factors and that risk factor modifications inarguably reduce CVD morbidity and mortality [3,4]. While therapeutic lifestyle changes are integral to general risk reduction, drug therapy proves necessary for patients whose cardiovascular risk is above critical thresholds. Substantial randomized and epidemiological evidence has been accumulated to foster the establishment of consensus guidelines that unequivocally recommend antiplatelet therapy (mainly aspirin) [5,6]and cholesterol-lowering therapy (mainly statins) for CVD prevention [7,8]. Therapeutic indications for both therapies share great similarities, while critical differences are identifiable. Despite the compelling evidence, the gap between recommended practice and actualized practice is large. While barriers to optimal translation and implementation of science to practice are admittedly considerable, they are not insurmountable and effective interventions are available to overcome a variety of commonly cited barriers. This article reviews current practice guidelines regarding antiplatelet therapy and cholesterol-lowering treatment for CVD prevention, available data of treatment gaps, documented barriers to guideline adherence, and promising interventions for practice improvement. We focus primarily on data from the United States but cite international studies when appropriate.

Practice guidelines

Recent medical advances have led to decreasing relevance of the distinction between primary and secondary prevention in association with a paradigm shift from viewing CVD as a dichotomous ''have-or-have-not'' condition to acknowledging the existence of a continuum of CVD risk. Cardiovascular risk is most commonly defined as absolute probability of having a major cardiovascular event e.g., myocardial infarction (MI), stroke or CVD death within a specified period of time. The current US model of determining absolute cardiovascular risk adopts Framingham risk scoring, which estimates aggregate risk for CHD [9,10] and stroke [11,12] over a 10-year period based on respective major risk factors. Treatment to lower the absolute risk can be risk factor specific e.g., smoking cessation or non-specific e.g., aspirin therapy. Treatments in the non-specific category are used to reduce risk once risk exceeds a certain threshold rather than being risk factor directed. Use of statins started as risk factor modifiers, but are being transitioned to the non-specific category [11—13].

The latest practice guidelines on antiplatelet therapy [5,6,14,15] and cholesterol-lowering therapy [7] underscore the importance of matching intensity of the treatment to absolute cardiovascular risk of the individual patient. These guidelines all recommend that antiplatelet and cholesterol-lowering therapies be initiated if absolute risk exceeds a certain threshold at which therapeutic benefit is believed to outweigh potential risk. If the absolute risk is low, initiation of such drug ther-

Table 1 Current practice guidelines on aspirin therapy for CVD prevention[a]

CVD risk categories	Recommended doses
Patients with angina, myocardial infarction, stroke or other cardiovascular diseases	75—235 mg
• Patients with increased risk of bleeding	• <100 mg
• Maintenance therapy	• 75—162 mg
Diabetics > 40 years or with other CVD risk factors	75—162 mg
Asymptomatic people who are at increased CHD risk (5-year risk of ⩾3% — USPSTF or 10-year risk of ⩾10% — AHA)	75—160 mg

[a] Aspirin therapy is contraindicated in individuals <21 years or having any of the following conditions: aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease. For these individuals, clopidogrel is recommended over ticlopidine for long-term administration.

apies is unjustified because of unfavorable risk-to-benefit balance and unwarranted financial burden. National guidelines published in other countries may vary in terms of the selection and weighting of risk factors for the assessment of absolute cardiovascular risk as well as the thresholds at which drug therapy should be initiated [16—18]. Nonetheless, those guidelines are fundamentally similar to US-issued guidelines.

Antiplatelet therapy

Table 1 summarizes current recommendations for antiplatelet therapy. National guidelines unequivocally recommend aspirin as a secondary prevention strategy in all non-contraindicated patients with known CVD, [5,6,19] given definitive clinical evidence regarding the efficacy and net benefit of aspirin in secondary cardiovascular prevention among both men and women [20]. As a primary prevention strategy, the American Diabetic Association explicitly recommends regular aspirin for all non-contraindicated persons with type 1 or type 2 diabetes over 40 or younger if they have additional cardiovascular risk factors [15]. For patients in whom aspirin is contraindicated or not tolerated, clopidogrel is recommended over ticlopidine for long-term administration [19]. Evidence is clear that aspirin therapy increases the risk of gastrointestinal bleeding and, to a lesser degree, the risk of hemorrhagic stroke [21,22]. When used for secondary prevention and for primary prevention in diabetes, the benefit from aspirin outweighs the harm [20].

Consensus is yet to be reached with respect to the threshold above which prophylactic use of aspirin confers net benefit for individuals without CVD or diabetes but otherwise at increased cardiovascular risk [14]. The latest results from the Women's Health Study concluded that aspirin lowers women's risk of stroke but it does not protect women from MI before they reach 65 years [23]. By contrast, aspirin lowers the risk of MI without affecting the risk of stroke in men [23]. As a result, careful ascertainment of the absolute benefit and risk on a case-by-case basis is essential to deciding on the use of aspirin therapy in men and, even more so in women, who have shown no clinical manifestations of CVD or diabetes.

Similar to American practice guidelines, those published in other countries also firmly recommend aspirin therapy in patients without contraindications, who have known CVD [16,24,25] but hold a more conservative view on the use of aspirin therapy in primary prevention and call for more research [24,25].

Cholesterol-lowering therapy

The US national cholesterol education program adult treatment panel (NCEP ATP) provides comprehensive algorithms for cholesterol management [7] and updates its recommendations as new evidence becomes available [8]. Low-density lipoprotein cholesterol (LDL-C) is the primary target of cholesterol-lowering treatment, and statins alone or in combination with other drugs or products e.g., nicotinic acid, ezetimibe, bile acid sequestrants, plant stanols, and plant sterols are recommended first-line drugs [7]. However, the clinical decision to initiate statin therapy must no longer be based solely on an abnormal lipid profile; instead, it should be based on global assessment of absolute cardiovascular risk (Table 2) [7,8]. New research continues to bolster the already strong evidence supporting the cardioprotective benefits of statins, especially in high-risk patients with or without known CHD even in the absence of an abnormal lipid profile [26,27]. On the other hand, primary prevention trials of statins suggest that patients at low risk of cardiovascular events should not be treated merely because of elevated cholesterol levels [7,13]. Researchers urge physicians to conduct prudent assessment of risk-benefit ratio

Table 2 Current practice guidelines on cholesterol-lowering drug therapy for CVD prevention

CHD risk	LDL threshold levels at which to initiate drug therapy[a]	LDL goal[a]
Low risk: 0—1 risk factor	⩾190 mg/dl (160—189 mg/dl: consider drug options)	<160 mg/dl
Moderate risk: 2+ CVD risk factors and 10-year risk <10%	⩾160 mg/dl	<130 mg/dl
Moderately high risk: 2+ CVD risk factors and 10-year risk 10—20%	⩾130 mg/dl (100—129 mg/dl: consider drug options)	<130 mg/dl (optional goal <100 mg/dl)
High risk: CHD or CHD risk equivalents[b]	⩾100 mg/dl (<100 mg/dl: consider drug options)	<100 mg/dl (optional goal <70 mg/dl)

[a] To convert mg/dl of LDL cholesterol to mmol/l, divide by 39.
[b] CHD equivalents include non-coronary forms of atherosclerotic disease, carotid artery disease, diabetes mellitus, and 2+ risk factors with 10-year risk for hard CHD >20%.

before recommending long-term stain therapy, particularly for primary prevention patients [28,29].

The fundamental concepts in ATP III are shared in cholesterol management guidelines released in other countries [16,18,24] that risk factors contributing to the development and progression of CHD are multiplicative and that therapeutic lifestyle change and drug therapy should be properly targeted to the risk profile of the individual. Nonetheless, these guidelines vary widely in the selection of risk factors in defining absolute risk and the determination of threshold risk levels for initiating drug therapy. By comparison, ATP III incorporates the latest evidence and recommends the most aggressive approaches.

Therapeutic gaps

Large treatment gaps exist despite the overwhelming evidence of the cardioprotective properties of aspirin and statins and the clear guidelines recommending their use.

Antiplatelet therapy

The literature suggests that antiplatelet therapy, predominantly aspirin therapy, is inadequately used across a variety of clinical settings. Aspirin use is most likely among hospitalized or recently hospitalized patients having acute cardiovascular events. Of 220,171 patients with suspected acute MI enrolled in the second national registry of myocardial infarction, 75% received aspirin within 24 h of hospital admission and only 69% of these early recipients were discharged with aspirin [17]. In a study of all area hospitals in metropolitan Worcester, Massachusetts, 91% of patients hospitalized with a validated acute MI received aspirin in 1997 vs. 49% in 1988 [30]. A study based on clinical trial data from 37 countries compared international patterns of care for patients with acute coronary syndromes and found comparable rates of aspirin use between the United States (85%) and other parts of the world, ranging from 75% in Eastern Europe to 91% in Australia/New Zealand [31]. Data from Europe also suggested comparably high rates (>80%) of aspirin use at 6 months or following a hospitalization for an acute coronary event or a coronary procedure [32]. Despite the obviously high rates of use, it is clear that aspirin is withheld from a proportion of even the highest risk patients for no apparent legitimate reasons.

Aspirin use is less likely in outpatients than in hospitalized or recently hospitalized patients and in otherwise healthy patients but at increased risk for CVD than in patients who have already had clinically manifest CVD. According to a national survey of US office-based physicians in 2002, aspirin, other antiplatelet medications, or anticoagulants were used among 44% of outpatient visits by patients having CHD [33]. A statewide telephone survey conducted in 20 states in 2001 showed that 74% of diabetic adults with CVD vs. only 38% of those without CVD used aspirin regularly [34]. Considerably lower rates of aspirin use were found using the Third US National Health and Nutrition Examination Survey (NHANES III) data, which were collected between 1988 and 1994. The rates were 37% of diabetic adults with CVD and 13% of those with CVD risk factors only [35]. A temporal trend analysis using visit-based data of outpatient care

in private physician offices and hospital outpatient clinics in the US showed only modest improvement in aspirin use for cardiovascular prevention and persistent wide treatment gaps. The proportion of patient visits where aspirin was reported increased from 22% (99% CI: 19–25%) in 1993–1994 to 33% (25–40%) in 2003 for patients with CVD, 4% (2–5%) to 12% (8–16%) for patients with diabetes, and 4% (3–5%) to 16% (11–21%) for patients with multiple cardiovascular risk factors [36].

A multitude of factors may contribute to the shortfalls in aspirin use. Some factors have been consistently found across studies, including advancing age, female gender, ethnic minority membership, non-cardiologist care, and high risk for recurrent cardiothrombotic events [17,34,35,37,38].

Cholesterol-lowering therapy

In a systematic review of studies published between 1966 and 2000, Olson and colleagues found that only 35% (range 6–62%) of patients with established CHD received cholesterol-lowering therapy [39]. However, many studies included in that review did not take into account the cholesterol levels of the patients. A medical chart audit study of all patients at a tertiary care center found that among patients having CHD who did not take statins, 88% were undertreated. Based on NHANES III, 82% of Americans with existing CHD were not at their target LDL-C goal of 100 mg/dl and 72% would require drug therapy to achieve the goal even after assuming a 10% LDL-C reduction with diet [40,41]. However, only 15% of those eligible individuals received cholesterol-lowering drug therapy, suggesting a gap of 89% [41]. Most recently, we examined statin use among outpatients in private physician offices and hospital outpatient departments in the US. In 2002, one year after the publication of ATP III Executive Summary [42], only half the patients having CHD or a CHD equivalent who were diagnosed with hyperlipidemia received a statin [43].

As to primary prevention, NHANES III data showed that 56% of 48.7 million adult Americans without CHD who had $\geqslant$2 risk factors had an LDL-C level above the recommended 130 mg/dl and 23% were eligible for drug therapy on ATP II [40]. The proportion of those eligible who actually receive cholesterol-lowering treatment was an alarming low 5%, and 70% of these persons did not receive dietary therapy either. These treatment gaps probably are even greater according to ATP III because Fedder et al. found a more than doubling effect in the number of patients eligible for primary prevention cholesterol-lowering drug therapy by switching to ATP III using Framingham risk scoring [44]. Our examination of US outpatient visits revealed that statins were reported in only 44% of patients without CHD who had hyperlipidemia and $\geqslant$2 risk factors [43].

Underutilization of lipid-lowering therapy is prevalent in many other countries as well. The second EUROASPIRE survey conducted in 15 European countries found that 61% (range 42–77%) of patients were taking lipid-lowering medications 6 months or more after being hospitalized for a coronary event [32]. Merely 16% of individuals eligible for lipid-lowering drugs for primary or secondary prevention were treated as reported in a population-based study from the Netherlands [45]. Barely 20% of the patients in a large secondary prevention cohort in Canada were prescribed statins, with prescription of statins diminishing progressively as baseline cardiovascular risk and future probability of death increased [46].

Treatment gaps also exist among patients receiving lipid-lowering therapy. Past research documented that the therapy is often not adequately titrated [47,48] and many patients are not at goal for their cholesterol levels [49]. In addition, persistence with continued statin therapy is problematic with approximately one-third of patients discontinuing the treatment after 6 months of initiation and one-half to two-thirds of patients discontinuing after 3 years [50].

In addition to baseline cardiovascular risk, a body of research showed that underutilization of lipid-lowering therapy unfavorably affects women, [51] the elderly, [47,52] and patients with angina vs. those with MI or revascularization [47,52]. Statin prescription differs also by practice, with cardiologists being more guideline adherent than primary care physicians [43].

Aspirin vs. statins

Past research has suggested that physicians may assign lower priority to aspirin therapy as opposed to other cardioprotective medications [53]. To explore the relative priority assigned to aspirin and statins, we examined trends in the prescribing of these medications using data between 1993 and 2002 from the national ambulatory medical care survey (NAMCS) and the outpatient department component of national hospital ambulatory medical care survey (NHAMCS). Complete descriptions of both surveys and yearly data can be found at http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm. The two surveys generated national estimates for medical services provided during outpatient visits in private physician offices (NAMCS)

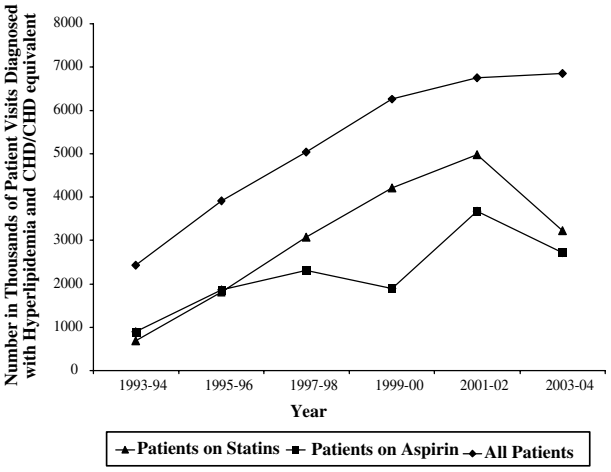

Figure 1 National Trends in Aspirin or Statin Use among Patients Visits Diagnosed with Hyperlipidemia and Heart Disease.

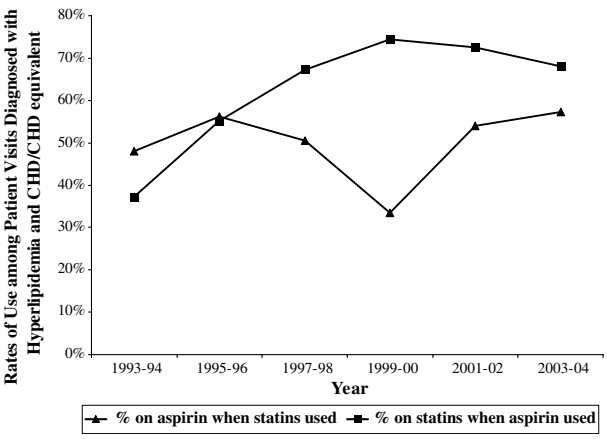

Figure 2 National Trends in Aspirin and Statin Use when the Other Therapy is Present among Patient Visits Diagnosed with Hyperlipidemia and Heart Disease.

and hospital outpatient departments (NHAMCS). To ensure comparability, our analysis specifically focused on patients having hyperlipidemia and CHD or CHD equivalents who did not have contraindications to aspirin, as documented on the standardized patient encounter form. According to practice guidelines, these patients ought to be treated with aspirin and a statin concomitantly. Aspirin use, as recorded during patients visits, more than doubled from 890,287 ± 136,015 (SD) in 1993–1994 to 1,853,624 ± 187,320 in 1995–1996 (Fig. 1). Thereafter, the number of patient visits in which aspirin was reported exhibited a generally increasing trend that was interspersed with modest declines. By 2003–2004, aspirin was recorded in 2,721,819 ± 388,276 patient visits. Statin use grew linearly from 1993 to 1994 (691,394 ± 115,712) through 2001–2002 (4982,007 ± 573,210) and declined modestly to 3,233,668 ± 389,047. Statin use exceeded aspirin use in 1999–2000 ($p < 0.05$). To further explore the relative priority assigned to aspirin and statins, we examined trends in the coprescribing of these medications. The proportion of patient visits on aspirin while a statin was used declined modestly from a peak of 56% (37–75%) in 1995–1996 to 33% (21–46%) in 1999–2000 but then rebounded to 57% (39–76%) in 2003–2004 (Fig. 2). In contrast, statin use among aspirin-treated patient visits grew successively from 37% (20–55%) in 1993–1994 to 75% (55–94%) in 1999–2000 and stabilized at 68% (50–86%) in 2003–2004. These results suggest that even though statins are themselves underused, aspirin may be given even lower priority for lowering cardiovascular risk despite its far greater cost effectiveness [54–56]. Also, data from the LIPID and CARE trials indicate that aspirin and statins used in combination are significantly more effective at reducing the relative risk of CVD events than when used alone [57].

Barriers to guideline adherence

Why do the gaps associated with aspirin therapy and statin therapy continue to persist? A survey of primary care physicians in five European countries about their attitudes towards cardiovascular treatment revealed that physicians face many barriers to the implementation of guidelines [58]. The most commonly cited barriers are lack of time, prescribing cost, patient compliance, too many guidelines, lack of awareness of guidelines, and lack of agreement with guidelines. These are common barriers cited by US physicians as well [59–61].

Studies of barriers to aspirin therapy indicate that underutilization of aspirin may be attributable to physician's perspectives including personal experiences with medications and difficulty transferring guidelines to complex clinical situations [53]. Assessment of patient risk to aspirin therapy can be puzzling, for example, when verbal and written medical history information do not agree [53]. Furthermore, physicians are yet to reach a consensus as to how much risk of excess bleeding is acceptable [62]. Data indicate aspirin use accounts for approximately 2.5% to 4.5% of the annual upper gastrointestinal events (symptomatic ulcers) and 1% to 1.5% of serious complications, such as severe bleeding, perforation, and ulceration [63]. These risk estimates should be evaluated in the context of average reductions of 15–40% in

cardiovascular events associated with preventive aspirin therapy [15,64—67].

Underutilization of statins is more prominent among patients at high or moderate risk of CHD who do not have a physician-noted diagnosis of hyperlipidemia [43]. Patients may be placed in the wrong risk stratification category, resulting in under- or mis-treatment. Physicians may be concerned with the side effects of statins, especially at high doses. Physicians may also be under prescribing statins because of cost, increased treatment complexity and workload related to the need to titrate, poor patient tolerability or adherence to treatment, and variation in treatment targets [60,61,68].

Cardiologists are most likely to prescribe both aspirin and statins [36,43]. However, in the managed care model, increasing numbers of patients do not see a cardiologist unless referred by a primary care physician who is expected to know approximately 400 practice guidelines and is less likely to prescribe either therapy [36,43,59,60,68]. In addition, physicians who are accustomed to prioritizing acute care issues may view aspirin therapy as a minor issue and thereby assign it a lower priority even compared to statin therapy, which is already underused. Statins are newer and more intensely advertised than aspirin, which may partially explain the preferential use of these drugs. Lipid-lowering medications already in 1998 ranked the fifth most promoted drug class in the US [69] Ample evidence suggests that marketing campaigns from pharmaceutical companies directed at health care professionals or consumers can both influence physician diagnosis and medication prescribing choices [70—74]. In addition, the industry, employers and insurers may exert an influence on physician prescribing indirectly through their relations to multiple facets of the health care system, e.g., reimbursement structures and use of formularies [75—78]. Patient factors can also significantly influence adherence to either drug therapy. Persistence of use of both aspirin and statins declines substantially with time, with the greatest drop occurring in the first 6 months of treatment [76,79,80]. Also, persistence is lowest in ethnic minorities, younger adults, women, and persons of low socioeconomic status [81—85]. Some studies found patients with more comorbidities or concurrent medications to have better long-term medication adherence [76,82,86]. In addition, fast improvements in risk factor outcomes (within 3—6 months) and regular follow-up monitoring tend to improve medication adherence as well [76,79,82].

Promising interventions to improve practice

Therapeutic gaps in the use of aspirin and statins for CVD prevention are just a small part of the overall quality chasm that exists in the US health care delivery system. Faced with rapidly advancing medical science and increasingly complex patient health care needs, today's US health care system fails to routinely deliver patient-centered care that is based on the best scientific knowledge [87]. Incremental improvements will not close the existing quality chasm. Instead, innovative strategies for reinventing the system are needed in four main areas: translating evidence to practice, using information technology, aligning payment policies with quality improvement, and preparing the health care workforce [87]. Evidence is mounting to demonstrate the effectiveness of intervention efforts that are in accordance with this general vision. A number of interventions have resulted in successful improvements in the use of aspirin and statins.

Dexter et al. [88] evaluated a computerized ordering system with physician reminders and found that it led to higher ordering rates of preventive therapies. Also, Siskind et al. showed that an automatic prescription tool which gives providers access to the patient's risk factors, drug initiation level and percentage of LDL reduction needed to reach NCEP goals, is effective in reducing LDL cholesterol levels [89].

An in-depth medical training program that teaches guideline-adherent use of cardiovascular drugs significantly improved the prescribing of aspirin and statins [90]. Likewise, a quality improvement program that involves a 3-tiered approach targeting patients, nurses and physicians led to increased use of aspirin and statins in patients having acute myocardial infarction [91]. In addition, treatment and discharge protocols as well as regular audits of prescribing habits and patient adherence to the regimen can increase assessment of lipid levels as well as statin prescriptions [92].

Over-the-counter availability of statins has been proposed as a potential strategy for rectifying the underutilization of this therapy [93] and research has been done to demonstrate its feasibility [94]. In 2004, simvastatin became available without prescription in UK pharmacies. In the US, applications for over-the-counter statins have been rejected by the Food and Drug Administration for a number of unsettled concerns, such as potential for misuse and abuse, drug safety and effectiveness without health professional involvement, consumers' ability to self-diagnose,

inadequate labeling, and drug cost [95]. Also, over-the-counter availability of aspirin has not necessarily insured its effective diffusion. Clearly, more research is needed before a rational policy decision can be reached.

Other schools of thought for promoting greater use of aspirin and statins include use of a single daily pill containing multiple drugs and vitamins (the polypill strategy) [96] and use of lower doses of more effective statins [61,97]. Some researchers also argue that low-dose, over-the-counter statins may represent one viable approach to addressing the treatment gap in the primary prevention population [98]. These strategies may decrease costs, simplify treatment decision-making, and improve patient compliance [61,99]. However, further research is clearly warranted.

In conclusion, the gap between the best possible care and actual care in the use of aspirin and statins as preventive cardiovascular therapies remains large. Barriers to closing the gap are formidable but not insurmountable. Evidence of effective intervention strategies is growing and should be applied in a timely fashion.

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