Formal Request for a National Coverage Determination for Aspirin Counseling for Cardiovascular Disease Prevention

Development Track

Track #1 for a new national coverage determination (NCD) request.

Benefit Categories (SSA Title XVIII)

Section 1861(s)(1)	Physicians services.
Section 1861(s)(2)(A)	Service furnished as an incident to a physician's professional service.
Section 1861(s)(2)(E)	Rural health clinic services and federally qualified health center services.
Section 1861(s)(2)(H)(i)	Services furnished pursuant to a contract under section 1876 to a member of an eligible organization by a physician assistant or by a nurse practitioner.
Section 1861(s)(2)(K)	Services which would be physicians' services if furnished by a physician and which are performed by a physician assistant (subsection (i)), nurse practitioner or clinical nurse specialist (subsection (ii)).
Section 1861(s)(2)(M)	Qualified psychologist services.
Section 1861(s)(2)(N)	Clinical social worker services.
Justification:	Per Public Law No: 110-275, the Secretary has the authority to expand Medicare coverage to include services the Secretary determines to be reasonable and necessary for the prevention or early detection of illness or disability based on evidence-based recommendations of the U.S. Preventive Services Task Force (USPSTF). Coverage will be determined by the National Coverage Determination (NCD) process and services must be recommended with a grade of A or B by the U.S. Preventive Services Task Force. The use of aspirin for cardiovascular disease prevention in selected groups is an A recommendation from the USPSTF (1996, 2002, and 2009). There is substantial evidence to support the effectiveness of aspirin in the prevention of coronary artery disease and cerebrovascular disease in eligible at-risk individuals (Wolff 2009). Using the criteria of cost-effectiveness and underuse,

Maciosek (2006) concluded that aspirin was the most valuable clinical preventive services and one that health care decision-makers should emphasize. In individuals where little benefit is expected from aspirin, the USPSTF recommends against aspirin use (a D recommendation). Because aspirin is available over-the-counter, providers also need to counsel against inappropriate aspirin use. To balance the known risks of aspirin with its benefits, the USPSTF recommends determining the suitability of aspirin through a shared decision-making approach with patients that requires extensive time investment by trained health professionals. Sufficient evidence is available to define the specific components of best practice through shared-decision making counseling (USPTF 2004, Sheridan 2010). This allows CMS to inform providers about the required tasks and to reimburse properly conducted aspirin counseling. There are multiple possible contexts in which such counseling might be delivered, including a stand-alone visit or as one service within a visit also providing other services. The current lack of a specific payment mechanism for aspirin counseling is a barrier to attaining appropriate aspirin use among Medicare beneficiaries. While other mechanisms can help CMS to improve aspirin counseling, these are unlikely to be effective on their own and would act synergistically with a targeted payment mechanism. Such a mechanism would highlight the importance of aspirin counseling and focus the activities of health providers on this critical prevention service.

Prepared for *Partnership for Prevention* by Randall S. Stafford, MD, PhD and Veronica Yank, MD, Stanford University, Program on Prevention Outcomes and Practices.

DESCRIPTION OF SERVICE: ASPIRIN COUNSELING FOR CARDIOVASCULAR DISEASE PREVENTION

Overview:

This request is for the provision of coverage for health professional aspirin counseling as detailed in the U.S. Department of Health and Human Services, Public Health Service (PHS) *Clinical Practice Guideline. Aspirin for the Prevention of Cardiovascular Disease: 2009 Update*. This statement builds on previous guidelines published in 1989, 1996 and 2002. The 2009 update emphasizes the use of shared decision-making between patients and their health provider to determine aspirin eligibility and encourage uptake in appropriate patients.

Aspirin's benefits derive from its ability to impair the function of platelets and thereby interfere with blood clotting. In doing so, aspirin reduces the occurrence of myocardial infarction and stroke by preventing the initiation and expansion of clots in the critical arteries of the heart and brain. This same mechanism explains aspirin's potential for adverse events related to excessive bleeding, particular bleeding in the gastrointestinal tract and hemorrhagic stroke. Because of these potentially life threatening risks, proper selection of patients for aspirin therapy is mandatory. Eligible patients should have a sufficiently high risk of cardiovascular disease events (so that the preventive benefit is sizable), but a low enough risk of adverse events such that a net benefit is expected. Below we review the available evidence that demonstrates aspirin's efficacy in reducing the risk of myocardial infarction in men by 32% and reducing the risk of cerebrovascular accident by 17% in women.

Data supporting the efficacy of aspirin use in appropriate populations is necessary but not sufficient to realize its potential public health benefits in those who would most benefit and mitigate its harms in those most at risk of adverse effect. Many patients who might benefit have not undergone the risk stratification and counseling necessary to alert them to this fact, whereas others may have started the medication on their own, as an over-the-counter therapy, without appropriately understanding its potential for harm. Thus, a "one size fits all" approach to aspirin prescribing has significant drawbacks. What is needed is a method of delivering appropriate advice regarding aspirin so that eligible patients receive aspirin, while patients in whom aspirin is not likely to be beneficial receive a recommendation not to take aspirin. The best delivery mechanism for this advice is individual counseling by a certified healthcare provider. A leading model for such counseling is that of patient-provider "shared decision-making," an approach endorsed by the USPSTF and others. Shared decision-making is defined as counseling by the provider and joint discussion between patient and provider through which the patient understands the condition being targeted and the preventive service, has weighed his or her values regarding the potential benefits and harms, and has engaged in decision-making at a level that he or she desires. This model of aspirin counseling is not widely used, and many patients who could benefit from aspirin are not taking this therapy. CMS strategies to encourage aspirin counseling might include provider and public education, coverage for related prevention services, provision of aspirin counseling "tool kits," and quality and performance measurement by CMS and other organizations. However, we would argue that to bring about changes in health provider practices that will substantially impact public health, provision by CMS of a reimbursement mechanism for aspirin counseling would be the most effective strategy and would be synergistic with these

others. Unless CMS provides a focused payment mechanism for aspirin counseling, aspirin likely will continue to be underused and the quality of provider-patient interactions around aspirin use will be suboptimal.

Balancing risks and benefits is an involved process that requires synthesis of information regarding cardiovascular risk factors, risk factors for adverse events, and consideration of patient values and preferences. These factors are known to vary greatly depending on gender, age, and the presence of cardiovascular risk factors. Appropriate use of aspirin requires considerable tailoring of therapy not only based on such clinical factors, but also on patients' own assessments of their personal response to risk. In particular, assessment for aspirin treatment relies on balancing the risk of adverse outcomes (e.g., gastrointestinal bleeding) with benefits from averted outcomes (myocardial infarction and stroke), events that patients may or may not consider comparable in the potential impact on their lives, and thus any discussion of balancing them requires exploration of personal values. As a result, it has been suggested by the USPSTF that determination of aspirin eligibility and a specific aspirin prescription should be determined through patient-health professional shared decision-making. (USPSTF 2004)

Currently, aspirin appears to be vastly under-used in eligible patients. Although a variety of estimates have been made, it is likely that 40% or less of eligible primary prevention patients are currently taking aspirin on a regular basis. The reasons for under-use of aspirin are complex, but likely relate to difficulties balancing aspirin's risks and harms, undervaluation of aspirin because of its low cost and over-the-counter status, and inadequate attention to primary prevention activities in primary care. In addition, lack of reimbursement for prevention tasks, including aspirin counseling, provides an additional disincentive to discussion and uptake of appropriate aspirin use. Based on both aspirin's cost-effectiveness and its current underuse, Maciosek, Coffield, et al. (2006) concluded that aspirin was most valuable clinical preventive services that can be offered in medical practice and one that decision-makers should emphasize. CMS is in an unusually powerful position to alter the landscape of aspirin counseling and aspirin use.

Since the first clinical practice guideline was published in 1989, the aspirin recommendation has become a well-established, nationally-recognized primary prevention intervention. It is endorsed and promoted by the American College of Preventive Medicine, the American Heart Association, and the American College of Cardiology. The American Medical Association's House of Delegates has passed a resolution calling for increased attention to the importance of aspirin counseling for the prevention of heart disease and stroke. Finally, the National Committee on Quality Assurance (NCQA) includes aspirin use as a HEDIS measure for eligible patients with coronary artery disease and diabetes. In addition, NCQA has developed a primary prevention performance measure assessing appropriate aspirin counseling that will be gathered via patient survey for the first time in 2010 (NCQA, 2009).

There is a particularly strong rationale for providing aspiring counseling coverage to Medicare beneficiaries. Because most beneficiaries are 65 years and older, many are at higher risk of stroke and heart attack than are younger individuals. As such, they may derive more benefit from aspirin. In addition, many non-elderly Medicare beneficiaries also may be at higher risk due to conditions that underlie their qualifying disability (e.g., chronic kidney disease). Throughout this request, we have framed our discussion broadly to encompass both elderly and non-elderly Medicare beneficiaries.

Coverage Specifications:
The science base for chemopreventive medication counseling and for aspirin use, more specifically, has been developing rapidly. This allows definition of best practices in aspirin counseling and enumeration of the components of counseling that might be required for reimbursement:

1. Initiation of discussion of aspirin's use in cardiovascular disease prevention.
2. Assessment of coronary artery disease/cerebrovascular disease risk and estimated benefits of aspirin use.
3. Assessment of the risk of adverse events, including gastrointestinal bleeding and hemorrhagic stroke.
4. Assessment of aspirin contraindications.
5. Discussion of risks, benefits, clinical alternatives, uncertainties surrounding treatment, and patient values through shared patient-provider decision-making.
6. Provision of specific advice, including aspirin formulation, frequency, and dose. If appropriate, advice to patient not to start aspirin with a plan to reassess in future.
7. Agreement on a plan for the subsequent steps, which can include, depending on the conclusion of the discussion and counseling, initiation of aspirin therapy (with a plan for subsequent assessment of adherence and for reinforcement), agreement regarding follow-up contact (e.g., visit, phone call) prior to definitive decision regarding initiation/no initiation, no further instances of shared decision-making on the topic (because of patient preference to not engage), or the like.

These coverage specifications are consistent with those described by the USPSTF in their 2009 recommendations, as well as a model practice program developed by the American College of Preventive Medicine (American College of Preventive Medicine, 2009). There are multiple possible contexts in which such counseling might be delivered, including as a stand-alone visit, a service bundled together within a new type of visit directed at cardiovascular risk reduction, or as one service within an existing type of visit that is also providing other services (e.g., as an adjunct to an evaluation and management (E/M) visit). Approaches to aspirin counseling and shared decision-making are discussed in further detail below.

Proposed Use:

To reduce the occurrence of coronary artery and cerebrovascular events among at-risk individuals who do not already have a history of coronary artery disease or cerebrovascular disease.

Medicare Population:

The Medicare population that would be targeted for aspirin counseling includes any Medicare enrollee who does not already have a history of coronary artery disease or cerebrovascular disease.

This preventive service focuses on individuals who do not have existing coronary artery disease or cerebrovascular disease, because it is expected that provision of aspirin to patients who

already have existing coronary artery disease or cerebrovascular disease will generally be reimbursed under Evaluation and Management codes for those underlying conditions. We envision that aspirin counseling may be provided either as a stand alone service or as an additional service provided at the same visit as Evaluation and Management (E&M) services. Even for those patients for whom aspirin counseling might theoretically be provided under an E&M code for a cardiovascular risk factor, a separate reimbursement mechanism will yield greater attention to appropriate counseling and result in wider implementation of this much needed service. The Medicare beneficiaries most likely to benefit from this new payment mechanism are those of older age, who have one or more broadly-defined cardiac risk factors, including high cholesterol, obesity, physical inactivity, metabolic syndrome, indicators of systemic inflammation, smoking, and hypertension. Even for patients who are 80 years and older (where the USPSTF finds "insufficient" evidence to recommend for or against aspirin use) there is much to be gained by aspirin counseling that engages patients in dialogue regarding aspirin use. Only through this tailored approach in the most elderly can aspirin be initiated where it is advantageous and avoided where clinical and patient concerns highlight the risks associated with aspirin use. In these ways, all Medicare patients are expected to benefit from provider counseling and shared decision-making on aspirin chemoprevention.

Clinical Preventive Service:

The U.S. Preventive Services Task Force (USPSTF), first convened by the U.S. Public Health Service in 1984, and since 1998 sponsored by the Agency for Healthcare Research and Quality (AHRQ), is the leading independent panel of private-sector experts in prevention and primary care. The USPSTF conducts rigorous, impartial assessments of the scientific evidence for the effectiveness of a broad range of clinical preventive services, including screening, counseling, and preventive medications. Its recommendations are considered the "gold standard" for clinical preventive services in the U.S.

Assessment of Aspirin's Medical Benefits

The USPSTF provided its first assessment of aspirin prophylaxis in 1989. (USPSTF 1989) It recommended that "low-dose aspirin therapy should be considered for men aged 40 and over who are at significantly increased risk for myocardial infarction and who lack contraindications." At the time of this review there were two clinical trials available, both conducted in mostly middle-age male physicians. These trials differed in their estimated efficacy of aspirin use, with the larger American Physician Health Study (Steering Committee PHS 1989) showing a 44% reduction in myocardial infarction (MI) and the smaller British Doctor's Study (Peto 1988) observing no benefit. It was argued that the preponderance of evidence supported the efficacy of aspirin, including trials in patients with known coronary heart disease.

In 1996, the USPSTF provided its second evaluation of aspirin use for primary prevention of cardiovascular disease (USPSTF 1996). At this time, its assessment was that there was insufficient evidence available to recommend for or against the use of aspirin as a preventive measure in men and women. It based this assessment on the lack of consistency between the two existing clinical trials in patients without CHD.

In 2002, the USPSTF updated its 1996 evaluation. (USPSTF 2002) With three clinical trials added to the available evidence—all three of which showed a benefit of aspirin (MRC 1998,

Hansson 1998, PPP, 2001)—the 2002 document "strongly recommends that clinicians discuss aspirin chemoprevention with adults who are at increased risk for coronary heart disease (CHD) (A Recommendation)." The USPSTF also incorporated risk stratification as a key element of decision-making around the use of aspirin. It recommended that individuals with an estimated risk of CHD events exceeding 3% in 5-years, based on their personal risk factor profile be considered for preventive use of aspirin.

In 2009, the USPSTF updated the 2002 recommendations on aspirin use for prevention based on a meta-analysis performed using information available through August 28, 2008. (USPSTF 2009) This meta-analysis included the Women's Health Study (Ridker 2005) indicating a benefit of aspirin on stroke risk, but not MI risk, in women. The USPSTF strongly recommends that clinicians discuss aspirin use for cardiovascular disease prevention with men ages 45-79 years and women ages 55-79 years. This is an "A" recommendation, meaning that the USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms. Specifically, the USPSTF found good evidence that aspirin is effective in reducing the incidence of myocardial infarction (primarily in men) and stroke (primarily in women). For men below 45 years of age and women below 55 years of age in USPSTF recommends against the use of aspirin for cardiovascular disease prevention (D recommendation). For those in the recommended age groups, the USPSTF further recommended a process of estimating the benefit of aspirin use as a function of estimated cardiovascular disease risk and estimating the potential for gastrointestinal (GI) bleeding that should be discussed in a shared decision-making process between health care professional and patient.

The USPSTF further recommends determining whether a patient's likelihood of benefit outweighs their likelihood of harm. For individuals ages 80 years and older, the USPSTF found insufficient evidence available to recommend for or against the use of aspirin (I recommendation). Despite these recommendations for the most elderly, this is a population at substantial risk of cardiovascular disease events who also experiences an increase risk of adverse events from aspirin. The lack of available studies in this population, however, impairs any ability to provide an evidence based recommendation. For this population, the USPSTF strongly suggests shared decision-making to account for individual characteristics and preferences, and to incorporate the recognized uncertainty about the balance of risks and benefits of aspirin use in the most elderly.

Concept Paper on Benefits of Provider Counseling Regarding Chemoprevention, with Shared Decision-Making as Model

The USPSTF published a commentary regarding shared decision-making being its "suggested approach" to counseling for chemoprevention where decisions are sensitive to patient preferences. (USPSTF 2004) While the document is explicit about being a concept paper, rather than a systematic evidence review or formal guidance document, it does state that its purpose is "to articulate its finding [of the USPSTF] that shared decision-making is a necessary tool for making recommendations to individual patients concerning interventions that have net benefit for some but not for others." Note that this definition specifically does not require that a definitive decision be reached regarding acceptance or rejection of the chemoprevention strategy under consideration at the time of discussion. The paper cites the benefits of provider counseling with a shared decision-making approach as deriving from ethical, interpersonal, educational, and utility perspectives (and gives references for this support). (Kaplan 1989; Emanuel 1992;

O'Connor 1999; Molenaar 2000) It also notes, at the time of publication in 2004, that evidence in support of shared decision-making having an impact on patient health outcomes is indirect and mixed. But it highlights that the strongest evidence in support of such impacts are studies on medication adherence and those in which patients perceive that they have been active participants in decision-making with their providers. (Kaplan 1989; Greenfield 1988; Rost 1991; Oliver 2001) The approach is endorsed by the USPSTF in its recommendation regarding aspirin chemoprevention. Further articles published after 2004 have continued to support the shared decision-making approach to counseling regarding chemoprevention. (Kripalani 2007; Joosten 2008; Nekhlyudov 2008; Maruthur 2009; O'Connor 2009; Carling *PLoS Med*: e1000134 2009).

Medical Benefits of Aspirin Counseling:

Clinical Background

Aspirin can reduce the risk of cardiovascular disease, the leading cause of death in the U.S. that accounts for annual direct and indirect costs of $500 billion. In men, aspirin reduces the risk of coronary artery disease events, particularly heart attacks. In the U.S. in 2006 there were 425,000 deaths from coronary heart disease, approximately 1 of every 6 deaths. In 2010, an estimated 785,000 first heart attacks and 470,000 recurrent heart attacks will occur (Lloyd-Jones 2010). Of all coronary events, 67% occur in individuals 65 years of age and older (NHLBI 2006). In women, aspirin reduces the risk of stroke. In 2006, strokes account for nearly 6% of deaths in the U.S. An estimated 610,000 first strokes and 185,000 recurrent strokes occur each year (Lloyd-Jones 2010). Of all strokes, 85% occur in those 65 years of age and older (NHLBI 2006).

Aspirin has been found to be useful in three clinical settings:

- In patients experiencing an acute event, such as a heart attack, aspirin can reduce the extent of harm and improve survival.
- In patients who already have known coronary artery disease or have suffered cerebrovascular accidents, aspirin can reduce the risk of recurrent events.
- Finally, and most pertinent to this request, aspirin can prevent the occurrence of first events in some patients without a history of cardiovascular disease.

Aspirin's benefits derive from its impairment of platelet function and resulting disruption of blood clotting. It does so by permanently inactivating platelet cyclo-oxygenases, whose inactivation greatly diminishes the platelet's potential for aggregation over its 8-10 day circulating life span. In doing so, aspirin reduces the occurrence of myocardial infarction and stroke by preventing the initiation and expansion of clots in critical arteries that serve the heart and brain. Aspirin has a distinct gender-specific pattern of preventive benefits for reasons that are not entirely understood. In men without known CHD/cerebrovascular disease/equivalents, aspirin reduces the relative risk of MI by 32% (Berger 2006), while in similar women it reduces the relative risk of ischemic stroke by 24% and the risk of all strokes by 17% (Berger 2006). In absolute terms, regarding the numbers needed to treat and according to different study data, aspirin use in as few as 16 and as many as 300 men for 10-years would be required to prevent one MI, depending on age and clinical risk factors. Aspirin use in as few as 30 and as many as 600 women for 10-years would be required to prevent one stroke, depending on age and clinical risk factors.

This same biological inactivation of platelet cyclo-oxygenases also explains aspirin's potential for adverse events related to bleeding. Bleeding associated with aspirin use is most commonly trivial, as with epistaxis, gum bleeding, and easy bruisability. Less common, serious bleeding in the gastrointestinal tract has been estimated in the range of 0.4 to 4% over 10-years of aspirin use, depending on patient age and gender. Hemorrhagic stroke is a particularly serious adverse event associated with aspirin use and occurs in an additional 0.1% of men taking aspirin for 10 years compared to those not taking aspirin. In four clinical trials, the risk in men was 0.28% for men taking aspirin vs. 0.15% for those not on aspirin (Berger 2006). The risk of hemorrhagic stroke does not appear to be increased in women. (Berger 2006) Because of these potentially life-threatening risks, careful selection of candidates for aspirin therapy is critical. In general, eligible patients should have a sufficiently high risk of cardiovascular disease events (so that the preventive benefit is sizable), but a low enough risk of adverse events such that a net benefit is expected.

Clinical populations

There are four groups of patients who are expected to receive aspirin counseling services: low risk patients, high risk patients, patients at elevated risk without CVD, and elderly patients 80 years of age and older. The specific nature of aspirin counseling is expected to differ substantially across these groups.

Low risk patients are those in whom aspirin use should generally be discouraged because of their low overall risk of MI and stroke. The USPSTF defines this population as comprising men under 45 years and women under 55 years who lack known coronary artery disease or its equivalents. Patients in these subpopulations generally receive limited benefit from aspirin in terms of the number of individuals requiring treatment to prevent one MI or stroke. They nonetheless experience the potential for adverse events and the cost and inconvenience of taking aspirin. While this is a limited population of Medicare beneficiaries, it is a defined sub-group that is important to identify and for whom counseling on aspirin avoidance is meaningful.

High risk patients are those with known coronary artery disease, past embolic stroke, or a risk equivalent (e.g., other atherosclerosis). Because this group of patients obtains a sizable preventive benefit from aspirin, their use of aspirin is well-established and supported by high profile recommendations, including those of the American Heart Association (Redberg 2009). Therefore, aspirin counseling is an integral component of their clinical management. Because aspirin use is considered secondary (not primary) prevention in patients with existing cardiovascular disease, most patients in this population are not covered by the USPSTF recommendations. In addition, aspirin counseling for most patients in this group would be expected to be encompassed within health professional evaluation and management of the underlying cardiovascular disease conditions. Nonetheless, there is an important sub-group of these high-risk patients for whom a coverage determination makes sense—namely those patients with coronary artery disease equivalents but without established disease for whom aspirin therapy would be considered to be a primary prevention strategy. Because of the potential for patients in this high risk sub-group to receive substantial benefit from aspirin use, these patients should be eligible for aspirin counseling.

Patients at elevated risk without CVD (or risk equivalents) generally have preventive benefits of aspirin that fall between those of low and high risk patients. The USPSTF defines this group as

men 45-79 years old and women 55-79 years old without coronary artery disease/cerebrovascular disease/equivalent conditions. Aspirin counseling is critical for this population because their intermediate risk status requires assessment of the benefits and risks of aspirin. Based on this assessment and shared decision-making between patient and provider, some patients will receive a specific recommendation for taking aspirin, while other patients will be discouraged from taking aspirin. While some patients in this elevated risk group receive provider evaluation and management services, the scope of these clinical activities does not necessarily include aspirin counseling. For example, professional evaluation and management of hypertension (in contrast to coronary artery disease) does not always include a discussion of aspirin. Patients with diabetes are a clinical subpopulation where aspirin counseling is complicated. While patients with diabetes would be expected to be at elevated risk of cardiovascular disease, past studies suggest reduced efficacy of aspirin in these patients.

The population of elderly patients 80 years and older without coronary artery disease, cerebrovascular disease, or equivalent conditions presents a particularly difficult context for clinical decision-making around aspirin use. If all other risk factors were held constant, men and women in this age range are likely to receive the greatest preventive benefit from aspirin, while having a correspondingly greater risk of some adverse events from aspirin use. In addition, there is very limited clinical trial evidence available for those aged 80 years and older. These complexities emphasize the importance of a shared decision-making approach to aspirin that fully accounts for additional clinical factors (e.g., risk of falls), as well as a range of patient values and preferences regarding aspirin's risks, benefits, inconvenience, cost, need for follow-up, and other factors. As with patients with elevated risk but without CVD, some patients will receive provider evaluation and management services, but the scope of clinical activities will not necessarily encompass aspirin counseling. Similarly, some patients will decide to initiate therapy, while others will not.

Provider Counseling and Shared Decision-Making Regarding Aspirin Chemoprevention:

The proposed counseling intervention is based on a model of shared patient and provider decision-making that is suggested by the USPSTF as an approach to preference sensitive medical decisions (USPSTF 2004). This model recognizes that prescribing aspirin involves both technical evaluation of risks and benefits, but also the inclusion of patient values and preferences. This may be particularly true for individuals for whom risk determinations are mixed or based on "insufficient" evidence, such as those with elevated risk without CVD and those 80 years of age and older. Even for younger patients or other risk groups, balancing the benefits and risks of aspirin is complex and deserves individualized counseling that is likely to improve long-term aspirin adherence.

As noted above, the 2004 USPSTF concept paper described shared decision-making as its "suggested approach" to counseling regarding chemoprevention (USPSTF 2004), and evidence published since that time has supported this approach as well. (Kripalani 2007; Joosten 2008; Nekhlyudov 2008; Maruthur 2009; O'Connor 2009; Carling *PLoS Med*: e1000134 2009) The USPSTF concept paper went on to define shared decision-making in the context of chemoprevention as counseling by the provider and joint discussion between patient and provider through which the patient: understands the seriousness of the condition being targeted for prevention, understands the preventive service (including risks, benefits, alternatives, and

uncertainties), has weighed his or her values regarding the potential benefits and harms, and has engaged in decision-making at a level that he or she desires. This definition specifically does not require that a definitive decision be reached regarding acceptance or rejection of the chemoprevention strategy under consideration at the time of discussion. The USPSTF further suggests that in those situations where a definitive decision is not reached there will be agreement between patient and provider on the next steps in the decision-making process (e.g., a follow-up visit or phone call, further reading by the patient on his or her own). For CMS coverage, aspirin counseling is far more than a provider simply mentioning aspirin as a recommended therapy to patients. As with the provision of tobacco cessation counseling, aspirin counseling is a complex process that can be defined and guided by evidence. Aspirin counseling requires active provider and patient participation in a well-defined sequence of tasks that facilitate a shared decision about whether aspirin is appropriate or not for a particular patient

While there are alternative models of provider counseling on chemoprevention other than shared decision-making, its endorsement by the USPSTF and others and its appropriateness for tailoring care where multiple considerations at present make it a preferred model for aspirin chemoprevention counseling.

Summary of Evidence

The USPSTF concept paper (USPSTF 2004) cited the benefits of provider counseling with a shared decision-making approach as deriving from ethical, interpersonal, educational, and utility perspectives (and gives references for this support). (Kaplan 1989; O'Connor 1999; Molenaar 2000) It also noted, at the time of publication in 2004, that evidence in support of shared decision-making having an impact on patient health outcomes is indirect and mixed. Nonetheless, it highlighted that the strongest evidence in support of its impact included studies on medication adherence and those in which patients perceived that they had actively participated in decision-making process. (Kaplan 1989; Greenfield 1988; Rost 1991; Oliver 2001) More recent evidence regarding the impact of provider counseling and shared decision-making on health outcomes remains heterogenous and mixed, but nonetheless suggests likely advantages of these approaches. (Kripalani 2007; Joosten 2008; Nekhlyudov 2008; Maruthur 2009; O'Connor 2009) Specific to the discussion of risk, there is emerging evidence about which forms of patient-provider risk communication are most consistent with patient values and preferences. (Carling *PLoS Med* 2009: e1000134; Carling *PLoS Med* 2009: e1000140; Griffin 2009). There is an accumulating scientific basis for defining the components of state of the art aspirin counseling that are, and will continue to be, of direct aid in specifying the critical features required for CMS reimbursement.

Summary of Tasks (of Provider Counseling and Shared Decision-Making)

The counseling intervention, using a shared decision-making model, involves a joint discussion between patient and provider by the conclusion of which the patient has undergone the collaborative processes that are described in Table 3 below. In addition, the provider has accomplished certain tasks that can then be documented for reimbursement purposes. These provider tasks encompass the more generic "coverage specifications" reviewed earlier in this document. These tasks could be delivered within the context of one or multiple types of visits (e.g., new stand-alone visit, new cardiovascular risk reduction visit, or existing type of visit , but with additional reimbursement). The table provides key examples of the documentation for the tasks that might be submitted by the provided for a coverage determination. In summary, by the

conclusion of the shared decision-making process regarding aspirin use, the patient and provider should have accomplished the processes and tasks outlined in Table 1.

Table 1. Essential Patient Processes and Provider Tasks of Shared Decision-Making

Patient Process*	Provider Tasks	Example Documentation
Understands the seriousness of the condition being targeted for prevention	• Assessment of coronary artery disease (CAD) and cerebrovascular disease risk	"Discussed with this 65-year-old male patient his 10-year risk for CHD event of 15%."
Understands the preventive service (including risks, benefits, alternatives, and uncertainties)	• Initiation of discussion of aspirin use in CAD and cerebrovascular disease prevention. • Assessment of: - Estimated benefits of aspirin use - Risk of adverse events (e.g., GI bleeding and hemorrhagic stroke) - Aspirin contraindications • Provision of specific advice (e.g., aspirin formulation, frequency, and dose). If appropriate, advice to patient not to start aspirin with a plan to reassess in future.	"Reviewed use of aspirin for chemoprevention and discussed the specific risks, benefits, and alternatives for him—for example, in the context of his history of hospitalization for PUD bleeding prior *to H. pylori* eradication. Advised of recommendation to initiate aspirin at 81 mg daily."
Has weighed his or her values regarding the potential benefits and harms	• Discussion of patient values through shared patient-provider decision-making	"Patient expressed fear of repeat GI bleed but also concern re 'having a heart attack like my dad' and wish to ponder pros/cons of aspirin therapy after doing further reading on topic."
Has engaged in decision-making at the level at which he or she desires and feels comfortable	• Agreement on a plan for the subsequent steps, which can include, - Initiation of aspirin therapy (with a plan for assessment of adherence and reinforcement) - Agreement regarding follow-up contact (e.g., visit, phone call) prior to a definitive decision regarding initiation/no initiation of aspirin - Patient preference to not participate further in shared decision-making	"Provided patient with website information and clinic handout on aspirin therapy. Reached joint agreement on plan: follow-up phone call in 1 week to discuss further patient concerns and decision regarding initiation of aspirin therapy."

*Adapted from USPSTF concept paper. (USPSTF 2004)

Intervals and Triggers for Discussion of Aspirin Chemoprevention

There are no definitive guidelines or studies on the optimal interval or triggers for repeat discussion of aspirin chemoprevention. The USPSTF's 2009 clinical guideline on aspirin for primary chemoprevention states that "a reasonable option [for discussions related to aspirin therapy] might be every 5 years in middle age and later" for those with relatively stable health status, including risk cardiovascular risk factors. (USPSTF 2009) It also suggests that a new discussion is a reasonable option "whenever other cardiovascular risk factors are detected." A potential trigger for repeat discussion not commented on by the 2009 guidelines, but which has

relevance within the framework of shared decision-making, is that of changing patient values. Over time patients may develop new views on the balance of value they place on risks versus benefits such that a new discussion of aspirin chemoprevention may be indicated. For example, a patient may more greatly value the benefit of stroke prevention after having to care for a parent disabled by an ischemic stroke. In summary, it would reasonable to cover reimbursement of repeat discussions of aspirin chemoprevention when at least of one of these triggers is met:

- General interval of 5 years: particularly in those with relatively stable health status in terms of cardiovascular and bleeding risk factors.
- Whenever relevant new risk factors arise: these may include cardiovascular risk factors or risk factors for adverse events from aspirin use (e.g., new gastrointestinal bleeding event).
- Whenever relevant patient values regarding risks and benefits of therapy change significantly.

Patient Sub-Groups with Specific Counseling Needs

Table 2 provides further guidance on a suggested approach to shared decision-making for selected sub-groups of patient who have specific counseling needs. One group of patients who may warrant special consideration, prior to further discussion of aspirin chemoprevention, are patients with low health literacy or numeracy, who have been shown to have worse health outcomes in general if these barriers are not identified and addressed. (Ad Hoc Committee on Health Literacy 1999; Cavanaugh 2008) Additional groups who might have specific counseling needs include those in the 80 or older age range, "high-risk" patients with coronary artery disease risk equivalents but no prior coronary artery disease events (i.e., "high risk" patients for whom aspirin use would nonetheless be primary prevention), patients who are not interested in participating in shared decision making (at least initially) (e.g., they may have concerns regarding such participation), and patients who need assistance clarifying their values (e.g., they may want examples of what other patients in similar situations have decided). The latter two sub-groups of patients are highlighted by the USPSTF concept paper as specific targets for fine-tuned counseling. (USPSTF 2004)

Table 2. Patient Sub-Groups with Specific Counseling Needs and Corollary Provider Tasks

Patient Sub-Group with Specific Needs	Corollary Provider Tasks	Example Documentation
Patients with low health literacy or numeracy	- Assessment of level of health literacy/numeracy and adjustment of discussion and any auxiliary materials (e.g., explanatory handouts) to literacy/numeracy level	"Upon questioning, discovered that patient cannot read, so we used pictures rather than written handouts to prompt the shared decision-making discussion, especially regarding the potential risks and benefits of aspirin for him."
Patients 80 years or older ("I" recommendation)	- Discussion of "insufficient (I)" evidence grade for aspirin chemoprevention but potential for large risk reduction	"We specifically discussed importance of patient values in context of 'I' evidence grade. Pt expressed 'I have huge fear of getting a stroke' but less concern regarding GI bleed."
Patients at "high risk" according to coronary artery disease risk equivalents but without prior events ("A" recommendation)	- Discussion of very strong evidence in support of aspirin chemoprevention for coronary artery disease risk reduction.	"Advised 49-year-old patient in Medicare disability that because of her risk factors she met criteria for being at 'high-risk' for cerebrovascular disease event, such that patients with similar risks were typically routinely placed on aspirin therapy, but that I also wanted to have a more detailed discussion with her

		regarding her views and values on the topic."
Patients for whom aspirin use is contraindicated ("D" recommendation)	- Discussion of risks of therapy likely outweighing its potential benefits	"Discussed with patient and answered his questions regarding my advice to discontinue self-initiated aspirin therapy because of his low risk for coronary artery disease event (age 43, no coronary artery disease RFs) and increased risk for adverse event for GI bleed (alcohol dependence)."
Patients not interested in participating in shared decision-making (e.g., may have concerns/ misconceptions regarding such participation*	- Explicit assessment and discussion of patient willingness to engage in shared decision-making	"After patient statement, 'I'm not the doctor—whatever you say is best,' initiated discussion of how in situations of medical uncertainty, doctors specifically seek patients' input, because their values can be the deciding factor re what to do. Patient decided wanted to have the conversation."
Patients who need assistance clarifying their values (e.g., may want to know what others might do in a similar situation*	- Provision of specific examples of how similar patients might incorporate their values into decision-making	"After patient asked for examples of how other patients thought about the issue, discussed how a patient who wanted to avoid a disabling MI at 'at all costs' might place special value on aspirin's benefits and decide to start therapy versus a patient who is very traumatized by the sight of any blood might place special value on its associated GI bleeding risk and decide against it."

* Patients sub-groups highlighted by the USPSTF concept paper as specific targets for fine-tuned counseling. (USPSTF 2004)

Tools to Assist Patients and Providers

The literature contains examples of various tools that can assist both patients and providers with the process of shared decision-making. The best studied of these tools are decision aids, which are used to help guide participants through the process of decision-making in complex or sensitive situations. Decision aids have been shown to increase patient knowledge, decrease decisional conflicts, and reduce the proportion of patients who are passive in decision-making in a recently updated Cochrane meta-analysis (O'Connor 2009). There is at least one checklist available for assessing the quality of decision aids. (Elwyn 2006) However, there remains debate among experts as to whether decision aids are the best approach to medical decision-making (Holmes-Hovner 2007) Specific to aspirin chemoprevention, the American College of Prevention Medicine (ACPM) in 2009 issued—for joint use by patient and provider in the context of a patient visit—a comprehensive package of materials on aspirin chemoprevention that includes a decision aid. (ACPM. "The aspirin advisor" 2009) These materials include specific patient and provider-specific decision aids. Overlapping targets of nascent investigation are patient values and preferences regarding tools/approaches to patient-provider communications specifically about risk, (Carling *PLoS Med* 2009: e1000134; Carling *PLoS Med* 2009: e1000140; Griffin 2009) but it is too early in this research to make conclusions about what tools or methods are preferred in chemoprevention counseling.

Other tools for patients that can be considered include office handouts and references to outside resources (e.g., trusted websites, articles, or books) that patients can use for further reading.

There are also tools available to providers. For example, the ACPM's package of materials on aspirin chemoprevention also includes a health provider guide to practice-level implementation and a discussion guide for the patient visit. (ACPM. "Implementation guide" 2009; ACPM. "Patient discussion guide" 2009).

SUPPORTING DOCUMENTATION:

Relevance of the Evidence Selected

Evidence supporting the effectiveness of the dual intervention of aspirin chemoprevention and provider counseling with shared decision-making in reducing the risk of cardiovascular disease events comes from several independent sources. We separately review the evidence concerning the efficacy of aspirin primary prevention and evidence pertaining to the provision of provider counseling.

Balance of Benefits and Harms in Aspirin Chemoprevention for Cardiovascular Disease Events

General Populations

1) Aspirin for the Primary Prevention of Cardiovascular Events in Women and Men: A Sex-Specific Meta-analysis of Randomized Controlled Trials. Berger JS, et al. *JAMA 2006;295:306-13.*

This meta-analysis captured all prospective, randomized controlled trials of aspirin therapy in participants without known cardiovascular disease that reported data on MI, stroke, and cardiovascular mortality published or reported between 1966 and March 2005. A total of 102 potentially relevant articles were identified of which 13 were randomized clinical trials of aspirin. Berger, et al. then excluded those RCTs that were not in patients at elevated risk, used aspirin in conjunction with other antithrombotics, reported preliminary results, did not evaluate the key outcomes of MI, stroke and total cardiovascular disease mortality, or were pilot studies. Six trials with a total of 95,456 individuals were available for meta-analysis, including three trials with only men, one with only women, and two that included both sexes.

Among 44,114 men, aspirin therapy was associated with a 14% (CI 95% 6-22%) reduction in cardiovascular events and a 32% (14-46%) reduction in MI. Among 51,342 women in these studies aspirin therapy was associated with a 12% (95% CI 1-21%) reduction in all cardiovascular events and a 17% reduction in all strokes (95% CI, 3-30%, Table 4). The risk of ischemic strokes was reduced by 24% (95% CI, 7-37%), offset by an increased number of hemorrhagic strokes, although this increase was not statistically significant (p=0.89). For these women, there was no significant effect on MI or cardiovascular mortality. There was no significant effect of aspirin on stroke or cardiovascular mortality in men. Aspirin treatment increased the risk of bleeding similarly in women (68% increase) and men (72% increase).

2) Aspirin for the Primary Prevention of Cardiovascular Events: An Update of the Evidence for the U.S. Preventive Services Task Force, 2009. Wolff T, et al. *Ann Intern Med* 2009;150:405-10.

The meta-analysis performed for the USPSTF assessed new evidence published in English between January 1, 2001 and August 28, 2008 in order to augment the previous USPSTF meta-analysis (Wolff 2009). A total of 726 articles were screened to identify evaluable literature. Published, peer-reviewed, randomized controlled studies were considered to constitute the

strongest level of evidence in support of guideline recommendations. Four new articles were deemed eligible for inclusion in a meta-analysis that evaluated the effect of aspirin use on key outcomes, were applicable to the U.S. population, had appropriate study designs and included individuals that were at elevated risk of cardiovascular disease events. When added to evidence published prior to 2001, a total of six clinical trials were available for meta-analysis (Table 3). Because these RCTs were identical to those used in Berger, et al.'s 2006 meta-analysis, the USPSTF primarily relied on the quantitative results of this earlier work. These gender-specific estimates suggest a benefit of aspirin in protection against MI in men, protection against stroke in women, but no statistically significant impact on overall mortality.

Based on the input of the Berger meta-analysis, the USPSTF developed new aspirin recommendations. These suggested that men ages 45-79 years and women ages 55-79 years would benefit from aspirin if benefit exceeded harm. They recommended against aspirin use in men below 45 years and women below 55. For those ages 80 years and older, there was insufficient evidence to recommend for or against the use of aspirin. For the target population of men 45-79, benefits were most likely to exceed risks for those with a 10-year risk of MI at or above 4% for those 45-59 years of age, 9% for those 60-69 years, and 12% for those 70-79 years. These calculations assumed a constant risk of hemorrhagic stroke of 0.1% and an age-graded risk of major GI bleeding that increased from 0.8% to 3.6%. It was also assumed that the relative harm of MI was equivalent to that of GI bleeding. Mean 10-year risk rates of MI for men of these ages are approximately 14% for men 45-59, 23% for men 60-69, and 30% for men 70-74 years. (http://www.framinghamheartstudy.org/risk/coronary.html) Coronary artery disease 10-year risk for men without risk factors (based solely on age and gender) is 1% for 45, 3% for 52, 6 % for 60, 13% for 70, and 19% for 79. (National Cholesterol Education Program calculator at http://hp2010.nhlbihin.net/atpiii/calculator.asp) Thus, a substantial fraction of men in these ages would be eligible for aspirin.

For women 55-79 years, benefits exceeded risks for those with a 10-year risk of stroke at or above 3% for those 55-59 years of age, 8% for those 60-69 years and 11% for those 70-79 years. These calculations assumed an age-graded risk of major GI bleeding that increased from 0.4% to 1.8%. It was also assumed that the relative harm of stroke was equivalent to that of GI bleeding. Mean stroke risk for women of these ages are approximately 3%, 7%, and 16%, respectively. Stroke risk for women without risk factors is 2% for 55, 3% for 60, 4% for 70 and 9% for 79. (D'Agostino 1994). Thus, most women would not be eligible for aspirin.

The USPSTF provides a caution that patients taking non-steroidal anti-inflammatory drugs (NSAIDs) present a special population. Not only do NSAIDs increase the GI bleeding risks of aspirin, but may also interfere with aspirin's beneficial impairment of platelet function. A shared decision-making approach is particularly important where decisions need to be tailored to patient-specific factors that add complexity to the discussion of aspirin's risks and benefits.

The assumption of equivalence between the harm of MI (for men) and stroke (for women), and the harm from GI bleeding has been questioned. Mortality and morbidity from GI bleeding is rare compared to MI and stroke. In the six primary prevention RCTs, death from GI bleeding was reported in 9 participants compared to 619 deaths due to vascular disease. Furthermore, individual patient valuation would likely consider these downstream effects of GI bleeding versus MI or stroke to be non-comparable. A recent clinical trial evaluating the continuation of

aspirin after the diagnosis of bleeding peptic ulcer suggests that withdrawing aspirin in these patients may result in net harm because of excessive cardiovascular mortality (Sung 2010).To the extent that patients (within their own value system consider the harm associated with MI or stroke to be greater than for GI bleeding, even those at substantially lower risk of MI and stroke than the USPSTF risk thresholds might consider benefits of aspirin to exceed harms.

3) Antithrombotic Trialists' Collaboration meta-analysis. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849-60.

This meta-analysis of aspirin efficacy included both patients with and without existing coronary artery disease. We focus solely on their evaluation of primary prevention, but note that consistent with past meta-analyses their evaluation of secondary prevention finds substantial and unequivocal benefit. The search strategy used in this study yielded the same six studies used in the Berger meta-analysis (Table 3). But unlike the Berger approach, the meta-analytic strategy analyzed data at the level of individual participants (N=95,456), rather than relying on information at the level of each clinical trial. This allowed an evaluation of the impact of aspirin in selected subgroups of participants (see below). The findings are consistent with those presented by Berger, although the ATTC chose the use of rate ratios as the metric for evaluating the effect of aspirin, rather than odds ratios. Unlike the Berger meta-analysis, information on men and women was combined without accounting for gender-specific differences in aspirin's effects. In addition, the outcomes examined were defined in a different manner (e.g., "non-fatal MI" was examined, rather than all MI) (Table 5). The magnitude of aspirin's effects on key outcomes were very close to those reported by Berger (2006). Statistically significant reductions with aspirin included a 23% (CI 95% 11-33%) reduction in non-fatal MI, an18% (95% CI 10-25%) reduction in "coronary artery events," and a 12% (CI 95% 6-18%) reduction in "serious vascular events;" mostly the combination of MI and stroke. There was also a 54% (CI 95% 30-82%) increase in the risk of "major extracranial bleeding" (most of which is GI bleeding) associated with aspirin. Other outcomes examined were not statistically significant.

The results of the ATTC meta-analysis were essentially the same as those in Berger (2006), but the interpretation was strikingly different. The interpretation of the ATTC findings was that, "In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds." This conclusion follows from the authors' emphasis on aggregate outcomes (especially "serious vascular events") and the combined analysis of men and women. Essentially the same logic is followed by Barnett, et al. (2010) in their recommendation against aspirin use in primary prevention.

There has been substantial criticism of the ATTC's meta-analysis, including comments by the USPSTF (Calonge 2009). Among the main criticisms are: 1) Inappropriate equating of harms from vascular events with those of extracranial bleeding (principally GI bleeding) (NB: as above under Berger 2006), 2) failure to distinguish patterns of impact by gender, and 3) the focus on the heterogeneous outcomes aggregated into "serious vascular events." The effective equivalence between GI bleeding and cardiovascular events implied by the ATTC interpretation has the potential for substantial impact on primary prevention patients at elevated risk. For example, greater "weighting" of cardiovascular benefits would result in significant "net benefit"

in this population. Despite the differences in interpretation, the results of this meta-analysis are nonetheless consistent with an effect of aspirin on some cardiovascular disease outcomes, but not others. Although this alternative approach should be weighed in any discussion of aspirin and its potential benefits, the failure to account for gender-specific differences makes it less useful in guiding tailored clinical practice. The differing interpretations of the same trials provided by the USPSTF and the ATTC reinforce the need for a shared decision-making approach where a careful discussion of the risks and benefits of aspirin for a particular patient can occur.

Demographic and Disease-Specific Populations

Several analyses have examined whether the beneficial impact of aspirin might differ for specific clinical subpopulations. This question is critical in assessing whether any subpopulation should be excluded from recommended aspirin counseling. Few differences have been observed.

Patients with diabetes are a particularly complicated subpopulation. Two 2008 RCTs of aspirin use in diabetics indicated no effect of aspirin (Belch 2008; Ogawa 2008). Several recent meta-analyses have also analyzed this issue in diabetics. Zhang, et al. (2009) analyzed 7 RCTs and concluded that aspirin did not have an impact on cardiovascular disease outcomes. DeBernardis (2009) examined data from 6 studies and found that there was no significant impact of aspirin on cardiovascular disease outcomes, but on sub-group analyses they noted a significant benefit in male diabetics, but not in women. Calvin, et al. (2009) examined a similar, but expanded list of 9 RCTs and similarly found that aspirin did not improve cardiovascular disease outcomes in diabetics. However, they pointed out that the estimates for diabetics were imprecise. They concluded that the effect of aspirin did not differ statistically between diabetics and non-diabetics. The recently released ADA guidelines depart from past recommendations in stating that other cardiovascular risk factors beyond diabetes should be the primary driver of aspirin use in patients with diabetes. (American Diabetes Association, 2010)

In subgroup analyses limited to the six major primary prevention trials (Table 1), the ATTC meta-analyses (ATTC 2009) observed no statistically significant differences for groups of patients defined by a number of demographic and clinical characteristics. For diabetics, the effect of aspirin compared to placebo on serious vascular events (0.88, 95%CI 0.67-1.15) was nearly the same as that for non-diabetics (0.87, 95%CI 0.79-0.96) were nearly identical. For smokers, there was a suggestion of possible reduction in benefit compared to non-smokers. For participants under age 65, the impact on serious vascular events (0.87, 95%CI 0.78-0.98) was similar to that for those 65 years and older (0.88, 95%CI 0.77-1.01).

Table 3: Clinical Trials of Aspirin Use for Primary Prevention

Study Name, Year of Publication	Participants	Location	Characteristics of Participants	% Women	Mean Age	Aspirin Dose	Control Group	Follow-up (Years)
British Doctor's Trial (Peto, 1988)	5,139	UK	Male physicians	0%	~60	500 mg Daily	No placebo	5.8
Physicians Health Study (Steering Committee PHS, 1989)	22,071	US	Male physicians	0%	53	325 mg Every other day	Placebo	5.0
Thrombosis Prevention Trial (MRC 1998)	5,085	UK	Men at high CVD risk	0%	57.5	75 mg Daily	Placebo	6.8
Hypertension Optimal Treatment trial (Hansson 1998)	18,790	Multiple	Men and women with hypertension	47%	61.5	75 mg Daily	Placebo	3.8
Primary Prevention Project (PPP, 2001)	4,495	Italy	Men and women with 2 or more CVD risk factors	58%	~65	100 mg Daily	No placebo	3.6
Women's Health Study (Ridker 2005)	39,876	US	Women health professionals	100%	54.6	100 mg Every other day	Placebo	10.1
Total	95,456			54%	~57			7.0

Source: Adapted from Berger (2006) and Wolff (2009)

Table 4. Meta-analysis (Berger 2006): Effectiveness of aspirin in primary prevention (N=6 RCTs, for men N=5, for women N=3)

Outcome	Men Odds Ratio (CI 95%)	Women Odds Ratio (CI 95%)
All Cardiovascular Events *	0.86 (0.78-0.94)	0.88 (0.79-0.99)
Myocardial Infarction	0.68 (0.54-0.86)	1.01 (0.84-1.21)
All Strokes	1.13 (0.96-1.33)	0.83 (0.70-0.97)
Ischemic Stroke	1.00 (0.72-1.41)	0.76 (0.63-0.93)
Hemorrhagic Stroke	1.69 (1.04-2.73)	1.07 (0.42-2.69)
Cardiovascular Mortality	0.99 (0.86-1.14)	0.90 (0.64-1.28)
Total Mortality	0.93 (0.85-1.03)	0.94 (0.74-1.19)
Major Bleeding	1.72 (1.35-2.20)	1.68 (1.13-2.52)

* Includes cardiovascular mortality, nonfatal MI, or nonfatal stroke (of all types).
Source: Berger JS, et al. 2006.

Table 5: ATTC Meta-Analysis (ATTC 2009): Effectiveness of aspirin in primary prevention (N=6 RCTs*).

Outcome	Rate Ratio (CI 95%)
Any Serious Vascular Event **	0.88 (0.82–0.94)
Non-fatal MI	0.77 (0.67–0.89)
Coronary Artery Disease death	0.95 (0.78–1.15)
Any Major Coronary Event	0.82 (0.75–0.90)
Non-fatal Stroke	0.92 (0.79–1.07)
Stroke Mortality	1.21 (0.84–1.74)
All Strokes	0.95 (0.85–1.06)
Hemorrhagic Stroke	1.32 (1.00–1.75)
Ischemic Stroke	0.86 (0.74–1.00)
Unknown Type of Stroke	0.97 (0.80–1.18)
Other Vascular Mortality	0.89 (0.64–1.24)
Any Vascular Mortality	0.97 (0.87–1.09)
Total Mortality	0.95 (0.88–1.02)
Major Extracranial Bleed	1.54 (1.30–1.82)

*The RCTs included are the same RCTs assessed in the Berger meta-analysis.
** Includes myocardial infarction, stroke (all types), or death from a vascular cause (including sudden death, pulmonary embolism, hemorrhage).
Source: ATT Collaborative, 2009.

Efficacy of Provider Counseling and Shared Decision-Making

Provider Counseling

There is a large body of evidence to suggest that effective counseling by physicians and other certified health professionals has a positive impact on patients' uptake of indicated health behaviors, overall well-being, and satisfaction with their medical care. The studies on counseling that are felt to be most pertinent to aspirin chemoprevention counseling are reviewed here, with key studies summarized in Table 6. Specifically, these studies address cardiovascular risk reduction (both tobacco cessation and cardiovascular risk reduction more generally) and medication adherence. Regarding provider counseling in the tobacco cessation literature, there is strong and consistent evidence that such counseling has an important impact on outcomes, including patient uptake of tobacco cessation strategies and, hence, cardiovascular disease risk reduction. The USPSTF 2009 guideline on the topic summarized the evidence and conferred on it an "A" recommendation, (USPSTF 2009) in part based on an updated meta-analysis (Fiore 2008) (Table 6), as well as an evidence report specifically examining the Medicare population. (DHHS 2001) Other areas pertinent to provider counseling on cardiovascular disease prevention include systematic reviews and trials on behavioral interventions, of which counseling was an intervention component. These have demonstrated reductions—albeit of mixed strength—in coronary heart disease risk in treatment groups. (Ebrahim 2006; Whitlock 2003; Maruthur 2009; Tonstad 2007) (Table 6) An overlapping body of evidence includes evaluations of the impact of personalized assessments and communication of information with patients regarding their cardiovascular health risks and risk reduction strategies. Systematic reviews of this evidence have demonstrated some positive findings regarding improved patient risk perception and certain cardiovascular risk reduction strategies and health outcomes. (Sheridan 2010; Soler 2010) Finally, a systematic review of medication adherence found evidence, again mixed, of improved medication adherence for patients who received provider counseling. (Kripalani 2007) (Table 6)

Table 6. Key Studies Assessing Impact of Provider Counseling on Patient Outcomes

Type of Counseling and Key Studies	Patient Population	Intervention	Outcomes Assessed	Major Findings
Tobacco cessation				
Fiore meta-analysis of physician counseling on tobacco-use abstinence (2008)	Users of tobacco	Counseling re tobacco cessation	Tobacco abstinence rate	Increased tobacco cessation among intervention groups
CVD risk reduction counseling				
Ebrahim Cochrane review of multiple risk factor interventions using counseling and education methods for primary prevention of CHD (2006)	General population, occupational groups, or high risk groups	Counseling and education re multiple risk factors	-Mortality -BP -Cholesterol -Tobacco use	Did not reduce mortality in intervention groups—but review notes that "a small but potentially important benefit of treatment (about a 10% reduction in CHD) may have been missed." Did reduce BP, cholesterol, and tobacco use More effective in higher risk populations

Whitlock systematic review of dietary counseling for women with high-risk CVD (2003)	Women with high risk for CVD	Counseling re diet	Daily food intake	Improved components of daily diet in intervention groups, but required high intensity intervention in most studies
Maruthur PREMIER Trial on coronary heart disease risk reduction (2009)	Patients with pre-hypertension or stage 1 hypertension	Counseling re lifestyle changes +/- diet advice	Framingham 10-year CHD risk score	Reduced 10-year risk scores in intervention groups
Tonstad trial on coronary heart disease risk reduction (2007)	Patients with hypertension	Counseling re lifestyle changes	-HTN -Waist circum-ferance -TG level	Found reduced increase in waist circumference and lower TG levels in intervention group, but no difference in HTN
CVD risk assessment and information				
Sheridan systematic review on global CHD risk assessment and information sharing (2010)	Patients with wide range of CHD risk	Risk assessment and information sharing re global CHD risk	-Accuracy of risk perception -Intent to initiate CHD prevention activity (e.g., use of ASA) -Adherence -Change in global CHD risk	Improved accuracy of risk perception May increase intent to initiate CHD prevention activity among patients at moderate-high CHD risk
Soler systematic review on health risk assessment and information sharing at worksite (2010)	Patients targeted through worksite health promotion programs	Risk assessment and information sharing	Many, including these related to CVD risk -Tobacco use -Dietary fat intake -BP -Cholesterol -Body compos-ition -Physical fitness -Summary health risk estimates	Found "strong or sufficient evidence" for improvements in the intervention groups in following areas related to CVD when the health risk assessment and information sharing had the additional component of education: - Tobacco use - Dietary fat intake - BP - Cholesterol - Summary health risk estimates Found "insufficient evidence" for impact when no education component in the intervention
Medication adherence counseling				
Kripalani systematic review of interventions to enhance medication adherence (2007)	Patients with - Dyslipemia - Thromboem-bolic disease - Asthma - HIV - Rheumatoid arthritis - Contraception	Counseling re medication adherence	Many, including -Cholesterol -INR -Peak flow, etc.	Mixed findings for intervention groups: Adherence most likely to increase with interventions that targeted: - Reduced dosing demands - Monitoring and feedback

CHD=coronary heart disease. BP=blood pressure. HTN=hypertension. TG=triglyceride. INR=international normalization ratio.

Shared Decision-Making

As part of its "A" recommendation that providers discuss aspirin use for primary chemoprevention with patients at increased risk of cerebrovascular disease, the USPSTF specifies that such a discussion should include an exploration of the potential risks and benefits of therapy, as well as particular patient values—both preferences and risk aversions. (USPSTF 2009) Such a recommendation is made more strongly for those situations in which the balance of benefits versus harms may be less clear for an individual or population sub-group—such as areas where an evidence grade of "I" for "insufficient" or "C" for "poor" has been assigned. In its concept paper suggesting shared decision-making as its preferred approach to chemoprevention counseling, the USPSTF describes its rationale for offering such informal guidance as an attempt to "articulate its finding that shared decision-making is a necessary tool for making recommendations to individual patients concerning interventions that have net benefit for some but not for others." (USPSTF 2004)

The USPSTF concept paper cites the benefits of provider counseling with a shared decision-making approach as deriving from ethical, interpersonal, educational, and utility perspectives (and gives references for this support). (Kaplan 1989; O'Connor 1999; Molenaar 2000) It also notes, at the time of publication in 2004, that evidence in support of shared decision-making having an impact on patient health outcomes is indirect and mixed. But it highlights that the strongest evidence in support of such impacts are studies on medication adherence and those in which patients perceive that they have actively negotiated or been active participants in decision-making with their providers, which have direct relevance to decision-making regarding aspirin chemoprevention. Since the publication of the USPSTF concept paper, a number of subsequent studies have examined the impact of shared decision-making on health and other outcomes, as well as patient and provider attitudes, barriers, and facilitators toward shared decision-making. These are discussed below.

Impact on Health, Medication Adherence, and Patient Knowledge, Satisfaction, and Well-Being

The impact of shared decision-making on multiple outcomes was examined in a 2008 systematic review of 11 studies (Joosten 2008), which found the interventions examined to be heterogenous but the overall methodological quality of the included studies to be high. The review notes that there is better evidence for positive health impacts of shared decision-making—on health outcomes, medication adherence, and patient knowledge, satisfaction, and well-being—when patients are asked to contemplate a decision with long-term health consequences (e.g., a treatment program) or when patients have chronic health conditions that are potentially impacted by the decision under discussion (e.g., ischemic heart disease, mental illness). In contrast, it found less evidence to support shared decision-making in scenarios where patients are making a decision about acute care or an isolated intervention. There is only one study of patients with cardiovascular disease (specifically, ischemic heart disease) included in the review, which found that patients in the shared decision-making group experienced an increase in knowledge. A recent trial in patient with hypertension examined the impact of nurse-led lifestyle counseling on hypertension control and markers of the metabolic syndrome (e.g., waist circumference, triglyceride level) and found risk reductions in the intervention group compared to controls for some outcomes. (Tonstad 2008) Another recent trial of cardiovascular disease risk management also assessed the impact of a nurse-led case-management intervention of which shared decision-making was a part and had mixed findings. It found no evidence of impact on health outcomes

such as lifestyle changes or cardiovascular risk (Koelewijn-van Loon *CMAJ* 2009), but did find evidence of significant improvements in patient risk perception, anxiety, and satisfaction (Koelewijn-van Loon *Prev Med* 2009). A recent evaluation of shared-decision making in asthma noted improved outcomes with this approach (Wilson 2010). There is a parallel emerging literature focused on patient preferences and values regarding patient-provider communications specifically about risk. (Carling *PLoS Med* 2009: e1000134; Carling *PLoS Med* 2009: e1000140; Griffin 2009) For all of these areas of investigation, the evidence is too limited to make definitive conclusions about which particular approaches to chemoprevention risk counseling and shared decision-making should be considered "best practices" at this time.

Patient Barriers, Facilitators, and Perceptions Regarding Shared Decision-Making

The USPSTF concept paper on shared decision-making cites evidence that patient willingness to participate in this process can vary according to patient characteristics. (USPSTF 2004) These can include age, level of education, steadfastness in preconceptions about the course of care, fear of regret if the decision turns out badly, membership in an ethnic group that does not value patient autonomy, and various types of poor understanding of various medical concepts—e.g., that medicine is an inexact science and that there is a distinction between medical problem solving (which requires a provider-based expertise) and decision-making (which can be collaborative between patient and provider), or low health literacy or numeracy at baseline. (Deber 1994; Blackhall 1995; Carrese 1995; Deber 1996; Frosch 1999; Ad Hoc Committee on Health Literacy 1999; Cavanaugh 2008) The recognition of this literature underlies the USPSTF decision to highlight the need for providers to assess patient concerns, misconceptions, or lack of understanding about shared decision-making in sub-groups of patients for whom these barriers may arise. Studies have reached similar conclusions. In a study of patient views of shared decision-making, Davis and colleagues found that patients in the intervention group had a greater perception that the healt h decisions they made were collaborative with their care team ("in consultation with their providers"). (Davis 2003) The Cochrane review on decision aids found that patients who were exposed to decision aids had lower decisional conflicts regarding feeling uninformed or unclear about personal values and also were less likely to be passive in the decision-making process. (O'Connor 2009)

Provider Barriers, Facilitators, and Perceptions Regarding Shared Decision-Making

The USPSTF concept paper on shared decision-making also cites evidence that provider willingness to participate in this process can vary according to a number of characteristics: time pressures, competing demands, cost, lack of training in the shared decision-making technique, lack of experience in communicating technical concepts to patients, and confusion regarding the risks/benefits of the decision under consideration. (USPSTF 2004; Jaen 1994; Kaplan 1996; Coulter 1997; Stange *J Fam Pract* 1998 (pp 363-368); Stange *J Fam Pract* 1998 (pp 419-424); Frosch 1999; Stange 2000) However, the same Davis paper cited immediately above also found that providers who performed shared decision-making with patients had excellent congruence with their patients on the decision made and also were highly satisfied with the interactions. (Davis 2003) The findings of a recent systematic review of provider-level barriers and facilitators to the implementation of shared decision-making confirm many of these outcomes. (Legare 2008) "Time constraints" was the barrier to implementation most frequently cited by providers. Conversely, the most frequently cited facilitators were provider motivation and perceptions of positive impact on the clinical process and on patient outcomes.

Expected Magnitude of Medical Benefits:

General Populations

In an analysis of clinical preventive services, Coffield, et al., estimated that improving aspirin use in eligible individuals from a current estimated level of 40% to 90% would lead to 45,000 fewer deaths per year (PFP 2007). Similarly, Farley, et al. (2010) identified aspirin use as a key, under-utilized prevention service and estimated that every 10% increase in the use of aspirin prophylaxis would lead to 8000 deaths prevented annually. In an analysis to determine national priorities for clinical prevention services, Maciosek, Coffield et al. and Maciosek, Edwards, et al. (both 2006) determined that aspirin counseling should be targeted for improvement because of both its clinically preventable burden and its cost-effectiveness. It was estimated that improved adherence to primary prevention aspirin guidelines would result in 590,000 quality-adjusted life years saved in a cohort of 4 million lives (0.15 QALY gained per person). Aspirin counseling, as well as childhood immunizations and tobacco cessation counseling were identified as the top national priorities for improvement in U.S. preventive care services. .

Medicare Population

It is difficult to determine what medical benefits might accrue to Medicare beneficiaries through improved aspirin counseling, given the complexity around decisions to implement or not implement aspirin chemoprevention among this population. Nonetheless, 72% of cardiovascular events occur in individuals over the age of 65 (NHLBI 2006). Using this proportion, it is estimated that improved aspirin counseling and the resultant use and adherence to aspirin would result in 33,200 fewer deaths in the Medicare population annually.

Cost-effectiveness of Aspirin Counseling and Use

Aspirin is among a small set of preventive services that have been shown to be cost saving or nearly cost saving. The analysis by Maciosek (2006) indicated that overall, aspirin use was cost-saving in that it saved more health care resources than were required to increase the use of aspirin. Of the range of 24 clinical preventive services recommended by the USPSTF, the only other cost-saving interventions were tobacco cessation counseling, childhood immunization, pneumococcal vaccination, and visual screening in adults.

There appear to be gender-specific differences in the cost-effectiveness of aspirin. For men, aspirin use is often cost-saving. In the base-case example of a 45-year-old man who does not smoke, is not hypertensive, and has a 10-year risk for coronary artery disease of 7.5%, aspirin was more effective and less costly than no treatment (Pignone 2006). This same cost-saving attribute would apply to patients at greater risk, as well. Thus, application of aspirin chemoprevention to the male population over 65 years of age would be cost-savings to an even greater extent. In women, aspirin is generally not cost-saving, but is nonetheless highly cost-effective. In the example of a 65 year-old women with a 3% estimate 10-year risk of stroke (7.5% for coronary disease), aspirin use cost $13 300 per additional QALY gained (Pignone 2007). In scenarios of women at greater age and higher risk, aspirin became more cost-effective or, in some cases, cost-saving.

Independent Experts for Further Consultation

Michael Pignone, MD, MPH, Associate Professor of Medicine, University of North Carolina, Chapel Hill, 5039 Old Clinic Building, UNC Hospital, Chapel Hill, NC 27599-7110, email michael_pignone@med.unc.edu .

Tracy Wolff, MD, MPH at U.S. Agency for Healthcare Research and Quality, 540 Gaither Road Rockville, MD 20850 email Tracy.Wolff@ahrq.hhs.gov .

Colin Baigent, BM, BCh, Professor of Epidemiology, Oxford University Clinical Trial Service Unit, Richard Doll Building, Oxford OX3 7LF UK email: colin.baigent@ctsu.ox.ac.uk .

Kathy Berra, ANP, Clinical Trial Nurse, Stanford Prevention Research Center, Stanford University 1070 Arastradeo Road, Palo Alto CA 94306. email: kberra@stanford.edu .

George K. Anderson, MD at AMSUS,9320 Old Georgetown Road, Bethesda, Maryland 20814-1653. Phone: (301) 897-8800, email george.anderson@amsus.org .

Stacey Sheridan, MD, Assistant Professor of Medicine, University of North Carolina, 5039 Old Clinic, UNC Hospital, Chapel Hill, NC, 27599-7110. Phone: 919-966-2276. email: stacey_sheridan@med.unc.edu .

REFERENCES IN ALPHABETICAL ORDER

1. Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, American Medical Association. Health literacy: report of the Council on Scientific Affairs. *JAMA* 1999;281:552–557.
2. American College of Preventive Medicine. Aspirin talks: start a life-saving conversation. "The aspirin advisor: a resource for patients and providers." 2009.
3. American College of Preventive Medicine. Aspirin talks: start a life-saving conversation. "Implementation guide: a practice manual for shared decision-making about aspirin." 2009.
4. American College of Preventive Medicine. Aspirin talks: start a life-saving conversation. "Patient discussion guide: a clinician's resource." 2009.
5. American Diabetes Association, Standards of Medical Care in Diabetes—2010. *Diabetes Care;* 2010 33:S11-S61.
6. Antithrombotic Trialists' Collaboration (ATTC), Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-60.
7. Barnett H, Burrill P, Iheanacho I. Don't use aspirin for primary prevention of cardiovascular disease. BMJ. 2010; 340: c1805.
8. Belch J, MacCuish A, Campbell I, et al. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008; 337: a1840.
9. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006; 295:306-13.
10. Blackhall LJ, Murphy ST, Frank G, Michel V, Azen S. Ethnicity and attitudes toward patient autonomy. *JAMA* 1995;274:820-825.
11. Calonge N, LeFevre M. USPSTF response to the ATT collaboration meta-analysis. Agency for Healthcare Research and Quality. Rockville, MD. 2009.
12. Calvin AD, Aggarwal NR, Murad MH, et al. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. *Diabetes Car.* 2009 Dec;32(12):2300-6. Epub 2009 Sep 9.
13. Carling CLL, Kristoffersen DT, Flottorp S, Fretheim A, Oxman AD, et al. (2009) The effect of alternative graphical displays used to present the benefits of antibiotics for sore throat on decisions about whether to seek treatment: a randomized trial. *PLoS Med* 6(8): e1000140. doi:10.1371/journal.pmed.1000140
14. Carling CLL, Kristoffersen DT, Montori VM, Herrin J, Schunemann HJ, et al. (2009) The effect of alternative summary statistics for communicating risk reduction on decisions about taking Statins: a randomized trial. *PLoS Med* 6: e1000134. doi:10.1371/journal.pmed.1000134
15. Carrese JA, Rhodes LA. Western bioethics on the Navajo reservation. Benefit or harm? *JAMA* 1995;274:826-829.
16. Cavanaugh K, Huizinga MM, Wallston KA, Gebretsadik T, Shintani A, Davis D, Gregory RP, Fuchs L, Malone R, Cherrington A, Pignone M, DeWalt DA, Elasy TA, Rothman RL. Association of numeracy and diabetes control. *Ann Intern Med* 2008;148:737–746.
17. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 2001;357:89-95.

18. Coulter A. Partnerships with patients: the pros and cons of shared clinical decision-makign. *J Health Services Res Policy* 1997;2:112-121.
19. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB: Stroke risk profile: adjustment for antihypertensive medication. the Framingham Study. Stroke 1994; 25:40-43.
20. Davis RE, Dolan G, Thomas S, Atwell C, Mead D, Nehammer S, Moseley L, Edwards A, Elwyn G. Exploring doctor and patient views about risk communication and shared decision-making in the consultation. *Health Expect.* 2003 Sep;6(3):198-207.
21. De Berardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 2009 Nov 6;339:b4531. doi: 10.1136/bmj.b4531
22. Deber RB. Physicians in health care management: 7. The patient-physician partnership: changing roles and the desire for information. *CMAJ* 1994;151:171-176.
23. Deber RB, Kraetschmer N, Irvine J. What role do patients wish to play in treatment decision making? *Arch Intern Med* 1996;156:1414-1420.
24. DHHS. Evidence Report and Evidence-Based Recommendations: Interventions to Promote Smoking Cessation in the Medicare Population. Prepared by RAND for the Centers for Medicare & Medicaid Services, Baltimore, MD. Contract no. 500-98-0281, 2001.
25. Ebrahim S, Bewisk A, Burke M, Smith D. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database Syst Rev* 2006;4: CD001561.
26. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. *BMJ* 2006;333: 417.
27. Farley TA, Dalal MA, Mostashari F, Frieden TR Deaths preventable in the U.S. by improvements in use of clinical preventive services. Am J Prev Med. 2010; 38: 600-9.
28. Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.
29. Frosch DL, Kaplan RM. Shared decision making in clinical medicine: past research and future direction. *Am J Prev Med* 1999;17:285-294.
30. Griffin JM, Lewis CL, Hawley S, Sheridan SL, Pignone MP. Randomized trial of presenting absolute v. relative risk reduction in the elicitation of patient values for heart disease prevention with conjoint analysis. *Med Decis Making* 2009;29:167-174.
31. Hansson L, Zanchetti A, Carruthers SG, et al, HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet.* 1998;351:1755-1762.
32. Holmes-Rovner M, Nelson WL, Pignone M, Elwyn G, Rovner DR, O'Connor AM, Coulter A, Correa-de-Araujo R. Are patient decision aids the best way to improve clinical decision making? Report of the IPDAS Symposium. *Med Decis Making* 2007;27:599-608.
33. Jaen CR, Stange KC, Nutting PA. Competeing demands of prikmary care: a model for delivery of clinical preventive services. *J Fam Pract* 1994;38:166-171.
34. Joosten et al. Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. *Psychother Psychosom 2*008;77:219-26.
35. Kaplan SH, Greenfield S, Gandek B, Rogers WH, Ware JE Jr, Characteristics of physicians with participatory decision-making styles. *Ann Intern Med* 1996;124:497-504.
36. Koelewijn-van Loon MS, van Steenkiste B, Ronda G, Wensing M, Stoffers HE, Elwyn G, Grol R, van der Weijden T. *Prev Med.* [Epub ahead of print] Improving lifestyle and risk perception through patient involvement in nurse-led cardiovascular risk management: A cluster-randomized controlled trial in primary care. 2009.

37. Koelewijn-van Loon MS, van der Weijden T, van Steenkiste B, Ronda G, Winkens B, Severens JL, Wensing M, Elwyn G, Grol R. Involving patients in cardiovascular risk management with nurse-led clinics: a cluster randomized controlled trial. *CMAJ.* 2009 Dec 8;181(12):E267-74. Epub 2009 Nov 30.
38. Kripalani et al. Interventions to enhance medication adherence in chronic medical conditions. *Arch Intern Med* 2007;167:540-550.
39. Legare et al. Barriers and facilitators to implementing shared decision-making in clinical practice: Update of a systematic review of health professionals' perceptions. *Patient Education and Counseling* 2008;73: 526-535.
40. Lloyd-Jones D, Adams RJ, Brown TM, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics —2010 update: a report from the AHA. *Circulation*. 2010; 121:e46–e215.
41. Maciosek MV, Edwards NM, Coffield AB, et al. Priorities among effective clinical preventive services: methods. *Am J Prev Med* 2006; 31: 90-6.
42. Maciosek MV, Coffield AB, Edwards NM, et al. Priorities among effective clinical preventive services: methods. *Am J Prev Med* 2006; 31: 52-61.
43. Maruthur, NM, Wang NY, Appel LJ. Lifestyle interventions reduce coronary heart disease risk: results from the PREMIER Trial. 2009 Apr 21; 119(15): 2026-3.
44. Medical Research Council. Thrombosis Prevention Trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998;351:233-241.
45. National Committee on Quality Assurance (NCQA), *Healthcare Effectiveness Data and Information Set (HEDIS) 2010*, NCQA, Washington DC, 2009.
46. National Institutes of Health, National Heart, Lung, and Blood Institute. *Incidence and Prevalence: 2006 Chart Book on Cardiovascular and LungDiseases.* Bethesda, Md: National Heart, Lung, and Blood Institute; 2006.
47. O'Connor AM, Bennett CL, Stacey D, Barry M, Col NF, Eden KB, Entwistle VA, Fiset V, Holmes-Rovner M, Khangura S, Llewellyn-Thomas H, Rovner D. Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD001431. DOI: 10.1002/14651858.CD001431.pub2.
48. Ogawa H, Nakayama M, Morimoto T, et al. Japanese Primary Prevention of Atherosclerosis wth Type 2 Diabetes: A randomized controlled trial. *JAMA* 2008;300:2134-2141.
49. Peto R, Gray R, Collins R, et al. Randomized trial of prophylactic daily aspirin in British male doctors. *BMJ* 1988;296:313-316.
50. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Ann Intern Med. 2006; 144: 326-36.
51. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. *J Am Coll Cardiol*. 2010; 55: 2878-86.
52. Redberg RF, Benjamin EJ, Bittner V, et al. ACCF/AHA 2009 performance measures for primary prevention of cardiovascular disease in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for Primary Prevention of Cardiovascular Disease). *Circulation*. 2009;120:1296–1336.
53. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293-1304.
54. Sheridan SL, Viera AJ, Krantz MJ, Ice CL, Steinman LE, Peters KE, Kopin LA, Lungelow D. The effect of giving global coronary risk information to adults: a systematic review. *Arch*

Intern Med 2010;170:230-239.
55. Soler RE, Leeks KD, Razi S, Hopkins DP, Griffith M, Aten A, et al. A systematic review of selected intervention for worksite health promotion: the assessment of health risks with feedback. *Am J Prev Med* 2010;38(2S):S237-S262.
56. Stange KC, Flocke SA, Goodwin MA. Opportunistic preventive service delivery. Are time limitations and patient satisfaction barriers? *J Fam Pract* 1998;46:419-424.
57. Stange KC, Flocke SA, Goodwin MA, Kelly RB, Zyzanski SJ. Direct observation of rates of preventive service delivery in community family practice. *Prev Med* 2000;31:167-176.
58. Stange KC, Jaen CR, Flock SA, Miller WL, Crabtree BF, Zyzanski SJ. The value of the family physician. *J Fam Pract* 1998;46:363-368.
59. Steering Committee for the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study.*N Engl J Med.* 1989;321:129-35.
60. Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding. A randomized trial. Ann Intern Med. 2010;152:1-9.
61. U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150:396-404.
62. U.S. Preventive Services Task Force. Shared decision making about screening and chemoprevention: a suggested approach from the U.S. Preventive Services Task Force. *Am J Prev Med* 2004;26:56-66.
63. U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med.* 2002;136:157-160.
64. U.S. Preventive Services Task Force, *Guide to Clinical Preventive Services,* Second Edition, Baltimore: Williams & Wilkins; 1996.
65. U.S. Preventive Services Task Force, *Guide to Clinical Preventive Services,* Baltimore: Williams & Wilkins; 1989.
66. Whitlock et al. The primary prevention of heart disease in women through health behavior change promotion in primary care. *Womens Health Issues* 2003;13:122-141.
67. Wilson SR, Strub P, Buist AS, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med. 2010;181: 566-77.
68. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009;150: 405-10.
69. Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract* 2010, 87: 211–8.