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Aspirin: An Overview of Randomized Controlled Trials

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ABSTRACT:

Aspirin or Acetylsalicylic acid (ASA) has remained one of the world's safest, least expensive and most consumed analgesics. Aspirin, along with its analgesic-antipyretic uses, is now also being considered for prevention of cardiovascular disease, cancer, and treatment of human immuno-deficiency virus infection. Aspirin, one of the first drugs to come into common usage, is still mostly the widely used in the world - approximately 35,000 metric tonnes are produced and consumed annually, enough to make over 100 billion standard aspirin tablets every year. Long-term therapy with aspirin is associated with a significant increase in the incidence of gastrointestinal hemorrhage. Aspirin can reduce thrombin generation with the subsequent attenuation of thrombin-mediated coagulant reactions such as factor XIII activation. Aspirin also acetylates lysine residues in fibrinogen resulting in increased fibrin clot permeability and enhanced clot lysis as well as directly promoting fibrinolysis with high-dose aspirin. Aspirin reduces the odds of serious atherothrombotic vascularents and death in a broad category of high risk patients by about one quarter. Furthermore, there is growing evidence that long-term use of aspirin decreases the risk of colorectal cancer, even at low doses. As aspirin is one of the most prescribed drugs worldwide and its clinical impact is huge, physicians need to consider the benefits and harms for each individual patient in order to maximize the benefits of aspirin. This review demonstrates that there is strong evidence that the use of aspirin reduces the risk of death and recurrent events in patients with various diseases.

KEY WORDS: Aspirin, Anti-inflammatory, Arthritis, Bleeding complication,Cardiovascular prevention, GIT Complication.

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1. INTRODUCTION

Acetylsalicylic acid (aspirin) was introduced as a potent anti-inflammatory and analgesic drug in 1892. Since then, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) or salicylates have been shown to exhibit additional effects. Aspirin is effective as a painkiller, an anti-inflammatory, and has actions that provide protection against serious diseases like heart attack and stroke. While there is not yet a clear aspirin blood pressure connection, the protective benefits are so large that routine, daily administration of aspirin is now recommended by the American Heart Association as a standard component of maintaining a healthy heart Long term use of aspirin in men and women has also been reported to protect against the development of colon cancer (40% decrease in risk) and other digestive system cancers, including cancers of the esophagus and stomach [1-3]. In animal studies, NSAIDs were found to inhibit chemically induced tumors of colon, tongue, esophagus, pancreas, bladder, breast, liver, skin, and various sarcomas [4-8]. Although Hippocrates prescribed chewing willow bark, which has aspirin-like properties, for pain relief in the fifth century B.C., the possible role of aspirin in reducing the risk of cardiovascular disease has been recognized only very recently. Such a possibility derives from the capacity of aspirin in low doses to inhibit cyclo-oxygenase-dependent platelet enzymes

virtually completely, resulting in the inhibition of agreeability for the life of the platelet. These effects are so profound that higher doses add little benefit but do increase the risk of side effects [9-12]. This trial of aspirin for the primary prevention of cardiovascular disease demonstrates a conclusive reduction in the risk of myocardial infarction, but the evidence concerning stroke and total cardiovascular deaths remains inconclusive because of the inadequate numbers of physicians with these end points. The Physicians' Health Study is a double-blind, placebo-controlled, randomized trial designed to test two primary-prevention hypotheses in a population of healthy male physicians: whether aspirin in low doses (Bufferin, Bristol-Myers Products, 325 mg every other day) reduces mortality from cardiovascular disease, and whether beta carotene (Lurotin, BASF, 50 mg on alternate days) decreases the incidence of cancer. Although the beta-carotene component of the trial is continuing at least through 1990, the Data Monitoring Board recommended the early termination of the blinded aspirin component of the trial on December 18, 1987. This decision was based on all available evidence, including three major considerations: the presence of a significant ($P<0.00001$) reduction in the risk of total myocardial infarction among those in the aspirin group; the fact that no effect of aspirin on cardiovascular mortality could be detected in the trial until the year 2000 or later, because of the exceptionally low cardiovascular death rates among the participating physicians; and the fact that aspirin was subsequently prescribed for more than 85 percent of the participants who experienced nonfatal vascular events, which made any finding about cardiovascular mortality particularly difficult to interpret[13]. The effectiveness of NSAIDs to treat inflammation and to prevent cancer has been attributed to their ability to inhibit prostaglandin production by inhibiting the cyclo-oxygenase enzyme prostaglandin H (PGH) synthtase[14-16]. However, other mechanisms cannot be excluded. For example, aspirin doses used to treat chronic inflammatory diseases or prevent cancer are higher than those required to inhibit prostaglandin synthesis [17-19]. Salicylic acid also plays a role in transcription of the pathogenesis-related genes in plants and heat shock transcription factor in mammalian cells[20].

2. HISTORY OF ASPIRIN INTRODUCTION

Acetylsalicylic acid (aspirin) was introduced as a potent anti-inflammatory and analgesic drug in 1892. Since then, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) or salicylates have been shown to exhibit additional effects. For example, administration of low dose aspirin to physicians and patients suffering from angina pectoris significantly reduced the rate of heart attack and stroke (by up to 50%). Long-term use of aspirin in men and women has also been reported to protect against the development of colon cancer (40% decreases in risk) and other digestive system cancers, including

cancers of the esophagus and stomach. Aspirin (acetyl salicylic acid (ASA) 3) has been one of the most widely used drugs in history. Since 1899, it has been used as an analgesic, an antipyretic, and an anti-inflammatory agent. Over the years, aspirin has been substituted by other agents due its side effects, especially in children [21-23]. However, there are studies that support a beneficial effect of aspirin in asthma patients. In the last 30 years medicines prescribed by doctors have changed beyond all recognition. Our better knowledge of the nature of diseases and their management has led to the replacement of many old remedies by new ones specifically designed for each illness. The change has been dramatic. Common conditions such as peptic ulcer, asthma, high blood pressure, infections and arthritis are much better treated, with higher cure rates and longer survival. We now have the first effective anti-viral drugs, and many types of cancer that were untreatable only a few years ago, are now brought under control. Yet it would be a mistake to assume that, to keep up with modern medicines, doctors have always had to turn to new drugs. One drug - very old in terms of our current prescription lists - has continued to flourish, and has even expanded its uses. It is highly effective, has a very good safety record, and is, after almost a hundred years; still the most trusted home remedy for pain, worldwide. It is also very cheap. It is aspirin. Everyone has known for years that aspirin is a fast and reliable painkiller that also reduces inflammation and cools fevers. More recently it has become just as well known as a help to people with heart complaints such as angina, coronary thrombosis and after coronary bypass surgery. It is becoming better known, too, in prevention of stroke. Among other diseases in which active research about aspirin is showing great promise - and in which it is now being increasingly used - are toxemia of pregnancy, diabetes, bowel cancer and dementia. How such an old drug can turn out to be so useful in so many crucial diseases makes a fascinating story. Astonishing advances in medical care need not depend entirely on the invention and introduction of new medicines.

3. THE CHEMISTRY OF ASPIRIN

Aspirin, also known as 'acetylsalicylic acid', has a chemical formula of $C_9H_8O_4$. Aspirin is analgesic, anti-inflammatory, antipyretic and is an inhibitor of platelet aggregation. It inhibits fatty acid cyclo-oxygenase by acetylation of the active site of enzyme and the pharmacological effects of aspirin are due to the inhibition of the formation of cyclo-oxygenase products including prostaglandins, thromboxanes and prostacyclin. Aspirin is prepared by chemical synthesis from salicylic acid, by acetylation with acetic anhydride[24].

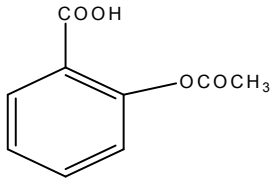

Figure 1: Aspirin

3.1 REACTION

3.1.1 Raw Materials

Phenol (C_6H_5-OH), Sodium Hydroxide (NaOH), Carbon Dioxide (CO_2), Acetic -Anhydride ($CH_3COOCOCH_3$), Hydrogen (H).

3.1.2 The Reactions

The production of aspirin from raw materials can be divided into four separate reactions. These are shown below.

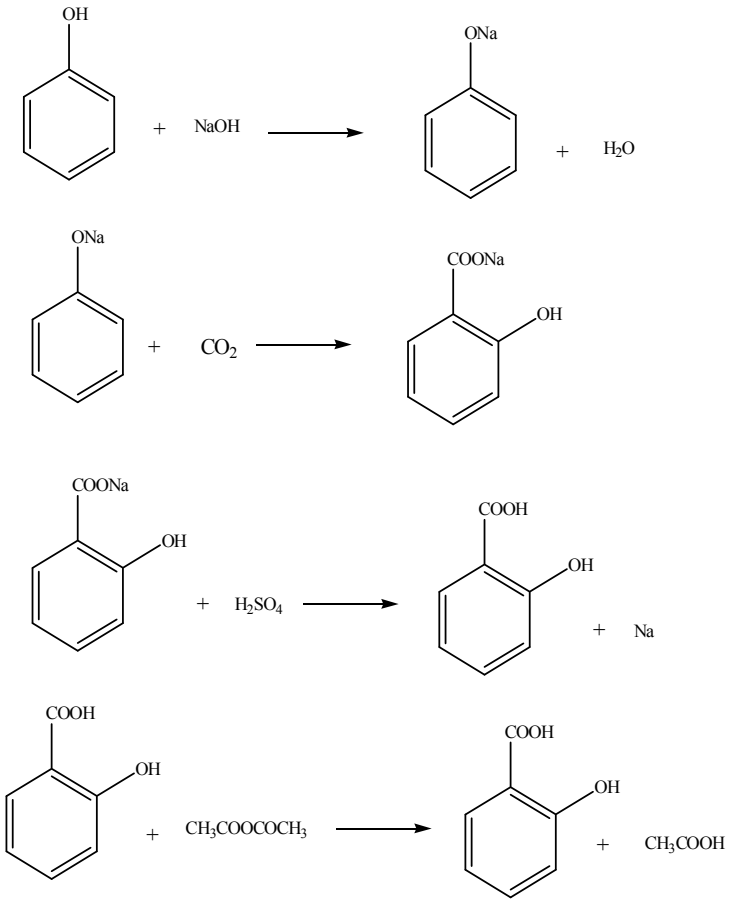

Figure 2: Production of Aspirin

3.2 MECHANISM OF ACTION OF ASPIRIN

The many effects of aspirin are believed to be mediated by the inhibition of cyclo-oxygenase (COX)-1 andCOX-2 enzymes, thereby blocking the production of PG. However, the concentrations of aspirin required to obtain a beneficial effect in asthma are higher than those required to inhibit COX[25-27]. Aspirin is a type of chemical called a "salicylate." Simple salicylates have been used as pain and fever reducers since the time of the ancient Greeks, more than 1,500 years ago. While aspirin has a large number of potential actions in the body, those related to heart health are straight-forward and well-understood. In the body, aspirin inhibits the formation of chemicals called "prostaglandins" by blocking an essential enzyme needed for their formation. Among the many properties of prostaglandins is their ability to promote blood cells to stick together. Thus, by blocking the formation of prostaglandins, aspirin decreases the likelihood of blood clots forming in your blood vessels. Since a large number of heart attacks and strokes are directly caused by small, spontaneously forming blood clots, the ability of aspirin to prevent the formation of these small clots means that heart attacks and strokes become less likely[28].

3.3 PHARMACOLOGY

Aspirin inhibits cyclo-oxygenase (prostaglandin synthetase) thereby reducing the synthesis of prostaglandins and thromboxanes. These effects are thought to be how aspirin produces analgesia, antipyrexia, and reduces platelet aggregation and inflammation. Most cells can synthesize new cyclo-oxygenase, but platelets cannot. Therefore, aspirin causes an irreversible effect on platelet aggregation. Aspirin has been shown to decrease the clinical symptoms of experimentally induced anaphylaxis in calves and ponies[29].

3.4 PHARMACOKINETICS

Aspirin is rapidly absorbed from the stomach and proximal small intestine in monogastric animals. The rate of absorption is dependent upon factors as stomach content, gastric emptying times, tablet disintegration rates and gastric PH. Absorption is slow from the GI tract in cattle, but approximately 70% of an oral dose will be absorbed. During absorption, aspirin is partially hydrolyzed to salicylic acid where it is distributed widely throughout the body. Highest levels may be found in the liver, heart, lungs, renal cortex, and plasma. The amount of plasma protein binding is variable, depending on species, serum salicylate and albumin concentrations. At lower salicylate concentrations, it is 90% protein bound, but only 70% protein bound at higher concentrations. Salicylate is excreted into milk, but levels appear to be very low. Salicylate will cross the placenta, and fetal levels may actually exceed

those found in the mother. Salicylate is metabolized in the liver primarily by conjugation with glycine and glucuronic acid via glucuronyl transferase. Because cats are deficient in this enzymatic pathway, they have prolonged half-lives and are susceptible to accumulating the drug. Minor metabolites formed include gentisic acid and 2, 3-dihydroxybenzoic acids, and 2, 3, 5-trihydroxybenzoic acids. Gentisic acid appears to be the only active metabolite, but because of its small concentrations, it appears to play an insignificant role therapeutically. The rate of metabolism is determined by both first order kinetics and dose-dependent kinetics depending on which metabolic pathway is looked at. Generally, steady-state serum levels will increase to levels higher (proportionally) than expected with dosage increases. These effects have not been well studied in domestic animals, however. The kidneys rapidly excrete salicylate and its metabolites by both filtration and renal tubular secretion. Significant tubular reabsorption occurs which is highly pH dependent. Raising urine pH to 5-8 can significantly increase salicylate excretion. Salicylate and metabolites may be removed using peritoneal dialysis or more rapidly using hemodialysis[30].

4. APPLICATIONS OF ASPIRIN IN VARIOUS DISEASES

4.1 ASPIRIN FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

A recent meta-analysis demonstrated that aspirin is protective in most types of patient at increased risk of occlusive events, including those with an acute myocardial infarction (MI) or ischaemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischaemia, peripheral arterial disease or atrial fibrillation (AF). Low dose aspirin 75-150 mg daily was found to be as effective as higher doses, the effects of doses lower than 75 mg were uncertain. For most healthy individuals for whom the risk of a vascular event is likely to be less than 1% a year, daily aspirin is probably inappropriate[31]. Many individuals are at an elevated risk of suffering serious to life-threatening cardiovascular events, such as myocardial infarction (heart attack), cardiac arrest, congestive heart failure, stroke, peripheral vascular disease, and/or claudication such as symptomatic peripheral arterial obstructive disease (PAOD). The risk factors are numerous and widespread throughout the world population. They include cigarette smoking, diabetes, hypercholesterolemia (high serum cholesterol), hypertension, angina, systemic lupus erythematosus, prior heart attacks or strokes, haemodialysis, hyperhomocysteine levels, obesity, sedentary lifestyle, receiving an organ transplant, and others. Many of these risk factors are mediated through vascular inflammation, endothelial dysfunction and atherosclerosis, which are major risk factors for cardiovascular events. In current clinical practice, low dose aspirin (ASA), is well documented for efficacy in both prevention and treatment of thrombotic diseases. Moreover, in

conditions such as myocardial infarction and stroke, platelet inhibition has become the standard of care. However, the use of ASA increases the risk of bleeding, which limits the dose of the agent and duration of treatment; another limitation of aspirin is represented by its gastro-intestinal and renal toxicity. The use of therapeutic doses of aspirin (typically 75 mg or more) is commonly associated with gastro-intestinal disturbances (e.g. nausea, dyspepsia, vomiting) and can also cause gastric mucosal damage such as ulceration. Dizziness, tinnitus, deafness and sweating are also known to occur with larger and/or repeated doses. It is well known that nitric oxide-releasing aspirin and in particular 2-(acetyloxy) benzoic acid 3-(nitrooxymethyl) phenyl ester, known as NCX 4016 or nitro- aspirin, exerts a wider range of antiplatelet actions compared to aspirin and shows superior antithrombotic activity[32]. "Cardiovascular disease" as employed herein refer to coronary and/or cerebrovascular event (s) and disease including primary myocardial infarction, secondary myocardial infarction, myocardial ischemia, angina pectoris (including unstable angina), congestive heart failure, sudden cardiac death, cerebral infarction, cerebral thrombosis, cerebral ischemia, transient ischemic attack, peripheral vascular diseases such as peripheral arterial obstructive disease (PAOD) .The term "coronary artery disease" (CAD) as employed herein refers to diseases including atherosclerosis of the coronary arteries, previous myocardial infarction, ischemia, angina pectoris and/or heart failure. The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment[33].

4.1 ASPIRIN AND ARTHRITIS:

Many drugs are used to decrease the joint pain and swelling caused by arthritis. The symptoms of arthritis are the result of an immune response by the body. In the case of arthritis, the immune system is confused and begins to fight its own tissues within the joints. This causes pain, swelling, heat, redness, and sometime stiffness of the joint. Aspirin can decrease these symptoms. Small amounts of aspirin help relieve headaches, mild pain, and fever. Higher doses relieve some of the symptoms of pain, heat, redness, and swelling brought on by arthritis. Aspirin can cause you to bleed more than normal. If you need surgery or dental work, tell the healthcare provider or dentist that you are taking aspirin. The tendency to bleed lasts for up to 10 days after you stop taking aspirin. Aspirin interacts with many other medicines. Tell your healthcare provider about all the other medicines you take. To avoid the risk of an overdose, you should also check with your provider if you take non-prescription painkillers[34].

4.3 ASPIRIN & GIT COMPLICATION

Gastrointestinal (GI) disturbances such as nausea, dyspepsia, and vomiting are the most common adverse effects of aspirin. Giving aspirin with food, minimizing the dose and co-prescribing an acid suppressant may minimize these symptoms. Peptic ulceration and GI hemorrhage can occur with aspirin probably through a combination of direct damage to the gut mucosa and systemically via the inhibition of prostaglandin synthesis. In theory, this should protect the gastric mucosa from local irritation although duodenal damage can still occur. Dispersible aspirin is more rapidly absorbed than standard aspirin and produces about half as much occult bleeding, probably by minimizing high localized concentrations and therefore direct mucosa damage and it is unclear what the clinical importance of such studies is in patients taking aspirin in the long-term. Enteric formulations are coated with a combination of cellulose, silicon or other inactive ingredients providing resistance to disintegration in the stomach; this property allows dissolution of the drug in the higher pH of the duodenum. It is known that these lesions are not good predictors of major upper gastro-intestinal complications[35]. Aspirin was efficacious at a dose of 30 mg a day, but a threshold dose for either the therapeutic or adverse effects of aspirin has yet to be established, and further attempts at dosage reduction might compromise therapeutic efficacy before adverse effects are eliminated completely. Insufficient evidence exists to support the view that modified release formulations are safer it may be that other symptomatic gastrointestinal adverse effects, such as nausea and epigastric pain, can be significantly reduced[36].

4.4 ASPIRIN USED IN CANCER

There is increasing evidence that regular use of aspirin may reduce the risk of developing certain cancers. For most cancers, the evidence comes from observational studies that cannot prove a causal link but nonetheless provide important information that can be tested more rigorously in prospective randomized trials. One example in this category is breast cancer.

Breast cancer prevention:-

There is stronger evidence that aspirin may prevent colorectal cancer (bowel cancer). This possibility was originally raised in observational studies and was subsequently tested in prospective randomized trials. It has now been shown that regular consumption of aspirin reduces the risk of colorectal cancer by about 40 percent after at least 5 years.

Colorectal cancer prevention:-

The mechanism by which aspirin may reduce cancer risk is probably the inhibition of the enzyme

cyclo-oxygenase 2 (COX-2): a recent study from the United States showed that aspirin reduced the risk of developing colorectal tumors that over-express COX-2 but not of tumours that do not have increased expression of this enzyme.

4.5 ASPIRIN & PREGNANCY COMPLICATIONS

Aspirin may reduce the risk of pregnancy complications in women with pre-eclampsia and in those with antiphospholipid antibody syndrome (APS, Hughes syndrome). APS is an uncommon autoimmune disorder associated with an increased risk of miscarriage, pre-eclampsia, low birth weight and foetal death. The use of aspirin may reduce the risk of these complications. Pre-eclampsia is associated with poor intrauterine growth, premature birth and maternal death. Evidence that aspirin may reduce these complications suggests aspirin has a modest benefit in reducing risk without a significant risk of hemorrhage; there is currently no way of identifying which women will benefit from treatment.

4.6 SIDE EFFECTS OF ASPIRIN

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention. Get emergency help immediately if any of the following side effects occur:

Any loss of hearing, Bloody urine, Confusion, Convulsions (seizures), Diarrhea (severe or continuing), Difficulty in swallowing, Dizziness, lightheadedness, or feeling faint (severe), Drowsiness (severe), Excitement or nervousness (severe), Fast or deep breathing, Flushing, redness, or other change in skin color, Hallucinations (seeing, hearing, or feeling things that are not there), Increased sweating, Increased thirst, Nausea or vomiting (severe or continuing), Shortness of breath, troubled breathing, tightness in chest, or wheezing, Stomach pain (severe or continuing), Swelling of eyelids, face, or lips, Unexplained fever, Uncontrollable flapping movements of the hands (especially in elderly patients), Vision problems.

Symptoms of overdose in children: Changes in behavior, Drowsiness or tiredness (severe), Fast or deep breathing.

Less common or rare: Abdominal or stomach pain, cramping, or burning (severe), Bloody or black tarry stools, Headache (severe or continuing), Ringing or buzzing in ears (continuing), Skin rash, hives, or itching, unusual tiredness or weakness, vomiting of blood or material that looks like coffee grounds.

Some side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects.

4.7 AVOID THESE COMMON MEDICINES CONTAINING ASPIRIN

(Boldface Products Require a Prescription) Alka Seltzer, Anacin, Arthritis Foundation Pain Reliever, ASA Enseals, Arthritis Strength Bufferin Analgesic Caplets, ASA Suppositories, Ascriptin and Ascriptin A/D, Aspergum, Asprimox, Axotal, Azdone, Bufferin (most formulations), Buffets II, Buffex, Cama Arthritis Pain Reliever, COPE, Dasin. **Darvon Compound 65:** Dolprin. **Easprin:** Empirin**,** Epromate. **Equagesic Tablets:** Equazine**,** Excedrin Extra-Strength AnalgesicTablets and Caplets**,** Excedrin Migraine**,** Fiogesic**,** Fiorgen PF. **Fiorinal** (most formulations): Fiortal, Gelpirin, Genprin, Gensan, Heartline, Headrin, Isollyl, Lanoprinal. **Lortab ASA Tablets:** Magnaprin**,** Anacin, Analgesic**,** Marnal**,** Micrainin**,** Midol**. Norgesic Forte** (most formulations): Aspirin Norwich, AspirinPAC, Orphengesic, Painaid, Panasal, Percodan Tablets, Persistan, Pravigard, Rhinocaps. **Robaxisal Tablets:** Roxiprim, Saleto**,** Salocol**,** Sodol. **Soma Compound with Codeine Tablets:** Adult Chewable Aspirin**,** Supac**. Synalgos DC Capsules:** Tenol-Plus**,** Trigesic**,** Tri-pain. **Talwin Compound:** UN-aspirin**,** Ursinus**,** Vanquish Analgesic Caplets**,** Wesprin Buffered**,** Zee-Seltzer[37].

5. THE FUTURE OF ASPIRIN

Despite the clearly demonstrated benefits of aspirin, it remains underutilized. In an attempt to increase the use of aspirin in patients, several governing medical bodies have been carefully reviewing their official recommendations. In early 2009, the American Heart Association - in response to newly analyzed data - updated their official recommendations to state that all women over 65 be considered for routine aspirin therapy.

6. CONCLUSION

Aspirin and other non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and tumor growth in many experimental systems, but it is unclear which of these tumor models are relevant to humans. Aspirin, along with its analgesic-antipyretic uses, is now also being considered for prevention of cardiovascular disease, cancer, and treatment of human immunodeficiency virus infection**.** Although there is strong evidence that the use of aspirin reduces the risk of death and recurrent events in patients with coronary artery disease. The beneficial effects of aspirin (acetylsalicylic acid) for the treatment of acute coronary syndromes have been shown in many studies.

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