The aspirin story – from willow to wonder drug

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Summary

The story of the discovery of aspirin stretches back more than 3500 years to when bark from the willow tree was used as a pain reliever and antipyretic. It involves an Oxfordshire clergyman, scientists at a German dye manufacturer, a Nobel Prize-winning discovery and a series of pivotal clinical trials. Aspirin is now the most commonly used drug in the world. Its role in preventing cardiovascular and cerebrovascular disease has been revolutionary and one of the biggest pharmaceutical success stories of the last century.

Keywords: willow, history, antiplatelet agent, acetylsalicylic acid, aspirin.

Weeping willow to salicylic acid

Willow bark has been used as a traditional medicine for more than 3500 years. Unknown to the ancient Sumerians and Egyptians who made use of it, the active agent within willow bark was salicin, which would later form the basis of the discovery of aspirin (Fig 1).

Evidence for this early use of willow as an analgesic and antipyretic first surfaced in 1862. Edwin Smith (1822–1906), an American trader living in Cairo purchased a pair of ancient documents, the provenance of which was unknown. These scrolls dated back to around 1500 BC and are amongst the most important historical documents in medicine (Bryan, 1931). One of these is now known as the *Edwin Smith Surgical Papyrus* and details 48 surgical cases and their management. The other is now known as the *Ebers Papyrus*. This was an Egyptian record of around 160 herbal and vegetable remedies. One of these remedies is the first written record of the use of *tjeret* or *salix* (now known as willow) for treatment of non-specific pains. This herbal knowledge was passed on as empires rose and fell. The use of willow bark for pain relief continued through ancient Greece, where it was recommended by Hippocrates to relieve the pain of childbirth, through to Roman times, when its use was recorded by Pliny the Elder (Jeffreys, 2004).

Many traditional therapies were used for pain relief over the following centuries but were not studied systematically. The study of natural remedies received a boost with the discovery that the bark of the cinchona tree had fever-relieving properties. This bark was imported at great expense from South America. Although it was unclear at the time, we now know that cinchona is a source of quinine, the first treatment for malaria. It was with this background that in 1763 the Reverend Edward Stone (1702–1768), an Oxfordshire clergyman and fellow of Wadham College at the University of Oxford, investigated the use of willow bark. His letter to the president of the Royal Society outlining his findings survives today. He described using willow bark as a treatment for aguish (fever and shivering): '*There is a bark of an Englifh tree that, which I have found by experience to be a powerful aftringent, and very efficacious in curing aguifh and intermitting diforders*'. Reverend Stone left the willow bark to dry on the outside of a baker's oven for 3 months then pounded and sifted it into a powder. He reported: '*It hath been given I believe to fifty perfons, and never failed in the cure, except in a few autumual and quartun agues, with which the patients have been long and feverely afflicted*' (Stone, 1763). This letter is likely to be the driving force behind the use of willow bark to treat fevers by many physicians of the time.

The active ingredient in willow bark was not discovered until 1828 when Johann Buchner (1783–1852) first refined willow bark into yellow crystals and named it Salicin (after Salix, the genus of the willow tree) (Schindler, 1978). In 1829, the process was further refined by Pierre-Joseph Leroux (1795–1870) in France (Leroux, 1830) and taken a step further in 1838 when Raffaele Piria (1814–1865) produced a stronger compound from the crystals isolated from willow bark, which he named salicylic acid (Piria, 1838) (Fig 2).

In 1852, the French chemist, Charles Gerhardt (1816–1856), was the first to modify salicylic acid with the introduction of an acetyl group in place of a hydroxyl group, but the compound was not stable (Gerhardt, 1853). Gerhardt has one of the first true claims to be the person to discover aspirin but the lack of stability of his newly derived compound stopped him from developing it further. Acetylation

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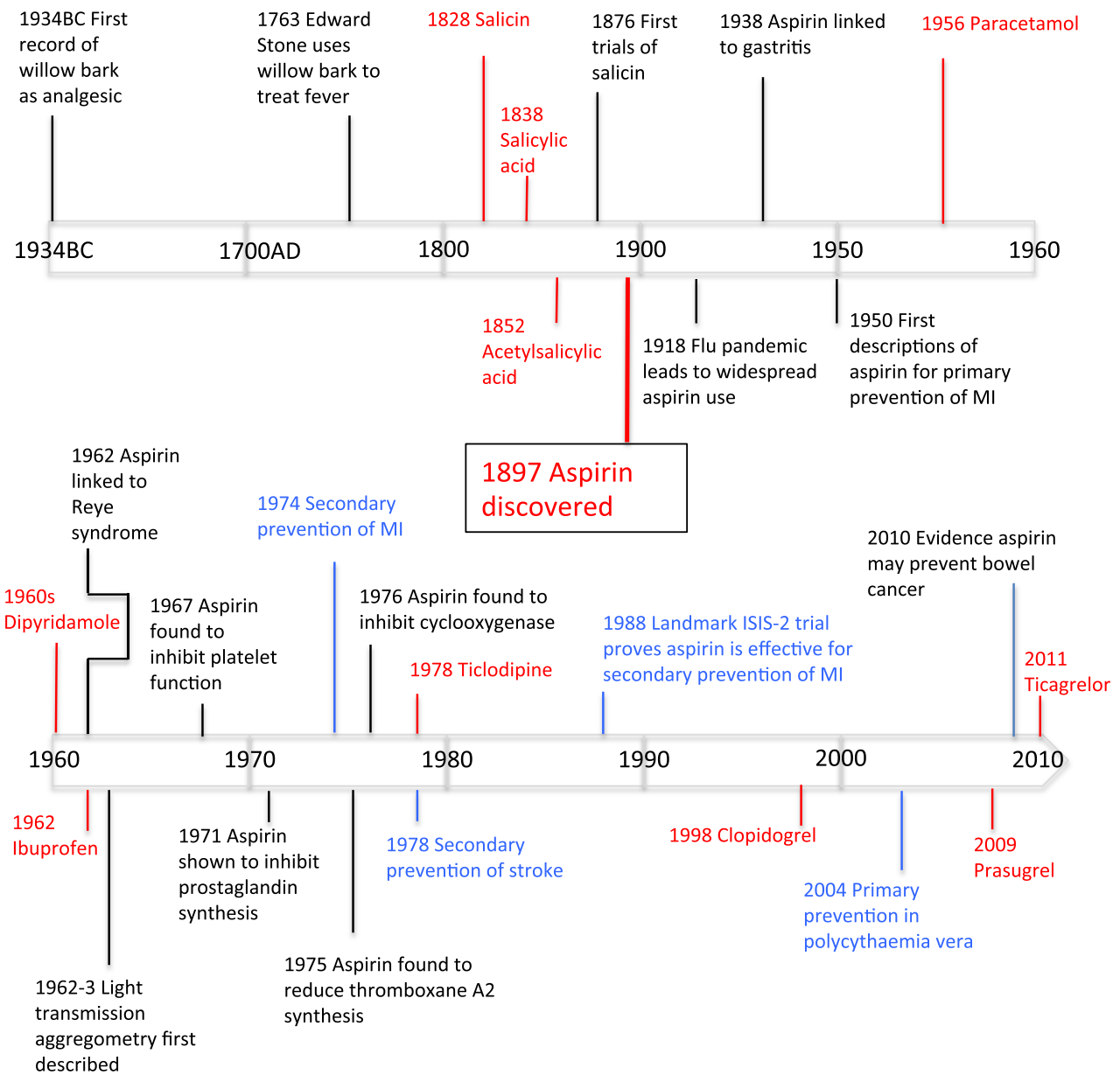

Fig 1. Timeline of the discovery of aspirin. Red text indicates new drug discovery. Blue text indicates landmark clinical trial. ISIS-2, Second International Study of Infarct Survival; MI, myocardial infarction.

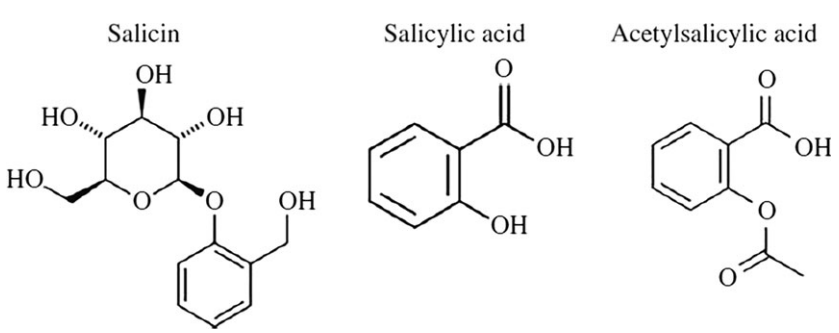

Fig 2. Molecular structure of salicin, salicylic acid and acetylsalicylic acid. Reproduced with permission from Wood (2015) From plant extract to molecular panacea: a commentary on Stone (1763) 'An account of the success of the bark of the willow in the cure of the agues'. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, **370**, pii:20140317.

of salicylic acid later proved to be the key step in reducing its irritant properties.

Early evidence for salicin

In 1876, the first clinical trial of salicin was published by Thomas Maclagan (1838–1903) a Scottish physician at the Dundee Royal Infirmary (MacLagan, 1876a,b,c). He investigated the effects of salicylate in relieving the symptoms of rheumatic fever. His first step was to take salicin himself: '*I determined to give salicin; but before doing so, took myself first five, then ten, then thirty grains without experiencing the least inconvenience or discomfort*'. He proceeded to treat eight patients with rheumatic fever with 12 grains of salicin every 3 h, demonstrating its antipyretic and anti-inflammatory effects (MacLagan, 1876a,b,c). Despite the clear antipyretic benefits of salicin, it was not taken up more widely due to complications with gastritis.

A breakthrough produces aspirin

In 1890, the German dye manufacturer, Bayer, set up a pharmaceutical division with research facilities for scientists. This followed early success deriving antipyretic medications from waste products of the dye manufacturing process. The establishment of this unit resulted in rapid development of a large number of drugs.

Three key figures in the discovery of aspirin at Bayer were Arthur Eichengrün (1867–1949) (the head of the pharmaceutical division, which was responsible for developing new drugs, Fig 3), Felix Hoffmann (1868–1946) (a chemist working for Eichengrün, Fig 4) and Heinrich Dreser (1860–1924) (the head of the pharmacology section, which was responsible for clinical trials). There is ongoing controversy over how the credit for the discovery of aspirin should be distributed.

In 1897, Eichengrün decided to develop a form of salicylate that did not cause gastric irritation. He allocated this task to Hoffmann. Hoffmann had studied as a pharmaceutical chemist at Munich University and in 1894 was hired by Farbenfabriken vormals Frederich Bayer & Company. Upon being allocated this task by Eichengrün, Hoffmann set to work trying to manipulate the salicylic acid that he extracted from dry meadowsweet leaves. He was able to acetylate a phenol group of salicylic acid, producing acetylsalicylic acid (Schmidt, 1934). His breakthrough was recorded in his laboratory book on 10 August 1897:

> 'When salicylic acid (100.0 parts) is heated with acetic anhydride (150.0 parts) for 3 hours under reflux, the salicylic acid is quantatively acetylated.. . .. . .By its physical properties, e.g. its sour taste without being corrosive, the acetylsalicylic acid differs favourably from salicylic acid, and is now being tested in this respect to test its usefulness.' (Jeffreys, 2004).

The acetylsalicylic acid (soon to be known as aspirin) was put through clinical trials by Dreser's pharmacology division. Initial reports were that it was a successful antipyretic but Dreser rejected it on the grounds that it may cause tachycardia and palpations. Ten days after his discovery of acetylsalicylic acid, Hoffmann produced a second famous drug: diacetylmorphine, also known as heroin. This drug was extraordinarily effective for pain relief and there was great hope that it would prove to be a non-addictive form of morphine.

Fig 3. Arthur Eichengrün (1867–1949). Reproduced with permission from Bayer AG, © Bayer AG.

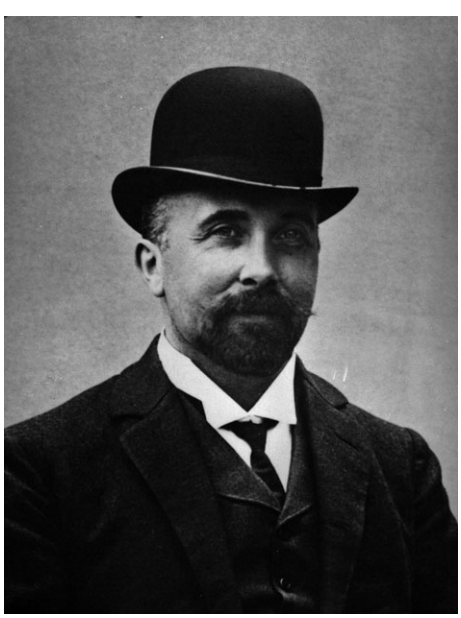

Fig 4. Felix Hoffmann (1868–1946). Reproduced with permission from Bayer AG, © Bayer AG.

Controversy over the discovery of aspirin

Eichengrün did not accept the rejection from the head of the pharmacology division and pushed ahead to run his own clinical trials, including taking the drug himself. These trials demonstrated it was an effective analgesic and had no apparent adverse effects on the heart. Dreser was not impressed and wrote a famous note in the margin of Eichengrün's report: 'This is the usual Berlin boasting. The product has no value' (Jeffreys, 2004). However following the intervention of the head of the unit who ordered further trials, Dreser accepted that the drug should be produced.

The name aspirin was agreed by a committee of those who had discovered the drug. The name was derived from a combination of acetyl and *spiraea* (the Latin name for meadowsweet). Although the uptake of aspirin in the medical community was initially slow, it soon took off and aspirin rapidly became known worldwide as one of the first analgesics. While Hoffmann and Eichengrün received no royalties for the development of aspirin, Dreser was paid royalties on every medication in his laboratory, and went on to make a personal fortune from the development of aspirin (Jeffreys, 2004).

Although Felix Hoffman is widely credited with the discovery of aspirin, there is some controversy over his claim (Sneader, 2000). At the time of the discovery, Bayer was producing large numbers of new drugs and no individual was specifically credited with the discovery. This changed in 1934, when Schmidt wrote a history of the discovery of aspirin after trawling through the Bayer archives (Schmidt, 1934). Notably, Eichengrün's contribution to the discovery was omitted. Eichengrün was a Jew and the rise of the Nazi party in Germany may have limited his ability to make a claim to a role. He had, by this time, left Bayer to set up his own company but was faced with heavy restrictions on his work. In 1938 he was forced to sell his business and in 1944 he was sent to the Theresienstadt concentration camp where he remained until the Russians liberated it in 1945 (Sneader, 2000).

In 1949, 15 years after the publication of the report attributing the discovery to Hoffmann, Arthur Eichengrün, published a manuscript emphasising that the work was performed under his direction. He went on to point out that he identified acetylsalicylic acid as the best compound they had isolated and was the first to call for clinical trials. He reported he had tested it on himself and had initiated the first trials. These trials demonstrated the antipyretic and analgesic effects of acetylsalicylic acid as well as its favourable side effect profile (Eichengrün, 1949).

The rise of aspirin

Within 3 years of its release onto the market, more than 160 scientific papers had been published extolling the virtues of aspirin. It went on to become enormously successful around the world. In 1918 following World War I, the world was hit by another tragic event, a worldwide outbreak of influenza. Approximately 50 million people died from the outbreak: more than died from fighting in the whole of World War I (Shanks, 2014). No cure could be found and vaccination was unsuccessful. Aspirin became widely used and was efficacious in relieving the symptoms of influenza, although it was not effective in reducing mortality. Its popularity was maintained thereafter and aspirin went on to be considered by the public and the medical profession as an effective antipyretic and analgesic, with few side effects when taken at standard doses (Lancet Editorial, 1935).

Aspirin slowly falls out of favour

Aspirin suffered a number of setbacks over the following years. After the invention of the gastroscope in 1932 it soon became apparent that aspirin use was associated with gastritis (Douthwaite, 1938; Douthwaite & Lintott, 1938). The development of new analgesic agents without these side effects, such as paracetamol in 1956 and ibuprofen in 1962, further dented aspirin's popularity. Further problems were identified in 1962 when aspirin was proposed to be associated with Reye syndrome in children (Mortimer, 1962). This condition is associated with an acute encephalopathy and fatty infiltration of the viscera and can be fatal. Over the following years, there was mounting evidence for this association (Linnemann *et al*, 1975) and aspirin is no longer recommended for anyone under the age of 16 years, although there are some exceptions, such as the treatment of Kawasaki disease.

A Nobel Prize for understanding how aspirin worked

While aspirin was an extraordinarily successful product, little was known about its mechanism of action. This started to become clearer later in the 19th century as scientific techniques improved.

One of the first manuscripts hypothesising how aspirin worked was published in 1960 by Harry Collier (1912–1983) (Collier & Shorley, 1970), a scientist working for Allen and Hanburys, a pharmaceutical company. He demonstrated that aspirin prevented bronchoconstriction in guinea pigs following administration of bradykinin. Aspirin did not exert an effect if it was given after bradykinin, leading him to hypothesise that aspirin inhibited bradykinin (Collier & Shorley, 1970). In 1963, Priscilla Piper (d. 1995), a PhD student from the University of London, joined Harry Collier to work on the mechanism behind the effects of aspirin. They pressed ahead with experiments for the next 5 years but struggled to make further inroads. At this point, Collier recommended that Piper should join John Vane's laboratory as a postgraduate student to learn new laboratory techniques and to take the investigation of the mechanism of aspirin further.

John Vane (1927–2004) is a key figure in the history of aspirin (Fig 5). He was born in Birmingham, United Kingdom in 1927 and went on to study chemistry at the University of Birmingham in 1944, before moving to the University of Oxford in 1946 to read pharmacology. His career went on to take him to the University of Sheffield and Yale in the United States before he returned to the United Kingdom to work in the University of London in 1955 where he developed the 'blood-bathed organ cascade'. This was a technique where blood was passed over two strips of tissue. The first 'upstream' strip was treated to induce it to release cytokines. He could then observe the effects on the downstream smooth muscle to see if it contracted in response to the cytokine that was released. He used this technique to dynamically measure levels of blood hormones, such as angiotensin and bradykinin (Flower, 2005).

Priscilla Piper worked with John Vane using this technique to examine how aspirin interacted with different cytokines. They were using a variant of the blood-bathed organ cascade where rabbit aorta was used as the 'downstream' tissue. They were able to demonstrate that aspirin antagonised an unknown cytokine that they named 'rabbit aorta contracting factor'. They went on to repeat Collier's experiments to demonstrate that injecting rabbit aorta contracting factor into the guinea pig induced anaphylaxis which was antagonised by aspirin (Piper & Vane, 1969). Vane was able to go on to demonstrate that rabbit aorta contracting factor was a prostaglandin and that aspirin inhibited its synthesis (Vane, 1971). The demonstration that aspirin inhibited prostacyclin synthesis paved the way for the future development of nonsteroidal anti-inflammatory drugs (NSAIDs) and other cyclooxygenase (COX) inhibitors and earned John Vane the Nobel Prize for Physiology or Medicine in 1982. He went on to be knighted in 1984.

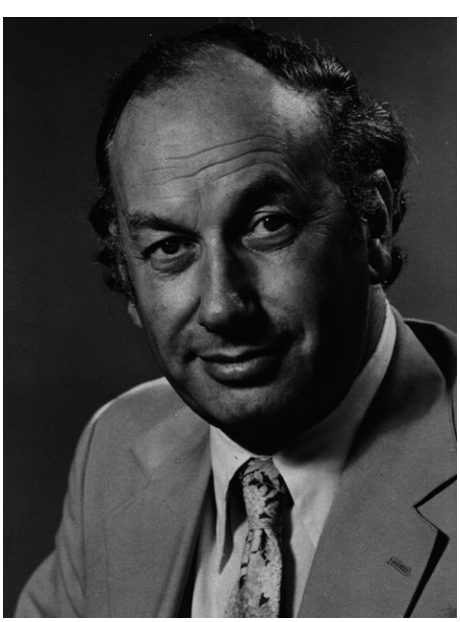

Fig 5. John Vane (1927–2004). Courtesy of the US National Library of Medicine.

The effect of aspirin on platelets

Platelets were first identified in 1865 by Max Schultze (1825–1874) (Schultze, 1865) and were found to be key to normal haemostasis in 1882 by Giulio Bizzozero (1846–1901) (Bizzozero, 1882). In 1961, with the role of platelets in pathological thrombus formation becoming increasingly clear, two Oxford scientists, John Poole and John French, postulated that inhibiting platelet function might be key to treating pathological thrombus formation. At the time, they were not aware of any agents that could successfully inhibit platelet function *in vivo* (Poole & French, 1961) and it would be several more years before the value of aspirin for preventing platelet aggregation was realised. In 1966, Armand Quick (1894–1978) noted that aspirin prolonged the bleeding time and noted that this was particularly pronounced amongst people with von Willebrand disease leading him to hypothesise that aspirin and von Willebrand disease may have similar effects (Quick, 1966).

A new technique, light transmission aggregometry, was developed in the early 1960s (Born, 1962; O'Brien, 1962, 1963) and this provided a tool to investigate aspirin's effects on platelets. In 1967, the US physicians, Harvey Weiss and Louis Aledort, reported that aspirin inhibited platelet function (Weiss & Aledort, 1967). They treated ten normal volunteers with either ten 300 mg capsules of aspirin, taken in divided doses, or the equivalent volume of lactulose. Bleeding time increased and platelet aggregation decreased in those treated with aspirin compared to controls.

It was known that arachidonic acid could induce platelets to release rabbit aorta contracting factor and, using the new tests of platelet function, it was shown that this resulted in platelet aggregation. In 1975, work led by Bengt Samuelsson (1934–) in Sweden demonstrated that rabbit aorta contracting factor was thromboxane A2 and that this was antagonised by the effects of aspirin and indomethacin (Hamberg *et al*, 1975). This work was augmented by the discovery of cyclo-oxygenase in 1976, which we now know to be the enzyme inhibited by aspirin, leading to impaired synthesis of thromboxane (Hemler *et al*, 1976).

Thromboxane A2 was known to induce vasodilation and aspirin antagonised this, suggesting a potentially prothrombotic effect. However its antiplatelet effect, which was becoming apparent, outweighed the effects of any vasoconstriction (Patrono *et al*, 1998).

Bengt Samuelsson went on to share the 1982 Nobel Prize for Medicine of Physiology with John Vane and Sune Bergstrom (1916–2004) (the first person to report the existence of prostaglandins). The mechanism of action of aspirin was finally proven more 70 years after its discovery.

Re-incarnation as an anti-platelet agent for the prevention of cardiovascular disease

In the early 1950s, long before aspirin's mechanism had been unravelled, a Los Angeles family doctor called Lawrence Craven (1883–1957) wrote to several American journals outlining his experience of using aspirin (Craven, 1950a,b, 1953, 1956). Initially he prescribed a chewing gum impregnated with aspirin to his patients to relieve post-operative pain from tonsillectomies. He noted that many of his patients used far more chewing gum than he had prescribed and often had serious bleeding complications. He deduced that aspirin might prevent thrombotic events. Craven went on to recommend aspirin to his patients and claimed to have treated more than 6000 people in this way. In 1957, Craven died from a myocardial infarction, which may have led many to question the value of his methods. His reports of the value of aspirin for prevention of myocardial infarction and stroke were largely forgotten for the next decade.

Through the 1970s there was an increased interest in the use of aspirin as an antiplatelet agent. The first randomised controlled trial using aspirin was published by Elwood *et al* (1974). A total of 1239 men discharged from hospitals in the UK with a myocardial infarction were identified. Participants were visited at home by the trial team and provided with either aspirin 300 mg daily or a matching gelatine capsule. While fewer participants treated with aspirin died in the following 6 months, the difference was not statistically significant and the trial was considered inconclusive. However, as further randomised controlled trial evidence accumulated, the overall benefit from the introduction of aspirin in this setting was a 25% reduction in recurrent myocardial infarction.

By 1980, six randomised controlled trials assessing the use of aspirin had been completed. In one of the first uses of meta-analysis, Sir Richard Peto (1943–) combined the results of these trials to demonstrate that aspirin reduced the risk of re-infarction by 21% (Peto, 1980). There were ongoing concerns about the risks of aspirin, with the incidence of a fatal bleed much more obvious to clinicians than the prevention of a myocardial infarction (Smith *et al*, 2014).

The Second International Study of Infarct Survival (ISIS-2 trial) recruited 17 187 patients, who were randomised to aspirin (160 mg/day), placebo, streptokinase or a combination of aspirin and streptokinase within 24 h of presenting with symptoms of myocardial infarction. When published in 1988, the clear reduction in mortality associated with aspirin therapy led to its widespread adoption (relative risk reduction 20% at 5 weeks) (ISIS-2 Collaborative Group, 1988) (Fig 6).

Early randomised controlled trial evidence in the setting of myocardial infarction was followed by evidence for aspirin in the treatment of stroke (relative risk reduction 31%) (The Canadian Cooperative Study Group, 1978). Two trials in 1991 clearly demonstrated that 30 mg (The Dutch TIA Trial Study Group, 1991) and 75 mg (The SALT Collaborative Group, 1991) per day were as effective as higher doses in prevention of cerebral ischaemia.

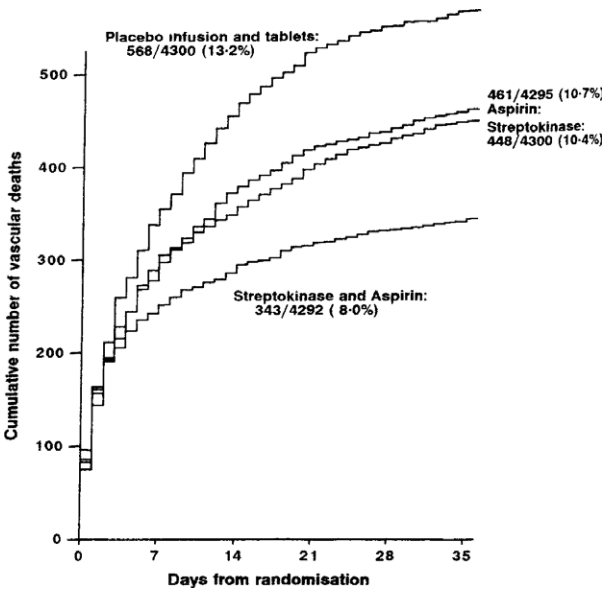

Fig 6. ISIS-2 trial results. Cumulative vascular mortality in days 0–35. Patients allocated to (i) active streptokinase only, (ii) active aspirin only, (iii) both active treatments, (iv) neither active treatment. Reproduced from: ISIS-2 collaborative group. (1988) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet,* **2**, 349–360. With permission from Elsevier (ISIS-2 Collaborative Group, 1988).

In 1994 the *British Medical Journal* devoted 50 pages to 'The aspirin papers' (Antiplatelet Trialists' Collaboration, 1994a,b,c). A meta-analysis by the Antiplatelet Trialists' Collaboration showed a reduction on vascular events by about one quarter (Antiplatelet Trialists' Collaboration, 1994a). Aspirin is now in widespread use for the prevention of cardiovascular disease. It is recommended at the time of acute myocardial infarction (National Institute for Health and Care Excellence, 2013; O'Gara *et al*, 2013) or ischaemic stroke as secondary prophylaxis (National Institute for Health and Care Excellence, 2008; Kernan *et al*, 2014). For those at high risk of cardiovascular disease, aspirin is recommended as primary prophylaxis (National Institute for Health and Care Excellence, 2015; Bibbins-Domingo, 2016).

Aspirin for the prevention of venous thromboembolism

Two recent studies examined the role of aspirin for secondary prophylaxis following initial treatment for venous thromboembolism (Becattini *et al*, 2012; Brighton *et al*, 2012). These studies demonstrated a 32% reduction in recurrence of venous thromboembolism compared to placebo.

Although aspirin was not compared to anticoagulants, the reduction in venous thromboembolism was considerably less than would be expected with an anticoagulant and the use of aspirin in this setting is not routinely recommended.

The potential of aspirin as primary thromboprophylaxis in surgical and medical patients had been shown by the third of 'The aspirin papers' (Antiplatelet Trialists' Collaboration, 1994c), which showed a 26% reduction in deep venous thrombosis (DVT). The Pulmonary Embolism Prevention (PEP) Trial found a 28% reduction in symptomatic DVT in major orthopaedic surgery (Pulmonary Embolism Prevention Trial Collaborative Group, 2000). However, thromboprophylaxis with anticoagulants gives larger reductions in thrombosis risk and so they are preferred (despite no head-to-head comparisons).

Aspirin is used for primary prophylaxis against venous thromboembolism in the small group of patients with multiple myeloma who are treated with lenalidomide or thalidomide (Lyman *et al*, 2015). Both of these chemotherapeutic agents are associated with a substantial increase in the incidence of venous thromboembolism and some form of venous thromboprophylaxis is recommended alongside their use. It should be noted that in each trial, there were fewer thrombotic events with low molecular weight heparin than with aspirin (Palumbo *et al*, 2011; Larocca *et al*, 2012).

Aspirin for stroke prevention in atrial fibrillation

Meta-analysis comparing aspirin to placebo found aspirin was associated with a non-significant lower risk of stroke [odds ratio (OR) 0·70, 95% confidence interval (CI) 0·47–1·07] (Aguilar & Hart, 2005). However when aspirin was compared to warfarin there was a lower risk of stroke with warfarin than aspirin (OR 0·68, 95% CI 0·54–0·85) (Aguilar *et al*, 2007). Although aspirin has been widely used in stroke prevention in atrial fibrillation, the National Institute for Health and Care Excellence concluded antiplatelet therapy to have limited benefits for patients with atrial fibrillation for preventing strokes and made a strong recommendation that aspirin should not be offered to patients at increased risk of stroke (National Institute for Health and Care Excellence, 2014).

Aspirin and haematological conditions

Myeloproliferative diseases

Aspirin is recommended for the prevention of cardiovascular events for patients with myeloproliferative diseases, such as polycythaemia vera and essential thrombocythaemia. The basis for this recommendation was the European Collaboration on Low-Dose Aspirin in Polycythaemia Vera (ECLAP1) trial, which randomised 518 patients with polycythaemia vera to aspirin or placebo. The risk of the combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis or death from cardiovascular causes was significantly lower in the group treated with aspirin (Landolfi *et al*, 2004). This has now become part of standard care for both patients with polycythaemia vera and essential thrombocythaemia (Harrison *et al*, 2010).

Thrombotic thrombocytopenic purpura and antiphospholipid syndrome

Due to the rarity of thrombotic thrombocytopenic purpura (TTP), randomised controlled trials are very difficult to perform, so management is extrapolated on the basis of observed clinical outcomes. Aspirin is recommended for TTP following treatment when the platelet count rises above 50×10^9/l (Scully *et al*, 2012), following the observation that following the introduction of aspirin and low molecular weight heparin thromboprophylaxis there was a lower incidence of thrombotic events compared to historical controls (Scully *et al*, 2007).

Thrombotic events associated with the acquired thrombophilia, antiphospholipid syndrome, are most commonly treated with anticoagulation. However there is evidence that people with antiphospholipid syndrome with a previous arterial event, such as a stroke, benefit equally from an anticoagulant or aspirin (Levine *et al*, 2004). For those who also have recurrent pregnancy loss, aspirin is recommended alongside low molecular weight heparin and also for those with previous pre-eclampsia or fetal growth restriction (Keeling *et al*, 2012).

Aspirin and acute bleeding

Approximately one quarter of patients with acute upper gastrointestinal bleeds (Hearnshaw *et al*, 2011) or haemorrhagic strokes are taking an antiplatelet agent (Lovelock *et al*, 2007) and the management is unclear.

For some time, platelet transfusion was recommended in a number of guidelines (Ferraris *et al*, 2012; Makris *et al*, 2013) on the basis of *in vitro* data (Vilahur *et al*, 2007; Li *et al*, 2012) and one small single arm study suggesting that the effects of aspirin could be reversed with the administration of 2–3 units of platelets (Thiele *et al*, 2012).

These findings have been called into doubt by the findings of a recent trial in patients with spontaneous intracranial haemorrhage who were taking an antiplatelet agent (most of whom were taking aspirin) (Baharoglu *et al*, 2016). Patients were randomly allocated to receive either one to two units of platelets or standard care (without platelet transfusions). Platelet transfusion failed to reduce new bleeding or expansion of the haematoma. More worryingly, it resulted in an increased risk of the composite endpoint of death and disability after 3 months. There are few other options at present; although some guidelines recommend consideration of desmopressin acetate, this is on the basis of little evidence

(Kozek-Langenecker *et al*, 2013; American Society of Anesthesiologists 2015; Rossaint *et al*, 2016). The optimal management of patients with these severe bleeding complications associated with aspirin is still unclear.

The future

Overall, despite aspirin being more than 100 years old, it continues to occupy a prominent place in the treatment of cardiovascular disease and there are no clear signs at present of it being displaced in the near future. There is, however, inter-individual variation in the response to aspirin, leading some to speculate on the existence of aspirin resistance. This is often defined as a failure to inhibit arachidonic acid-induced platelet aggregation by at least 95% (Reilly & FitzGerald, 1987). However there are problems with achieving consistency in testing for aspirin resistance and there are dramatically different rates of 'aspirin resistance' between studies (Le Quellec *et al*, 2016). The position of most guideline groups is that, at present, testing for aspirin resistance is a research tool only (Patrono *et al*, 2004; Michelson *et al*, 2005), but it remains to be seen if, using more consistent techniques, it is possible to identify individuals who will benefit most (or least) from aspirin. Several ongoing trials are assessing whether it is possible to personalise antiplatelet treatment according by using platelet function tests (NCT01959451) or point-of-care genetic tests (NCT01742117) to personalise the choice of antiplatelet agents.

A potential role for the regular use of aspirin to reduce the long-term risk of several cancers (Rothwell *et al*, 2010; Algra & Rothwell, 2012) could open up a whole new era of aspirin use.

Conclusion

Aspirin has come a long way since the use of willow bark by the ancient Sumerians and Egyptians. It is now the most commonly used drug in the world and has proved life saving in the prevention of cardiovascular disease. It is unclear what the future will bring for aspirin with the development of new antiplatelet medications. However, we owe an enormous debt to all those who discovered aspirin, identified its mechanism, and demonstrated how it reduces the risk of cardiovascular death.

Author contributions

MD prepared the first draft of the manuscript and DK and MD revised the manuscript to produce the submitted article.

Conflict of interest

The authors have no conflicts of interest to declare.

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