



Warfarin

materially informed drug

1920s
During the 1920s cattle in the US and Canada started dying mysteriously. Farmers knew it was due to mouldy hay, but could do nothing about it.

Poster designed and researched by Jane Dickson.

With thanks to the D3 team: Tony Cornford, Ela Klecun, Will Venters, Valentina Lichtner & Ralph Hibberd

1922
Frank Schofield, a veterinary scientist living in Ontario made the link between the dying cattle and the rotting sweet clovers (*Melilotus alba* and *Melilotus officinalis*) in their feed. It became known as Sweet Clover Disease.

Lee Roderick and his team at the Agricultural Experimental Station of North Dakota make the link between coumarin and a lack of prothrombin - a clotting factor in the blood - so isolating the cause of the internal bleeding in cattle.

1929
Carl Link and his team synthesize dicoumarol in their laboratory.

Wisconsin Alumni Research Foundation (WARF) is given the patent rights for dicoumarol. In the same year, dicoumarol is shown to work as an anticoagulant for humans.

1940
Dicoumarol is made available to treat thrombosis and myocardial infarction.

Carl Link, while recovering from a lung infection in a rat infested sanatorium has the idea of using warfarin as a rodenticide. First registered for this use in the US in 1948.

1941
Human use re-considered when a US army recruit attempts suicide with a high dose of warfarin and is successfully saved with vitamin K.

Joseph Stalin the Soviet dictator is allegedly poisoned with warfarin by one of his inner circle in 1953.

1944
Endo Products Inc. introduce coumadin onto the market. Endo was later acquired by du Pont.

US President Dwight Eisenhower suffers a heart attack and is prescribed Coumadin, thus popularising rat poison as a human medication.

1948
Late 1950s: hirudin, a specific thrombin inhibitor, isolated from leech saliva; served as a prototype for the design of thrombin inhibitors.

Research over a 30 year period shows that warfarin is effective in secondary prevention - lowering the death rate of people who have had a heart attack.

1951
Wiegman & Vossepoel develop a computer program for long term anticoagulation control.

1976 - 1981 differences between UK & US thromboplastin lead to extensive research into bleeding risks. Randomized trials result in the development of a target range for blood clotting called the International Normalised Ratio (INR).

1953
Heike Moeller, a German student demonstrates that she is able to test and monitor her own INR during a doctor-patient seminar. This leads to the development of a self-testing machine.

1989 initial crystal structure of thrombin reported.

1954
1998 Barr Laboratories sue DuPont Merck for publicly attacking their generic warfarin and initiating a national campaign to curb access to generics, in order to protect Coumadin's market share from competition.

1989 - 1995: Six clinical trials show that warfarin, now a generic, is effective at preventing strokes in people with atrial fibrillation. This prompts even more widespread use of warfarin.

1956
1998 Thrombosis prevention trial: randomised 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.

Ann Daly & Farhad Kamali's team at Newcastle University are the first to demonstrate a statistically significant association between CYP2C9 genotype and sensitivity to warfarin. The study also confirms that patients needing a low dose of warfarin are significantly more likely to have suffered serious bleeding events whilst taking the drug.

1959
2001 BMS buys DuPont Pharma, (including warfarin) for \$7.8 billion in 2001.

2002 Research shows an association of gene CYP2C9 (which encodes a liver enzyme that breaks down warfarin) with major bleeds.

1960
2003-4 the UK Committee on Safety of Medicines receives several reports of increased INR and risk of haemorrhage in people taking warfarin and drinking cranberry juice.

2005 Association of gene VKORC1 (encodes the target of warfarin) with warfarin dose. This polymorphism explains 30% of the dose variation between patients.

1975-1981
2005 A 2005 report concludes that self-testing and patient self-management are as effective methods of monitoring oral anticoagulation therapy as clinic monitoring.

The Food and Drug Administration (FDA) in the US updates warfarin labelling, adds PGx information to warfarin label and approves first test kit.

1977
2006 systematic review and meta-analysis of 14 randomized trials showed home testing led to a reduced incidence of complications (thrombosis and major bleeding) and improved time within therapeutic range.

The International Warfarin Pharmacogenetics Consortium introduce the international standard algorithm for gene-guided dosing of warfarin. This approach has been adopted by large US medical centres and the FDA states that it will prevent 17,000 strokes a year in the US.

1978
2006 ximelagatran (a rival anticoagulant) withdrawn from the market owing to potential liver toxicity.

2007 The 2009 A large National Institutes of Health (NIH) Random Control Test (RCT) initiated.

1982
2008 The American College of Medical Genetics & Genomics (ACMG) and the guidelines from the American College of Chest Physicians (ACCP) do not recommend home/self testing.

2009 2011: Apixaban approved as an alternative to LMWH for short-term VTE prevention.

1984
2010: US Food and Drug Administration (FDA) mandates inclusion of dose recommendations based on genotype in the warfarin prescribing information leaflet accompanying the drug.

2011: 33.9 million prescriptions of warfarin are dispensed at retail pharmacies in the US in 2011 (data from the NHS Information Centre and IMS Health).

1986
2012: CHAD (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke) score recommended by the European Society of Cardiology.

2012: over 10.1 million prescriptions of warfarin written in England alone, with approximately 1% of the UK population being prescribed this drug at any given time.

1988
2012: Dabigatran approved as an alternative to warfarin for use in Stroke Prevention in Atrial Fibrillation (SPAF).

2014: 31 million prescriptions are written for warfarin in the United States in 2014.

1989
2016: BNF released as a smart phone app, marking the truly digital nature of medicine prescription.

2017: 2 machines for mobile genetic testing for warfarin sensitivity released in 2017 one from the University of Liverpool and one from the University of Newcastle.

1998
Now more than 165,000 mobile health apps on the market.

The Delivering Digital Drugs (D3) Project runs from 2014 - 2017. Shows how drugs such as warfarin have become digital drugs.

2001
2017: Warfarin digital drug.