

Ministry of Defence

Synopsis of Causation

Diabetes Mellitus

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. Diabetes mellitus describes several syndromes of abnormal carbohydrate metabolism that are characterised by hyperglycaemia. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of resistance to the action of insulin.
- 1.2. **Type 1 diabetes (T1DM)**. Previously known as insulin-dependent (IDDM) or juvenile-onset diabetes. It is characterised by an autoimmune-mediated destruction of the pancreatic beta cells that are responsible for the production of insulin, leading to an absolute deficiency of insulin.
- 1.3. **Type 2 diabetes (T2DM)**. Previously known as non-insulin-dependent (NIDDM), maturity-onset, or adult-onset diabetes. It is, by far, the most common type of diabetes (~90%) and is characterised by varying degrees of resistance to the action of insulin with relative insulin deficiency. It is a progressive disorder with decreasing ability to produce insulin over time, leading to increased therapeutic requirements.
- 1.4. Diabetes mellitus can arise as a feature of various diseases, genetic or acquired, referred to collectively as **secondary diabetes**.
- 1.5. **Genetic causes of secondary diabetes**. There are a large number of genetic syndromes associated with the development of diabetes, although collectively these account for probably only 1-2% of the total number of cases of diabetes.
- 1.6. **Acquired causes of secondary diabetes**
 - 1.6.1. **Pancreatic disease**. The pancreas is responsible for production and release of insulin and therefore any disease that destroys pancreatic tissue can result in diabetes.
 - Haemochromatosis. A genetic condition characterised by excessive iron deposition in various organs of the body, including the pancreas. Diabetes affects around 50% of people with this condition
 - Cystic fibrosis. Diabetes usually arises in the late teens or early twenties
 - Acute or chronic pancreatitis. Inflammation and destruction of the pancreas, secondary to alcohol or gallstones, can lead to diabetes
 - Pancreatic cancer
 - Pancreatic surgery
 - 1.6.2. **Endocrine disease**. Any endocrine condition where there is excessive production of a hormone that opposes the action of insulin, i.e. increases glucose levels, can cause diabetes.
 - Hyperthyroidism (excess thyroid hormone production)
 - Acromegaly (excess growth hormone production)

- Cushing's syndrome (excess cortisol production)

1.6.3. **Drugs.** There are a large number of drugs that cause or worsen diabetes.

- Glucocorticoids, which are used in conditions such as chronic lung disease, rheumatoid arthritis, inflammatory bowel disease and polymyalgia rheumatica
- Drugs used to lower blood pressure: diuretics, (mainly thiazide diuretics), β -blockers
- Drugs used to treat HIV infection

1.7. Treatment of secondary diabetes is the same as for type 1 or type 2 diabetes, depending on severity i.e. insulin or oral medication, although the underlying cause should also be treated.

2. Clinical Features

- 2.1. **T1DM.** Tends to present during childhood or adolescence although it can occur at any age.
- 2.2. **T2DM.** Tends to present during the fifth and sixth decades, usually in obese people. The rise in the prevalence of obesity is being mirrored by a rise in the prevalence of T2DM, which is being seen in increasingly younger patients and some adolescents. T2DM is much more common than T1DM and accounts for approximately 90% of all cases of diabetes mellitus.
- 2.3. Patients with T1DM tend to present acutely with the classical symptoms of diabetes: polyuria, polydipsia and weight loss. However, some may have a slower onset more akin to T2DM and are said to have a variant of T1DM known as latent autoimmune diabetes mellitus in adults (LADA). Other presenting symptoms include blurred vision or recurrent genital tract infections, such as thrush. Some patients may present acutely unwell with diabetic ketoacidosis (DKA), characterised by hyperventilation, abdominal pain, vomiting, dehydration and, later on, coma. DKA is a serious condition with a high mortality.
- 2.4. Patients with T2DM may be without symptoms or may have the classical symptoms mentioned above. T2DM may also present with the complications of diabetes, such as retinopathy or nephropathy, as the disease may have been present for a number of years before the diagnosis is made.
- 2.5. Over many years, patients may develop the complications of diabetes (see section 4 - prognosis).
- 2.6. Patients with T2DM frequently have other abnormalities in addition to hyperglycaemia which increase their risk of developing macrovascular and microvascular complications. These include obesity, hypertension, dyslipidaemia, and clotting abnormalities.
 - 2.6.1. **Obesity.** This is defined by the body mass index, (BMI) being in excess of 30 (calculated as the ratio of weight [kg] / height [m]²). Obesity is one of the most important risk factors for developing diabetes and about 80% of patients with T2DM are obese. The risk increases progressively as the body weight increases; a person with a BMI of 35 has an 80-fold greater risk than someone with a BMI of 22.
 - 2.6.2. **Hypertension.** This is twice as common in patients with diabetes as in the general population, and is present in up to a third of patients with T1DM and up to half with T2DM. Current guidelines recommend treatment with anti-hypertensive medication, aiming to maintain blood pressure values below 130/80 mm Hg, particularly in those who have nephropathy.
 - 2.6.3. **Dyslipidaemia.** Lipid abnormalities in patients with T2DM are common and the characteristic cluster is known as “diabetic dyslipidaemia”. This refers to high levels of triglycerides and decreased high-density lipoprotein (HDL) cholesterol. Low-density lipoprotein (LDL) cholesterol is often normal but there is an increase in the number

of small dense LDL particles, which are more likely to cause atherosclerosis.

- 2.6.4. **Clotting abnormalities.** T2DM is characterised by an increased tendency for platelets to aggregate, and impairment in some of the plasma proteins responsible for regulating the breakdown of clots, a process known as fibrinolysis. One such protein is plasminogen activator inhibitor-1 (PAI-1). Impaired fibrinolysis is associated with a higher rate of cardiovascular events.

3. Aetiology

3.1. Type 1 and type 2 diabetes are very distinct diseases in terms of the underlying aetiology.

3.2. Type 1 diabetes

3.2.1. T1DM is an autoimmune disorder, resulting in the destruction of the β -cells in the islets of Langerhans, areas of endocrine tissue within the pancreas.

3.2.2. The lifetime risk of developing diabetes is greatly increased when another member of the family has T1DM (6% risk in a child if a parent has T1DM, 5% risk in a brother/sister, and 30% risk in an identical twin).

3.2.3. Environmental factors most likely trigger the onset of diabetes in genetically predisposed individuals. The process progresses over months or years and T1DM occurs when approximately 60% of the β -cells have been destroyed.

3.2.4. Evidence for an environmental trigger for the onset of diabetes is based on epidemiological research. For example, people who have migrated from an area of low incidence of T1DM to an area of high risk, adopt the same risk as the population to which they move. The most commonly associated factors are viruses (e.g. Coxsackie B virus), various food components (e.g. cow's milk and wheat proteins), and low exposure to sunlight. There is no direct evidence to support a cause and effect but only to suggest a possible association between these factors and the development of diabetes.

3.3. Type 2 diabetes

3.3.1. T2DM develops due to a combination of insulin resistance (the body's inability to respond to the glucose lowering effects of insulin) and a decreased ability of the β -cells to produce insulin. Whilst the β -cells are able to meet the insulin secretory demand, normal glucose levels can be maintained but as β -cell function declines, progressive hyperglycaemia ensues. In the early stages it is often postprandial glucose levels that are most abnormal.

3.3.2. T2DM has a genetic component: 10% of patients with T2DM will have an affected brother/sister. However, the genetics are much more complex than in T1DM.

3.3.3. Environmental influences have a significant role in the development of T2DM. The main risk factors for developing T2DM are reduced physical activity and obesity, with the risk increasing exponentially as body weight increases.

4. Prognosis

- 4.1. The life expectancy of patients with diabetes is significantly reduced. Death occurs prematurely due to the high incidence of macrovascular and microvascular disease. In type 2 diabetes, cardiovascular disease is the most common cause of death (approximately 75%).
- 4.2. **Macrovascular disease**
 - 4.2.1. **Myocardial infarction (MI)**. The risk of a myocardial infarction is increased 2- to 4-fold in T2DM. Patients with T2DM without a previous MI can have the same risk for coronary heart disease (CHD) events as non-diabetic patients who have already had a MI (about 20% after 7 years).¹
 - 4.2.2. **Stroke**. Strokes related to clot formation within the brain, rather than haemorrhage, are 2- to 4-times more common in patients with diabetes, and survival rates are lower.
 - 4.2.3. **Peripheral vascular disease** (poor circulation in the legs). This can cause no symptoms, pain in the legs on exertion (intermittent claudication), or pain at rest (critical ischaemia). In severe cases, it can result in lower limb gangrene. Diabetes is the leading cause of non-traumatic amputation which is 15-times more likely than in people without diabetes.²
- 4.3. **Strategies to reduce macrovascular disease**
 - 4.3.1. **Smoking cessation**. Smoking is a major independent risk factor for cardiovascular disease.³ Vigorously encouraging smoking cessation is an essential aspect in the management of diabetes.
 - 4.3.2. **Controlling blood pressure (BP)**. The UKPDS (United Kingdom Prospective Diabetes Study) in patients with T2DM demonstrated a large reduction (44%) in the number of strokes with treatment of hypertension, but a non-significant reduction in the risk of myocardial infarction or amputation.⁴ The British Hypertension Society (BSH) guidelines recommend optimal BP goals for people with diabetes of systolic BP <130 mm Hg and diastolic BP <80 mm Hg.⁵ Despite best practice, these levels may be difficult to achieve and people will require more than one antihypertensive agent. The BSH guidelines provide a treatment sequence algorithm for logical therapeutic combinations. ACE inhibitors may be of particular benefit, particularly in patients with microalbuminuria.⁶
 - 4.3.3. **Lipid lowering**. Trials such 4S (simvastatin),⁷ CARE (pravastatin),⁸ the Heart Protection Study (simvastatin),⁹ WOSCOPS (pravastatin),¹⁰ CARDS (atorvastatin)¹¹ and ASCOT (atorvastatin)¹² have demonstrated major cardiovascular risk reduction for both primary and secondary intervention with statins. Most, if not all, patients with diabetes over the age of 40 are at sufficiently increased cardiovascular risk that they should be treated for life with LDL-lowering medication.

- 4.3.4. **Glycaemic control.** Extended follow up of the DCCT (Diabetes Control and Complications Trial), in patients with T1DM, has shown that improving glycaemic control can reduce the risk of macrovascular disease in the longer term.¹³ The UKPDS, in patients with T2DM, showed only a borderline significant 16% reduction in MI risk with good glycaemic control,¹⁴ but a 39% MI risk reduction in overweight patients treated with metformin.¹⁵
- 4.3.5. **Aspirin.** The merits of daily aspirin therapy in patients with macrovascular disease are widely accepted. The absolute benefit of aspirin is greatest in patients over the age of 65 years with diabetes or diastolic hypertension. The best evidence for the use of aspirin comes from the Hypertension Optimal Treatment (HOT) trial, in which low-dose aspirin reduced major cardiovascular events by 15% and myocardial infarction by 36% in the whole group and by similar amounts in patients with diabetes.¹⁶ The risk of non-fatal bleeds (including intra-cerebral and gastro-intestinal) was more frequent.
- 4.3.6. According to the American Diabetes Association, aspirin is recommended for secondary prevention in diabetics with a history of myocardial infarction, vascular bypass, stroke or transient ischemic attack, peripheral vascular disease, claudication, or angina. Aspirin is also recommended for primary prevention in any diabetic patient with an additional cardiovascular risk factor e.g. age >40 years, cigarette smoking, hypertension, obesity, albuminuria, hyperlipidaemia, or a family history of coronary heart disease. In spite of these recommendations, aspirin use in patients with diabetes is quite low.

4.4. Microvascular disease

- 4.4.1. **Retinopathy.** Diabetes is the commonest cause of blindness in the working population, often as a result of retinopathy, which is the commonest clinically significant microvascular complication of diabetes. The risk of retinopathy increases the longer someone has diabetes and the more poorly controlled it is.

In T1DM, retinopathy is uncommon within the first 5 years but its incidence increases gradually thereafter. In T2DM, 20% have evidence of retinopathy within 2 years of diagnosis and 60% within 15 years. Retinopathy may be detected and treated early using retinal screening.

- 4.4.2. **Nephropathy.** Diabetic nephropathy refers to renal damage arising from the presence of diabetes. The progression of the condition reflects increasing leakage of protein from the kidneys. Most of this protein is albumin, as this is the most abundant of the plasma proteins. The initial abnormality occurs when only a small amount of protein is leaked from the kidneys, so called “microalbuminuria”. This can only be detected by sensitive assays, not by dipstick. When the amount of protein in the urine is more significant, it is known as proteinuria. This amount can be detected by a dipstick. This can progress to end stage renal disease, which may require dialysis.

4.4.3. **Neuropathy.** There are various forms of diabetic neuropathy:

- i) **Peripheral neuropathy.** This is probably the most common form of neuropathy, usually affecting the extremities of the lower limbs. Later it may affect the upper limbs, often ascending up the legs or arms towards the trunk. For this reason, the distribution of diabetic peripheral neuropathy is sometimes referred to as being in a “glove and stocking” distribution. The neuropathy may cause a loss of sensation which can lead to damage as injuries go unnoticed or can be associated with severe, disabling pain. Weakness tends not to be a problem. Complications arising from neuropathy include foot ulceration (often occurring in combination with poor circulation), damage to the joints (known as “Charcot arthropathy”) and swelling of the leg.
- ii) **Pressure palsies.** A number of nerves travel through confined spaces and can sometimes become compressed and damaged, causing weakness. This is known as “pressure palsy”. One such example, carpal tunnel syndrome, is caused by compression of one of the nerves responsible for hand movements as it crosses the wrist. Pressure on the nerve causes weakness and wasting of some of the muscles of the hand.
- iii) **Mononeuropathies.** This means single nerves are affected. One such example occurs when one of the nerves supplying the muscles responsible for eye movements (e.g. the third cranial nerve) becomes damaged. The patient develops double vision because the eyeballs are unable to move in a coordinated fashion.
- iv) **Autonomic neuropathy.** The autonomic nervous system is responsible for controlling many of the body’s involuntary actions, for example, bladder or bowel function, erections, and preventing falls in blood pressure on standing. When the autonomic nervous system is affected by neuropathy there can be a variety of symptoms. These include vomiting after eating due to delayed emptying of the stomach, diarrhoea due to bacterial overgrowth from stagnant bowel contents when movement of the bowels is slowed, impotence (see below), and dizziness on standing.

4.5. **Strategies to prevent microvascular disease**

- 4.5.1. Both the DCCT trial in T1DM¹³ and the UKPDS trial in T2DM¹⁴ showed that the risk of retinopathy, microalbuminuria, and neuropathy fell as the degree of glycaemic control improved.
- 4.5.2. Treatment of hypertension in the UKPDS trial reduced the risk of microalbuminuria.⁴
- 4.5.3. Other important factors are the duration of diabetes and hypercholesterolaemia (high cholesterol).

4.6. **Other complications of diabetes**

- 4.6.1. Cataract and glaucoma are more common in diabetics.

- 4.6.2. There are several musculoskeletal manifestations of diabetes including diabetic cheiropathy, Dupuytren's contracture, and limited joint mobility. These problems occur as a result of abnormal collagen deposition in the connective tissues, usually affecting the joints of the hands.
 - 4.6.3. The fracture risk in type 1 and 2 diabetes is increased. Bone mineral density is reduced in T1DM but increased in T2DM and in these circumstances the fracture risk relates to factors other than just bone mineral density e.g. increased risk of falls due to hypoglycaemia, neuropathy, or eye disease.
 - 4.6.4. Impotence (failure to achieve or maintain an erection) may be caused by factors other than neuropathy, including drugs such as β -blockers, commonly used to treat high blood pressure in diabetes, vascular disease, or Peyronie's disease.
- 4.7. **Future directions in treatment of diabetes**
- 4.7.1. **Pancreatic transplantation.** Until fairly recently, the only definitive treatment for T1DM was pancreatic transplantation, which is often performed in combination with kidney transplants. Only about 1,500 whole pancreas transplants occur annually worldwide, due to the high cost and limited availability of possible donors.
 - 4.7.2. **Islet cell transplantation** was introduced in 2000 and involves removing only the insulin producing cells (known as the islets) from a donor's pancreas.
 - 4.7.3. **Stem cell therapy.** The aim of stem cell related research is to use primitive cells (sometimes from embryos) which have the ability to transform into insulin producing islet cells.
 - 4.7.4. **Gene therapy.** This therapy is still a long way off, but the aim is to introduce genes into the body that can be incorporated into cells and stimulated to produce insulin.

5. Summary

- 5.1. Type 1 diabetes tends to occur at a younger age and to present acutely, and is a result of an absolute insulin deficiency. Treatment with insulin is required for life.
- 5.2. Type 2 diabetes occurs in older, usually obese, people. It presents insidiously, is often associated with insulin resistance, and patients are relatively insulin deficient. It is a progressive disorder that needs increasing therapy with time. Treatment is initially with diet but oral agents are almost always required in addition, with many patients requiring insulin therapy in the longer term.
- 5.3. Long-term diabetes results in a number of complications, so-called microvascular and macrovascular disease.
- 5.4. Microvascular complications include retinopathy, nephropathy, and neuropathy.
- 5.5. Macrovascular complications include heart disease, stroke, and amputations.
- 5.6. The rate of complications can be reduced by good diabetic control and control of associated risk factors such as dyslipidaemia and hypertension.

6. Related Synopses

7. Glossary

arthropathy	Any disease or disorder involving a joint.
atherosclerosis	The “furring up” of the arteries supplying an organ.
autoimmune	A process whereby the body’s own immune system destroys its tissues.
cardiovascular disease	Disease affecting the heart or blood vessels.
cataract	Cloudiness of the lens causing blurred vision.
cheiropathy	Stiffness and reduced movement in the joints of the hands.
claudication	Pain or fatigue in the legs or arms due to poor supply of oxygen to the muscles.
diabetic dyslipidaemia	Showing an elevation of triglycerides and lowering of high-density lipoprotein (HDL) cholesterol with an increase in small dense low-density lipoprotein (LDL) cholesterol.
dipstick	The process (using a hand-held dipstick) whereby urine is tested for sugar, blood, or protein to assess for signs of kidney damage.
diuretics	Drugs that cause urine to be excreted by the body.
Dupuytren’s contracture	Stiffness and reduced movement usually in the third and fourth fingers.
end stage renal disease	Severe damage to the kidney such that dialysis or transplantation is necessary.
epidemiological	Based upon the study of populations.
fibrinolysis	A normal, ongoing process that dissolves fibrin and results in the removal of small blood clots.
glaucoma	Eye disease characterised by an increase in intra-ocular pressure.
glucocorticoids	Steroids.
glycaemic	Relating to blood glucose (sugar).
hyperglycaemia	Showing an elevation of the blood glucose concentration.
hypertension	High blood pressure.

insulin	A peptide hormone that enables the body to metabolise and use glucose.
ischaemia	Reduced blood flow to an area of the body due to an obstructed vessel.
ketoacidosis	A life-threatening condition in which ketones, which result from the breakdown of fat for energy, accumulate in the bloodstream and the pH of the blood decreases.
macrovascular	Relating to damage to organs supplied by large blood vessels (for example, the heart or brain).
microalbuminuria	The presence of a small amount of protein leaking from the kidneys into the urine.
microvascular	Relating to damage to organs supplied by small blood vessels (for example, the eyes or kidneys).
myocardial infarction	Heart attack.
nephropathy	Damage to the kidneys.
neuropathy	Damage to the nerves (usually those involved in sensation).
Peyronie's disease	Thickening of part of the shaft of the penis causing a bend and an inability to achieve an erection.
polyuria	The passage of large volumes of urine.
polydipsia	Thirst.
proteinuria	Too much protein in the urine.
retinopathy	Damage to the light sensitive layer of the eye (the retina).

8. References

1. Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998 Jul;339(4):229-34.
2. Morris AD, McAlpine R, Steinke D, Boyle DI, Ebrahim AR, Vasudev N et al. Diabetes and lower limb amputations in the community. A retrospective cohort study. *Diabetes Care* 1998 May;21(5):738-43.
3. Yudkin JS. How can we best prolong life? Benefits of coronary risk factor reduction in non-diabetic and diabetic subjects. *BMJ* 1993 May;306(6888):1313-8.
4. UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998 Sep;317(7160):703-13.
5. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004;18:139-85.
6. Dagenais GR, Yusuf S, Bourassa MG, Yi Q, Bosch J, Lonn EM et al; HOPE investigators. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. *Circulation* 2001 Jul;104(5):522-6.
7. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994 Nov;344(8934):1383-9.
8. Sacks FM, Pfeffer MA, Moyer LA, Rouleau JL, Rutherford JD, Cole TG et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996 Oct;335(14):1001-9.
9. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002 Jul;360(9347):7-22.
10. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995 Nov;333(20):1301-7.
11. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ et al; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004 Aug;364(9435):685-96.

12. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003 Apr;361(9364):1149-58.
13. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005 Dec;353(25):2643-53.
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes: UKPDS 33. *Lancet* 1998 Sep;352(9131):837-53.
15. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes: UKPDS 34. *Lancet* 1998 Sep;352(9131):854-65.
16. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998 Jun;351(9118):1755-62.