What are Cardiovascular Diseases (CVDs)?

- Diseases of the heart
- Vascular diseases of the brain
- Diseases of blood vessels.

Biggest cause of deaths worldwide (17 million in 2008)
- 40–59 year olds: ca. 40% people with CVD
- 60–79 year olds: ca. 70% people with CVD
- 80% of CVD deaths due to stroke and heart attack

1. CVDs due to atherosclerosis:
- ischaemic heart disease or coronary artery disease (e.g. heart attack)
- cerebrovascular disease (e.g. stroke)
- diseases of the aorta and arteries, including hypertension and peripheral vascular disease

2. Other CVDs
- congenital heart disease
- rheumatic heart disease
- cardiomyopathies
- cardiac arrhythmias

Rheumatic heart disease is caused by damage to the heart muscle and heart valves from rheumatic fever, following a streptococcal pharyngitis/tonsillitis.

The heart valves can remain stretched and/or scarred, and normal blood flow through damaged valves is interrupted. Blood may flow backward through stretched valves that do not close properly, or may be blocked due to scarred valves not opening properly. When the heart is damaged in this way, the heart valves are unable to function adequately, and heart surgery may be required. Untreated, RHD causes heart failure and those affected are at risk of arrhythmias, stroke, endocarditis and complications of pregnancy.

Once the acute illness has gone away, patients need to take penicillin, or an equivalent antibiotic, for many years to prevent recurrences. This is a very important treatment because the risk of heart valve damage increases if rheumatic fever recurs.


Malformations of heart structures present at birth are known as congenital heart defects. They may be caused by: (i) a close blood relation between parents (consanguinity); (ii) maternal infections (e.g. rubella); (iii) maternal use of alcohol and drugs (e.g. warfarin); and (iv) poor maternal nutrition (e.g. deficiency of folic acid). In some cases the cause remains unknown. Examples of congenital heart disease include holes in the septum of the heart, abnormal valves and abnormalities in heart chambers. It is the most common birth defect and was present in 48.9 million people globally (2015).

Cardiac arrhythmias occur when the electrical impulses that coordinate your heartbeats don’t work properly, causing your heart to beat too fast, too slow or irregularly. They are classified as tachycardia (resting heart rate > 100 beats/min) and bradycardia (resting heart rate < 60 beats/min).

Atrial fibrillation is one of the common tachyarrhythmias arising from the atria. It is characterized by predominantly uncoordinated atrial activation with consequent deterioration of mechanical function of the heart. Atrial fibrillation increases the risk of stroke fivefold. Once atrial fibrillation is diagnosed, drugs are given to control the heart rate and anticoagulants are given to prevent stroke.

It can be caused by coronary artery disease, high blood pressure, drugs, alcohol abuse, electrolyte imbalance, diabetes.

https://www.mayoclinic.org/diseases-conditions/heart-arrhythmia/symptoms-causes/syc-20350668

Classes of CV Drugs Covered in this GM:

- Antithrombotic drugs
- Anticoagulants (blood thinners)
- Antiplatelet medications
- Cardiac glycosides
- Diuretics
- Beta blockers
- Calcium channel blockers
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers

Not Covered in this GM:
- Cholesterol lowering drugs
- CV devices

Some Background

In Atherosclerosis, fatty material and cholesterol are deposited inside the lumen of medium- and large-sized blood vessels (arteries). These deposits (plaques) cause the inner surface of the blood vessels to become irregular and the lumen to become narrow, making it harder for blood to flow through. Blood vessels also become less pliable as a result. Eventually, the plaque can rupture, triggering the formation of a blood clot. If the blood clot develops in a coronary artery, it can cause a heart attack; if it develops in the brain, it can cause a stroke.

**Behavioural Risk Factors:**
- tobacco use, physical inactivity, unhealthy diet, alcohol abuse

**Metabolic Risk Factors:**
- Raised Blood Pressure (hypertension)
- Raised Blood Sugar (diabetes)
- Raised Blood Lipids (cholesterol) - Not included in todays presentation
- Overweight and Obesity

**Other Risk Factors:**
- income, education, age, genetic, psychological

Cardiomyopathy makes it harder for the heart to pump blood to the rest of your body. The main types of cardiomyopathy include dilated, hypertrophic (thickening of heart muscle) and restrictive cardiomyopathy. It can lead to heart failure, blood clots, valve problems and cardiac arrest.

**Risk Factors:**
- high blood pressure, tissue damage from heart attack, valve problems, obesity

![Cardiovascular (CV) Drugs](https://www.mayoclinic.org/diseases-conditions/cardiovascular-diseases/publications/atlas_cvd/en/)

**Distribution of CVD deaths**


**10 most important risk factors for all deaths**

**Antithrombotic Drugs** (anticoagulants and antiplatelet drugs)

*How do they work and why are they different?*

- Fibrin and platelets most important components of a thrombus (clot)
- Fibrin is a protein that forms a mesh that traps red blood cells
- Platelets, a type of blood cell, form clumps that add to the mass of the thrombus
- Both fibrin and platelets stabilize the thrombus and prevent it from falling apart
- Fibrin is the more important component of clots that form in veins
- Platelets are the more important component of clots that form in arteries

**Anticoagulants** slow down clotting, thereby reducing fibrin formation and preventing clots from forming and growing.

**Antiplatelet agents** prevent platelets from clumping and also prevent clots from forming and growing.

**Anticoagulants:** They’re given to people at a high risk of getting clots, to reduce their chances of developing serious conditions such as strokes, heart attacks, deep vein thrombosis and, pulmonary embolism.

**Example for Anticoagulant**

Factor Xa (FXa) is essential in formation of thrombin, a key mediator of both fibrin formation and platelet activation. Inhibition of FXa interrupts both the intrinsic and extrinsic activation pathways of thrombin production. FXa together with FVa, calcium, and phospholipids, a prothrombinase complex is formed, which converts prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin and activates platelets, eventually leading to the formation of thrombus or blood clots. This process involves signal amplification, with one molecule of FXa activating many molecules of prothrombin to thrombin. Therefore, inhibition of FXa may be more effective than inhibition of thrombin.

**Selected Anticoagulants on the Market:**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>1941: first coumarin anticoagulant</th>
<th>1954: approved for medical use</th>
<th>(most commonly prescribed, ca. 40% market share)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dicoumarol (NP)</td>
<td>warfarin</td>
<td>vitamin K antagonist (VKAs)</td>
<td>Oral or IV</td>
</tr>
<tr>
<td>phenindione</td>
<td>heparin</td>
<td>natural glycosaminoglycan</td>
<td>Injected into vein</td>
</tr>
<tr>
<td>warfarin</td>
<td>dalteparin</td>
<td>made from pig intestines antithrombin III agonist</td>
<td>Avg MW 12-15 kDa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 unit of heparin (Howell unit) = 0.002 mg of protein</td>
<td></td>
</tr>
</tbody>
</table>

**Novel Oral Anticoagulants (NOACs)**

- Rapid onset and offset of action, no strong drug or food interactions, less frequent monitoring and re-dosing (1/day)

**Direct Factor Xa Inhibitors (no antidote)**

- **rivaroxaban** (Xarelto®) Bayer/J&J, 2011 FDA Approval
  - First oral direct Xa inhibitor
  - $5.64 billion (2017 sales)

- **apixaban** (Eliquis®) Pfizer/BMS, 2012 (EU), 2014 (US)
  - $4.87 billion (2017 sales)

- **edoxaban** (Savaysa®) Daiichi Sankyo, 2011 (Japan) 2015 (US)

- **betrixaban** (Bevyxxa®) Portola, 2017 (US)

**Vitamin K antagonists (VKAs)**

- **Dicoumarol** (1941: first coumarin anticoagulant)
- **Warfarin**
- **Phenindione**
- **Heparin**
  - Natural polysaccharide
  - Made from pig intestines
  - Antithrombin III agonist
  - Avg MW 12-15 kDa
  - 1 unit of heparin (Howell unit) = 0.002 mg of protein

**Antiplatelet Drugs**

- **Aspirin**
- **Clopidogrel**
- **P2Y12 receptor inhibitors**
Cardiovascular (CV) Drugs

Evolution of apixaban (Eliquis®) as direct factor Xa inhibitor

- **DX-9065a (Initial Benchmark)**
  - Selective FXa inhibitor (IC_{50} 41 nM)
  - No thrombin inhibition (conc > 2000 µM)
  - Daiichi Pharmaceutical Company

- **Starting Point (Screening)**
  - FXa K_i = 38.5 µM

- **DPC423**
  - FXa K_i = 0.15 nM

- **SA662**
  - FXa K_i = 0.15 nM

- **Razaxaban**
  - FXa K_i = 0.19 nM
  - *J. Med. Chem.* 2003, 46, 4405

- **Apixaban**
  - FXa K_i = 0.08 nM

**Review of FXa Inhibitors:**

**MedChem Route**

1. 5-Br valeryl chloride
2. KOtBu
3. PCl_5
4. Li_2CO_3
5. morpholine

**Name Rxn**

- 1. Et_3N
- 2. TFA

- **isoxazole overlayed with the pyrazole analog (allows for substitution at 3-position)**

- **razaxaban and apixaban overlayed**
Cardiovascular (CV) Drugs

\textbf{Antiplatelet Drugs}

- Heart attack, chest pain (angina), strokes, transient ischemic attacks (little strokes)
  - They are effective in the arterial circulation, where anticoagulants have little effect

\textbf{COX inhibitor (thromboxane A2 antagonist)}

- aspirin
  - COOH
  - OAc
  - 1980– (for CV)

\textbf{Adenosine diphosphate (ADP) receptor inhibitors (P2Y$_{12}$ antagonist)}

- ticlopidine (Ticlid®)
  - Sanofi, 1978 (France), 1991 (US)
  - first in class thienopyridine drug

- clopidogrel (Plavix®)
  - Sanofi, 1998 (US)

- ticagrelor (Brilinta®)
  - Daiichi Sankyo/Eli Lilly 2009 (US)
  - as the first in class thienopyridine drug


- ATP (pIC$_{50} = 3.5$)
  - natural antagonist (starting point)

- ticagrelor (Brilinta®)
  - AstraZeneca, 2011 (US)
  - orally bioavailable

\textbf{cangrelor (Kengreal®)}

- Medicines Company, 2015 (US)
  - ca. $125/g (Oakwood)

\textbf{ciloglazol (Pletaal®)}

- Otsuka, 1999 (US)

\textbf{Glycoprotein (GP) IIb/IIIa inhibitors}

- epifibatide (Integrilin®)
  - Medichem (Effient®)
  - Merck, 2014 (US)
  - Protease-activated receptor-1 (PAR-1) antagonist

- tirofiban (Aggrastat®)
  - Medicure Pharma, 2010 (US)
  - GP IIb/IIIa inhibitors

\textbf{Synthesis of ticagrelor}

1. ClCO$_2$Et, 2. NaN$_3$, 3. toluene, $\Delta$
2. HCl
3. H$_2$O$_2$
4. HCl
5. L-tartaric acid
62% (5 steps)

\textbf{Synthesis of ticagrelor}

1. CH$_3$N$_2$, Pd(OAc)$_2$
2. LiOH
50%

\textbf{Synthesis of ticagrelor}

1. ClCO$_2$Et
2. LiOH
50%

\textbf{Synthesis of ticagrelor}

1. CH$_3$N$_2$, Pd(OAc)$_2$
2. LiOH
50%

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1. CH$_3$N$_2$, Pd(OAc)$_2$
2. LiOH
50%
Cardiovascular (CV) Drugs

**Beta Blockers**

Medications for hypertension and to manage abnormal heart rhythms. They reduce blood pressure by blocking the effects of adrenaline. The heart beats more slowly and with less force thereby reducing blood pressure. Additionally, they also act as vasodilators.

While once a first-line treatment for hypertension, they are not as effective as diuretics, ACE inhibitors, or calcium channel blockers, and were downgraded in June 2006 to fourth-in-line (UK). Additionally, at usual doses they carry an unacceptable risk of provoking type 2 diabetes.

Banned by IOC (lower heart rate and reduce tremors) → used by surgeons

Beta receptors are found on cells of the heart muscles, smooth muscles, airways, arteries, kidneys, and other tissues that are part of the sympathetic nervous system and lead to stress responses, especially when they are stimulated by adrenaline. Beta blockers interfere with the binding to the receptor of adrenaline and other stress hormones, and weaken the effects of stress hormones.

>20 β-Blockers Commercialized

**Synthesis of Timolol (Merck)**

```
\begin{align*}
\text{S}_{2}Cl_2, \text{DMF, }\Delta \\
\text{Ac}_2\text{O}, \text{NH}_3, \text{NaH} \rightarrow \text{NH}_3 \text{BuH} \\
\text{NHMs} \rightarrow \text{timolol} (\text{Betimol}\text{®, 1978 (US)})
\end{align*}
```

**Acebutolol (Sectral®)**

```
\begin{align*}
\text{acebutolol (Sectral®)} & \rightarrow \text{atenolol (Tenormin®)} \\
\text{atenolol (Tenormin®)} & \rightarrow \text{nadolol (Corgard®)} \\
\text{nadolol (Corgard®)} & \rightarrow \text{ carvedilol(Coreg®)} \\
\text{carvedilol(Coreg®)} & \rightarrow \text{timolol (Betimol®)}
\end{align*}
```

**Vorapaxar (Zontivity®)**

```
\begin{align*}
\text{1. Pd(C), H}_2 \\
\text{2. Br}_2 \rightarrow \text{Br} \\
\text{3. PPh, Bu_3SnH, Pd(PPh)_3} & \rightarrow \text{OH} \text{ BuC} \\
\text{OH} & \rightarrow \text{HCl} \text{ BuC} \\
\text{HCl} & \rightarrow \text{OH} \text{ BuC} \\
\text{OH} & \rightarrow \text{HCl} \text{ BuC} \\
\text{HCl} & \rightarrow \text{NH}_3 \text{ BuH} \\
\text{NH}_3 & \rightarrow \text{NHMs} \\
\text{NHMs} & \rightarrow \text{timolol}
\end{align*}
```

US and Canadian commercial rights acquired by Aralez Pharma in 2016
Hypertension, elevated blood pressure indicated by systolic or diastolic pressures exceeding 140 mmHg or 90 mmHg, is an increasingly important medical problem as the general population becomes older and more overweight. A recent summan...

Calcium Channel Blockers (CCBs)

- Medications that disrupt the movement of calcium (Ca^{2+}) through calcium channels.
- Used as antihypertensive drugs.
- Particularly effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients.
- Used to alter heart rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris (reduced blood flow to the heart).

In the body's tissues, the concentration of calcium ions (Ca^{2+}) outside of cells is about 10000-fold higher than the concentration inside of cells. Embedded in the membrane of some cells are calcium channels. When these cells receive a certain signal, the channels open, letting calcium rush into the cell. The resulting increase in intracellular calcium has different effects in different types of cells. CCBs prevent or reduce the opening of these channels and thereby reduce these effects.

CCBs used as medications primarily have four effects:

- By acting on vascular smooth muscle, they reduce contraction of the arteries and cause an increase in arterial diameter, a phenomenon called vasodilation (CCBs do not work on venous smooth muscle).
- By acting on cardiac muscles (myocardium), they reduce the force of contraction of the heart.
- By slowing down the conduction of electrical activity within the heart, they slow down the heart beat.
- By blocking the calcium signal on adrenal cortex cells, they directly reduce aldosterone production, which correlates to lower blood pressure.

Selected CCBs on the market:

- Nifedipine (Adalat®) Bayer, 1975 (US)
- Felodipine (Plendil®) AZ, 1988 (US)
- Amlodipine besylate (Norvasc®) Pfizer, 1988 (US)
- Verapamil (Cardizem®) 1982 (US)
- Flunarizine (Sibelium®)
- Diltiazem (Cardizem®) 1982 (US)
- Benzothiazepine

Cardiovascular (CV) Drugs

Calcium Channel Blockers (CCBs)

Commercial Synthesis of Diltiazem

Analogues at Roche

Route by Roche (Synthesis 1990, 6, 539)

Process Route by Roche (J. Org. Chem. 1992, 57, 851)

Auxiliary synthesis

>90% auxiliary recovered and reused (2 steps)
Angiotensin-Converting-Enzyme (ACE) Inhibitor

Treatment of hypertension, heart failure and after a heart attack (taken for life once started)
Relaxes blood vessels and decreases blood volume → lower pressure and decreased oxygen demand from the heart

- Inhibits ACE which is an important component of the renin-angiotensin system (hormone system that regulates blood pressure and fluid balance).
- ACE catalyses the formation of angiotensin II from its precursor, angiotensin I
- Angiotensin II is a powerful vasoconstrictor and increases blood pressure

<table>
<thead>
<tr>
<th>Name</th>
<th>Year, Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril (Capoten®)</td>
<td>BMS 1981 (US)</td>
</tr>
<tr>
<td>Enalapril (Vasotec®)</td>
<td>Merck, 1984 (US)</td>
</tr>
<tr>
<td>Lisinopril (Zestril®)</td>
<td>Merck/AZ, 1987 (US)</td>
</tr>
<tr>
<td>Ramipril (Altace®)</td>
<td>Sanofi, 1991 (US)</td>
</tr>
<tr>
<td>Quinapril (Accupril®)</td>
<td>Pfizer, 1991 (US)</td>
</tr>
<tr>
<td>Trandolapril (Mavik®)</td>
<td>Novartis, 1992 (US)</td>
</tr>
<tr>
<td>Fosinopril (Monopril®)</td>
<td>BMS, 1991 (US)</td>
</tr>
</tbody>
</table>

Angiotensin-Converting-Enzyme (ACE) Inhibitor Pharmacological Parameters

<table>
<thead>
<tr>
<th>IC50 (nM)</th>
<th>Therapeutic Dose (mg)</th>
<th>T½ (hrs)</th>
<th>Vmax (mm/min)</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>1.2</td>
<td>2.5–40</td>
<td>1–2</td>
<td>2–8</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.2</td>
<td>5–40</td>
<td>1</td>
<td>6–9</td>
</tr>
<tr>
<td>Quinapril</td>
<td>8.5</td>
<td>5–40</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Benazepril</td>
<td>1.7</td>
<td>5–40</td>
<td>1</td>
<td>1–2</td>
</tr>
<tr>
<td>Ramipril</td>
<td>100</td>
<td>1–2.5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>7</td>
<td>10–80</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Value reported for bio-assay, †highly variable, "Elimination phase, "Apparent elimination phase, "Terminal phase, N₂ = not reported.

Process Route

1. BzCl
2. MeOH, H₃PO₄
3. MsOH, PPh₃, DIAD, Et₃N
4. NaOH


1. BnOCOCl
2. I₂, PPh₃
3. K₂CO₃
4. Bu₂SnH, AIBN

Fosinopril Synthesis

Med Chem Route?

1. MeOH, H₃PO₄
2. NaBH₄
3. PhCHO, pTsOH
4. NaOH

Bz cleavage & hydrogenation


Angiotensin-Receptor Blockers (ARBs)

AT1 receptors promote aldosterone secretion and Na retention by stimulation of angiotension receptors present on the adrenal cortex → elevated blood pressure due to vasoconstriction

AT2 receptors are present only in low levels and not associated with CV homeostasis.

The final step of the renin angiotensin cascade is the activation of angiotensin II receptors AT1 and AT2 by angiotensin II.

ACE inhibitors suppress RAS by blocking the formation of angiotensin II

Until 1995, ACE inhibitors only drugs capable of the RAS blockade (undesirable side effects such as a dry cough)

Angiotensin II AT1 receptor blockers more direct way to develop specific inhibitors of the RAS

Blocks the pathway more specifically than ACE inhibitors

**NH**
\[ \text{losartan (Cozaar\textsuperscript{®})} \]
Merck, 1995 (US)

**NH**
\[ \text{valsartan (Diovan\textsuperscript{®})} \]
Novartis, 1997 US)

**NH**
\[ \text{irbesartan (Avapro\textsuperscript{®})} \]
Sanofi/BMS, 1998 (US)

**NH**
\[ \text{telmisartan (Micardis\textsuperscript{®})} \]
Bl, 1999 (US)

**NH**
\[ \text{candesartan cilexetil (Atacand\textsuperscript{®})} \]
Takeda/AZ, 1998 (US)

**NH**
\[ \text{eprosartan mesylate (Teveten\textsuperscript{®})} \]
GSK, 1997 (US)

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GSK, 1997 (US)
Hypertension, elevated blood pressure indicated by systolic or diastolic pressures exceeding 140 mmHg or 90 mmHg, is an increasingly important medical problem as the general population becomes older and more overweight. A recent summary of research in the area of hypertension indicates that 50 million Americans and as many as one billion people globally suffer from hypertension (NHLBI, www.nhlbi.nih.gov, 2007). More importantly, the treatment of hypertension is leading to retention of water in the urine.

Frequent urination is due to the increased loss of water that has not been retained from the body as a result of a concomitant relationship with sodium loss from the convoluted tubule.

**Diuretics (Water Pills)**
- Helps rid your body of salt (sodium) and water
- Makes kidneys release more sodium into urine and sodium takes water with it from blood
- Decreases the amount of fluid flowing through blood vessels, reducing pressure on vessel walls

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that most people try thiazide diuretics first to treat high blood pressure and heart problems related to high blood pressure.

In addition, also prescribed for heart failure, liver failure, tissue swelling (edema) and certain kidney disorders, such as kidney stones.

**Thiazide and thiazide-like diuretics (>10 commercialized)**
- Inhibit the body's ability to reabsorb sodium at the ascending loop in the nephron, which leads to an excretion of water in the urine, whereas water normally follows sodium back into the extracellular fluid.

**Potassium-sparing diuretics**
- Potassium is retained and not as much is lost into the urine as with other diuretics.

**Furosemide (Lasix®)**
- 1962 (US)

**Bumetanide (Bumex®)**
- 1970 (US)

**Ethacrynic acid (Edecrin®)**
- 1960 (US)

**Chlortalidone (Hygroton®)**
- 1961 (US)

**Indapamide**
- 1967 (US)

**Amiloride (Midamor®)**
- 1981 (US)

**Eplerenone (Inspra®)**
- 2002 (US)

**Review on synthesis of other spironolactone derivatives**
- *Steroids* 2017, 118, 76

**Other methods of installing C-7 Carbon by Pfizer:**
- Pd carboxylation (*Synlett* 2008, 418)
- Furan 1,6-addition/oxidative cleavage to carboxylic acid (*Org. Lett.* 2006, 8, 2111)

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**Synthesis of Chlortalidone (J. Am. Chem. Soc. 1957, 79, 2028)**

**Synthesis of Amyloride (Med-Chem Route)**

**Synthesis of Eplerenone WO1997021720A2 (Pharmacia)**

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**Chlortalidone (Hygroton®)**

**Dihydrochlorothiazide**

**Indapamide**

**Amiloride (Midamor®)**
Hypertension, elevated blood pressure indicated by systolic or diastolic pressures exceeding 140 mmHg or 90 mmHg, ... an increasingly important medical problem as the general population becomes older and more overweight. A recent summ

becoming more complicated as the population ages, because many patients will take drugs to treat conditions such as diabetes, rheumatoid arthritis, atherosclerosis, and so on

or dropsy, as it was called in those days. help those suffering from abnormal fluid buildup, discovering in physician William Withering is credited with rather than from laboratory chemistry. English 200 years 'The cardiac drug digoxin, in use for more than 200 years, stemmed from an herbal remedy other than from laboratory chemistry. English physician William Withering is credited with discovering in 1775 that the foxglove plant could help those suffering from abnormal fluid buildup, or dropsy, as it was called in those days.

n a 1785 report, Withering writes that he was asked to evaluate a home remedy for dropsy compounded by Mrs. Hutton, "an old woman in Shropshire." Her herbal concoction made cures after the more regular practitioners had failed," according to his report.

Withering, who was also a botanist, quickly figured out that of the 20 or so herbs in the woman's remedy, foxglove was the key ingredient. In his report, he noted that foxglove was particularly helpful for his patients who developed dropsy after suffering from scarlet fever or bad sore throats. Scarlet fever and strep throat, both caused by a Streptococcus bacterium, can damage the heart valves. Improperly functioning valves can lead to congestive heart failure—a condition in which fluid builds up in the body's tissues because of the heart's weak pumping action.

Withering used dried foxglove leaves in his dropsy remedy. The leaves contain a number of glycosides—chemicals that are composed of a sugar and a cardenolide (which has a five-membered lactone ring)—that are called by the umbrella term digitalis. The flowers, seeds, and sap also contain digitals, but less than the leaves have. According to GSK, farmers in the Netherlands grow fields of woolly foxglove, which is a member of the snapdragon family. Bales of dried foxglove leaves are shipped to the U.S. Here, processing facilities macerate the leaves and extract digitalis using an aqueous-alcohol solvent. Further treatment and processing yields powdered digoxin, which is compounded into tablets, injectable solutions, elixirs, and capsules. It takes about 1,000 kg of dried foxglove leaves to make 1 kg of pure digoxin, the company adds.

https://pubs.acs.org/cen/coverstory/83/8325/8325digoxin.html

Cardiovascular (CV) Drugs

Cardiac Glycosides

Family of compounds derived from the foxglove plant (Digitalis purpurea)

increase the output force of the heart and decrease its rate of contractions by acting on the cellular sodium-potassium ATPase pump.

Treatments for congestive heart failure and cardiac arrhythmias relative toxicity prevents them from being widely used.

The cardiac drug digoxin, in use for more than 200 years, stemmed from an herbal remedy other than from laboratory chemistry. English physician William Withering is credited with discovering in 1775 that the foxglove plant could help those suffering from abnormal fluid buildup, or dropsy, as it was called in those days.

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Cardiovascular disease death rates by selected drug class introductions, 1900-2006

A. Antiarrhythmics (1960)
B. Alpha Blockers (1953)
C. Diuretics (1958)
D. Non-selective Beta Blockers (1967)
E. Beta Blockers (1973)
F. Alpha Agonists (1974)
G. Selective Beta Blockers (1978)
H. Nitrates (1980)
I. Fibric Acid Derivatives (1981)
J. RAAS Blocking Agents (1981)
K. Vasodilators (1981)
L. Calcium Channel Blockers (1981)
M. Antihypertensive Combos (1983)
N. Alpha Beta Blockers (1984)
O. Statins (1987)
P. Nicotinic Acid Derivatives (1997)
Q. Antihyperlipidemic Combos (2001)

Sources: