Book of Cardiology

A STUDY BUFFALO STUDY GUIDE

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Definitions/Classifications

Hypertensive Emergency

- Target organ damage, such as acute left ventricular failure, acute myocardial ischemia, aortic dissection, encephalopathy, papilledema
- Generally treated with IV drugs → much more severe situation
- Must be careful not to over-treat and cause hypotension

Hypertension Urgency

- Asymptomatic
- DBP > 130mmHg
- Often treated with oral drugs over the course of a few days

American Classifications

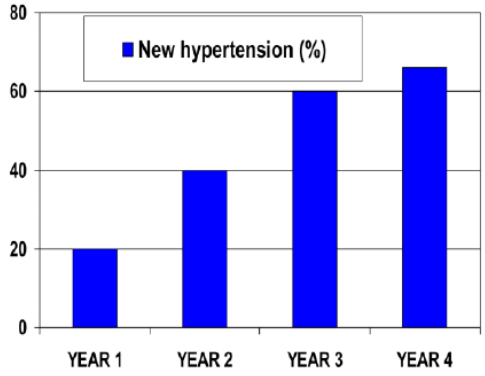
Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	And/or	< 80
Normal	< 130	And/or	< 85
High-normal	130-139	And/or	85-89
Stage 1 (mild hypertension)	140-159	And/or	90-99
Stage 2 (moderate to severe hypertension)	≥ 160	And/or	≥ 100-109
Isolated Systolic Hypertension (ISH)	≥ 140	And/or	<90

- If SBP and DBP fall into different categories → use the most severe one

Epidemiology

Overview

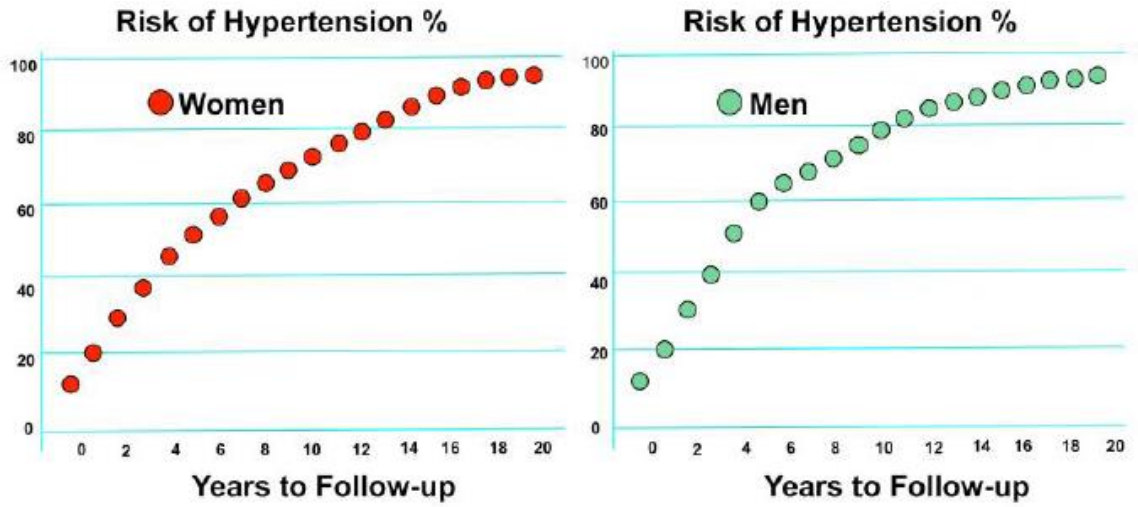
- 1 in 5 (22%) of Canadians 18-70 years old have hypertension
- Over 40% of Canadians aged 56-65 have hypertension
- 50% of Canadians > 65 years old have hypertension
- Patients with high normal blood pressure (130-139/85-89mmHg) will develop hypertension within 4 years (90%), and almost half by 2 years



The patients of this study were overweight → risk factor for hypertension

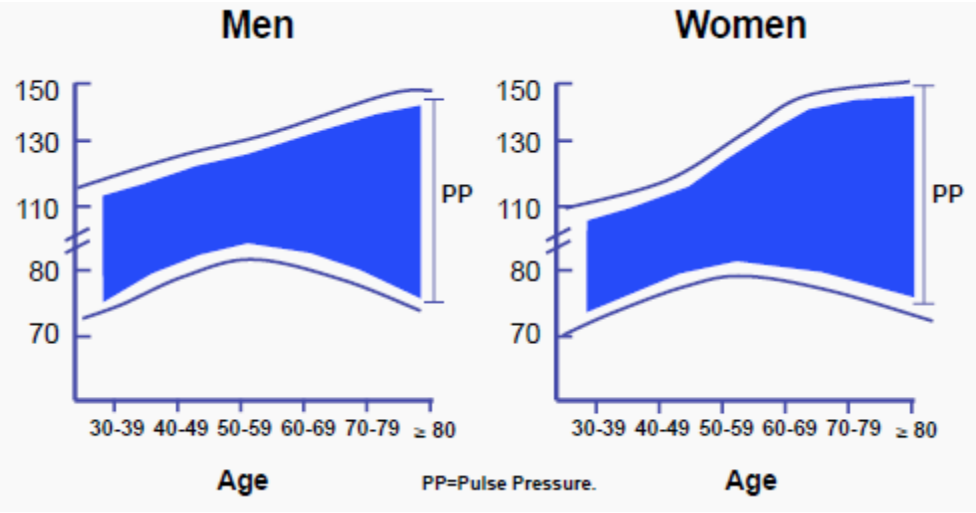
If you can treat these people earlier it is far easier to manage and reduce costs to the patient and healthcare system

Lifetime Risk of Hypertension



- Nearly everyone will become hypertensive if they live long enough

Blood Pressure Distribution



- Pulse pressure = the difference between systolic and diastolic pressures
    - Generally, the higher the PP, the worse the prognosis
    - However, PP is not regularly monitored/used, as the risks associated with SBP and DSP are fairly well understood on their own, and PP tends to increase with SBP

Etiology

Essential (Primary) Hypertension

- Called essential because it was once thought that blood pressure increased naturally and was necessary to promote health at an older age
- Represents 90% of all hypertensive cases
- Hypertension with no exact etiology known
    - Possible Factors
        - Increased sympathetic neural activity
        - Increased angiotensin II and aldosterone activity
    - Hypertension risk factors may promote development

Secondary Hypertension

- 10% of all cases
- Hypertension with a definitive known cause
- Examples
    - Obesity
    - Renovascular disease
    - Drug Causes
        - Examples
            - Oral Contraceptives
            - NSAIDs
            - Cocaine
    - Hyperaldosteronism
    - Pheochromocytoma
        - Rare
        - Tumour of the adrenal gland → excessive adrenergic hormone production
    - Endocrine disorders
        - Cushing's syndrome
        - Hypo- and hyperthyroidism
        - Hyperparathyroidism
    - Sleep apnea
    - Coarctation of the aorta
        - Rare
        - A region of constriction in the aorta
        - May require surgical intervention
- Removing these causes may correct the hypertension
    - NB: there are often multiple causes; fixing one may not correct the entire problem! May need to target multiple at a time

Pathophysiology

- Definition: Elevated arterial blood pressure

$$BP = PVR * CO = PVR * SV * HR$$

    - Cardiac Output → Primary determinant of systolic pressure
    - Peripheral Vascular Resistance → Primary determinant of diastolic pressure
    - Hypertension means you have at least one of these at an elevated value
        - They are all possible targets of treatment

Risk Factors

Non-Modifiable

- Age
    - Risks increase with age in both men and women
- Gender
    - Male > Female
- Family history
    - Premature cardiovascular disease (age < 55 in men and < 65 in women)

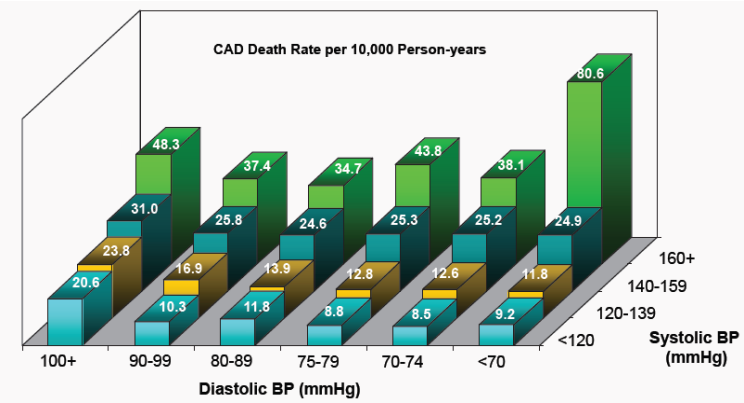
Modifiable

- Abdominal obesity
- Poor dietary habits

- High sodium intake
- Sedentary lifestyle
- High alcohol consumption
- Dysglycemia
- High stress
- Patients with high normal blood pressure
- Smoking
- Dyslipidemia
- Prescription drugs
    - NSAIDs, including coxibs
    - Corticosteroids and anabolic steroids
    - Oral contraceptives and sex hormones
    - Vasoconstricting/sympathomimetic hormones
    - Calcineurin inhibitors (cyclosporine, tacrolimus)
    - Erythropoietin and analogues
    - Antidepressants (MAOIs, SNRIs, SSRIs)
    - Midodrine
- Other
    - Stimulants like cocaine
    - Licorice root

Clinical Presentation & Complications

- Hypertension is a significant risk factor for:
    - Cerebrovascular disease
    - Coronary artery disease
        - Risks of CAD based on SBP and DBP



        - In general, systolic blood pressure is a bigger concern than diastolic
        - This is especially true when SBP is much more elevated than DBP
            - Consider: High PP = more severe disease
            - This is why Isolated Systolic Hypertension (ISH) is so dangerous
    - Congestive heart failure
    - Renal failure
    - Peripheral vascular disease
    - Dementia
    - Atrial fibrillation
    - Erectile dysfunction

Assessment & Diagnosis

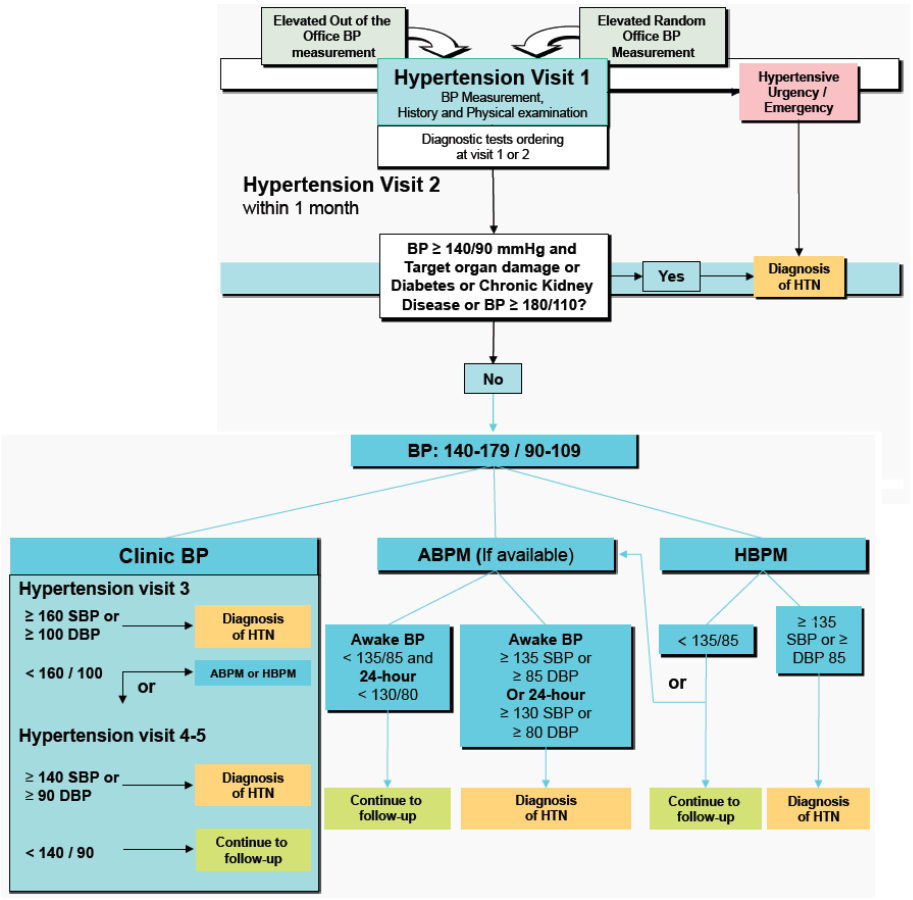
- Blood pressure should be measured at all **appropriate physician visits**

- Appropriate depends on the situation
  - e.g. a healthy 20 year old male probably doesn't need to evaluated, but a 40 year old with a history of CAD in the family may require more monitoring
  - Note: younger hypertensive patients tend to be missed because they are perceived as "more healthy"
- It is more important to have an idea of a patient's trend - individual values without a baseline are not very useful
- Used to:
  - Screen for hypertension
  - Assess cardiovascular risk
  - Monitor antihypertensive treatment
  - Assess blood pressure in those with high normal blood pressure
  - These patient should be screened at least annually

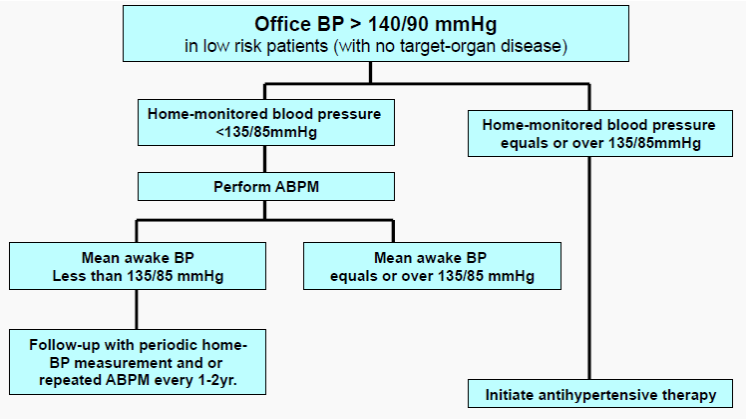
Assess Overall Cardiovascular Risk

- 90% of hypertensive Canadians have other cardiovascular risks
- Important to manage hypertensive patients for:
  - Dyslipidemia
  - Dysglycemia (e.g. impaired fasting glucose, diabetes)
  - Smoking
  - Abdominal obesity
  - Unhealthy eating
  - Physical inactivity
  - **Also important to warn the patient about these → they can have serious health impacts**
- Search for target organ damage
  - Cerebrovascular disease
    - Severe events - patients will probably know if it has occurred to them
      - Examples
        - Transient ischemic attacks
        - Ischemic or hemorrhagic stroke
        - Vascular dementia
  - Hypertensive retinopathy
  - Left ventricular dysfunction
  - Left ventricular hypertrophy
    - Once you have dysfunction you tend to get hypertrophy
  - Coronary artery disease
    - Myocardial infarction
    - Angina pectoris
    - Congestive heart failure
  - Chronic Kidney Disease
    - Hypertensive nephropathy (GFR < 60mL/min/1.73m^2)
    - Albuminuria
  - Peripheral artery disease
    - Intermittent claudication (pain when you walk)
    - Ankle brachial index < 0.9
  - Search for exogenous potentially modifiable factors that can induce/aggravate hypertension
    - See risk factors for examples

Diagnostic Algorithm

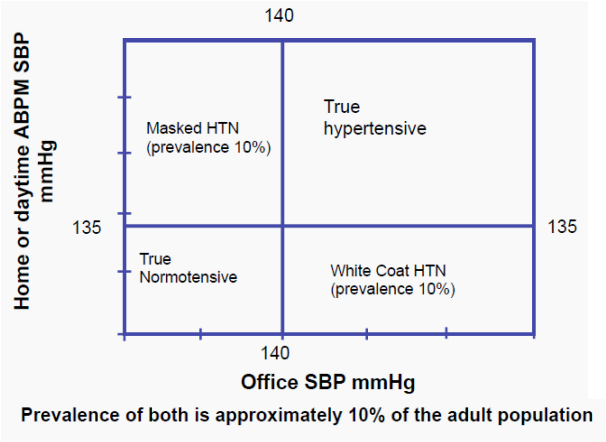


- Home Blood Pressure Monitoring (HBPM)
- Ambulatory Blood Pressure Monitoring (ABPM)
    - Device that is attached to the patient to take periodic blood pressure readings
    - Acts like 4-5 visits in one go → this is why you can diagnose with less readings
    - Suggested Use



        - Depending on the situation, a patient's home BP readings may be sufficient
    - Diagnosis either requires significant elevations or multiple confirmed readings (recall: you are looking for trends)
    - Visits 3-5 typically occur every 3-4 weeks

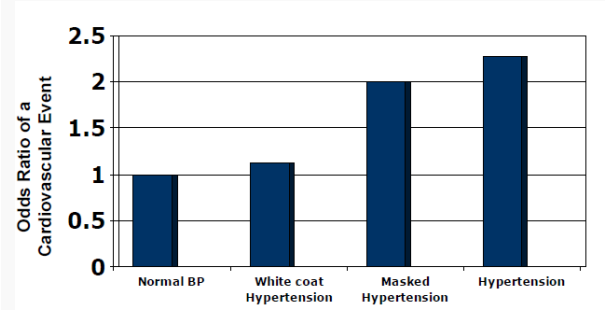
Masked Hypertension



Prevalence of both is approximately 10% of the adult population

White Coat Hypertension is an elevated blood pressure that only occurs in a clinical setting where a health care provider is measuring the patient's blood pressure

Could just be due to anxiety



Masked hypertension is the most dangerous as you will never find it unless a patient is monitoring at home and it carries almost the exact same risks as diagnosed hypertension

Screening for Secondary Causes of Hypertension

- Screen when:
  - Severe or refractory hypertension
    - Hypertension resistant to 3 or more drugs at the maximum tolerated doses
  - Acute rise in BP with a previously stable BP
  - Proven age of onset before puberty
  - Hypertension when age < 30 in a non-obese, non-black person with a negative family history for hypertension

Routine Laboratory Testing

- Should be investigated in patients with hypertension:
  - Urinalysis
    - Protein
      - Should be negative
        - Initial test is qualitative (dipstick test)
      - ≥ 1+ indicates renal disease
        - Can be quantified through a protein:creatinine ratio
      - Negative result does not rule out albuminuria
      - If required, can run a more accurate test (albumin:creatine ratio)
        - Typically only used in diabetic patients or those will renal disease
    - Glucose
      - Should be negative
      - If positive → DM
    - Ketones
      - Should be negative
      - If positive → Diabetic ketoacidosis or starvation
    - Nitrites
      - Should be negative
      - If positive → bacteria present

        - Leukocytes
            - Should be negative
            - If positive → WBC present due to infection
    - Blood chemistry (potassium, sodium, creatinine)
        - Provides measure of kidney function
        - Helpful in identifying secondary causes of hypertension
        - May help guide therapy
    - Fasting glucose
    - Fasting total cholesterol, HDL, LDL, triglycerides
    - Standard 12-leads ECG
        - Gives a measure of heart rate, can identify rhythm abnormality, or may detect left ventricular hypertrophy
    - Optional tests for specific subgroups:
        - Those with diabetes or CKD should be assessed for urinary albumin excretion (microalbuminuria)
            - Those suspected of having an endocrine cause for hypertension

Treatment/Prevention

Benefits of Treatment

- Younger than 60 years old → reducing blood pressure by 10/5-6mmHg
    - Reduces risk of stroke by 42%
    - Reduces risk of coronary event by 14%
- Older than 60 years old → reducing blood pressure by 15/6mmHg
    - Reduces overall mortality by 15%
    - Reduces cardiovascular mortality by 36%
    - Reduces incidence of stroke by 35%
    - Reduces coronary artery disease by 18%
- Older than 60 years old with isolated systolic hypertension (SBP ≥ 160mmHg and DBP < 90mmHg)
    - 42% reduction in risk of stroke
    - 26% reduction in the risk of coronary events
- Reduction of Mortality Associated with Blood Pressure

Reduction in SBP (mmHg)	Mortality due to Stroke	Mortality due to CHD	Total Mortality
2	-6%	-4%	-3%
3	-8%	-5%	-4%
5	-14%	-9%	-7%

    - Even if a patient fails to meet targets a small reduction of blood pressure still provides a benefit
    - Consequences of hypertension are costly on the health care system → early treatment can reduce these costs significantly

Indications for Treatment

- Threshold for Initiation of Treatment & Targets

Condition	Initiation SBP/DBP (mmHg)	Target SBP/DBP (mmHg)
Systolic/Diastolic hypertension	≥ 140/90	< 140/90
Isolated systolic hypertension	SBP > 160	< 140
Home BP measurement (no diabetes, renal disease, or proteinuria)	≥ 135/85	< 135/85
Diabetes (currently undergoing debate)	≥ 130/80	<130/80
Chronic Kidney Disease	≥ 140/90	<140/90

- Clinical BP of 140/90mmHg has a similar risk of:

Home pressure average	135/85mmHg
Daytime average BP	135/85mmHg
24-hour average BP	130/80mmHg

Goals of Therapy

1. Optimally reduce cardiovascular risk by reaching target blood pressure
    - Targets

Condition	Target (mmHg)
Isolated systolic hypertension	<140
Systolic/diastolic hypertension	
Systolic BP	<140
Diastolic BP	<90
Diabetes	
Systolic BP	<130
Diastolic BP	<80

2. Improve patient adherence

Non-Pharmacological Options

Sodium Reduction

- Sodium should be reduced to < 1500mg/day in normotensive patients to prevent hypertension
    - 65mmol Na^+ or 3.8g NaCl
- Up to 17% of hypertension can be attributed to high sodium diets
- Effects of Sodium Restriction
    - Hypertensives
        - 5.1/2.7mmHg drop in BP with an average reduction of 78mmol of sodium/day
        - 7.2/3.8mmHg drop in BP with an average reduction of 100mmol of sodium/day
    - Normotensives
        - 2.0/1.0mmHg drop in BP with an average reduction of 74mmol of sodium/day
        - 3.7/1.7mmHg drop in BP with an average reduction of 100mmol of sodium/day
    - Reducing average daily intake from 3500mg to 1700mg/day in Canada would result in:
        - 1 million fewer hypertensives
        - 5 million fewer physicians visits a year for hypertensive
        - Healthcare cost savings of $430 to $540 million per year related to fewer office visits, drugs, and laboratory costs for hypertension
        - Improvement of the hypertension treatment and control rate
        - 13% reduction in CVD
        - Total health care cost savings of over $1.3 billion/year
- Recommended Intakes of Sodium

Age	Adequate Intake (mg)	Upper Limit (mg)
19-50	1500	2300
51-70	1300	2300
> 70	1200	2300

    - 2300mg = 1 level teaspoon of salt
    - 80% of sodium intake is through processed foods
    - Only 10% is added at the table or in cooking

Diet Modification

- Increase intake of fresh fruits, vegetables, low fat dairy products, dietary and soluble fibre, whole grains and proteins from plant sources
- Reduce saturated fat, cholesterol, and salt in accordance with *Canada's Guide to Healthy Eating*

Regular Physical Activity

- Accumulation of 30-60 minutes of moderate intensity cardiorespiratory activity 4-7 times per week in addition to daily activities

Low Risk Alcohol Consumption

- ≤ 2 standard drinks/day and less than 14/week for men and 9/week for women

Body Weight

- Maintenance of Ideal Body Weight
  - BMI = 18.5-24.9kg/m^2
- Weight loss in patients who are overweight (BMI > 25)
- Waist circumference of:

Race	Men	Women
European, Sub-Saharan African, Middle Eastern	< 102cm	< 88cm
South Asian, Chinese	< 90cm	< 80cm

Smoking Cessation/Avoidance

Y U NO DO TRAC TRAINING??

Summary of Effects of Non-pharmacological Interventions

Intervention	Amount	Decrease in BP (SBP/DBP in mmHg)
Sodium reduction	-1.8g or 78mmol/day	5.1/2.7
Weight loss	Per kg lost	1.1/0.9
Alcohol intake	-3.6 drinks/day	3.9/2.4
Aerobic exercise	120-150 min/week	4.9/3.7
Dietary patterns	DASH diet	
	Hypertensive	11.4/5.5
	Normotensive	3.6/1.8

Note: these are averages among very diverse populations → actual changes may vary

Pharmacological Options

- Essentially any agent imaginable; see considerations and algorithms about which agents to use

Indications for Pharmacological Treatment

- Patients at low risk with stage 1 hypertension (140-159/90-99mmHg)
  - Lifestyle modification can be the sole therapy
  - A 3 month trial would typically be appropriate
- Pharmacological treatment can be considered if:
  - Patients with risk factors or target organ damage (i.e. compelling indications) and are not already at target
    - **Compelling Indications**
      - Ischemic heart disease
      - STEMI or non-STEMI
      - Left ventricular systolic dysfunction
      - Cerebrovascular disease
      - Left ventricular hypertrophy

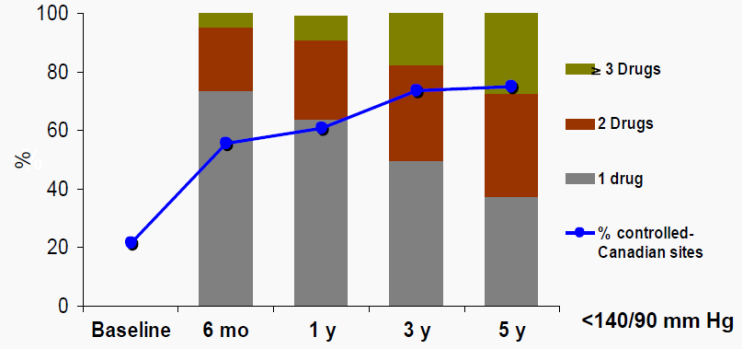
- Non-diabetic CKD
- Renovascular disease
- Smoking
- Diabetes Mellitus
- With nephropathy
- Without nephropathy

- Patients with stage 2 hypertension (≥ 160/100-110mmHg)

Considerations

Number of Agents Needed

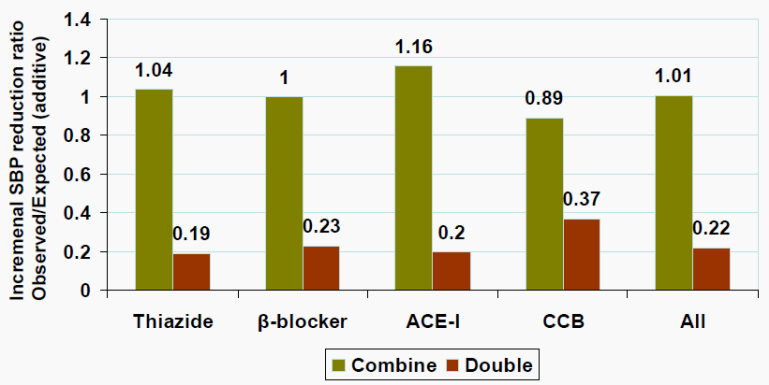
- Important to inform patients 1 drug will rarely treat hypertension; often need 2-3



  - This is not a failing of the patient, but the reality of the disease
  - You also getter better benefit with multiple agents than just increasing the dose of 1
  - The systolic target is more difficult to achieve, however it may also be considered the more important target (compared to diastolic)

Combination Therapy vs. High Dose Monotherapy

- Increasing doses provide diminishing returns



  - Doubling dose provides about a 20% further reduction
  - Adding a new agent can provide over twice the reduction in

- Lower doses provide nearly the same effect as a standard dose

Class	Half Standard Dose (mmHg)	Standard Dose (mmHg)	Twice Standard Dose (mmHg)
Thiazides	7.4	8.8	10.3
β-Blockers	7.4	9.2	11.1
ACEIs	6.69	8.5	10.0
ARBs	7.8	10.3	12.3
CCBs	5.9	8.8	11.7

  - Drugs dosed at half the standard dose provide 80% of the effect of a full dose
  - Combination therapy of lower dosed drugs provides additive effects with less than additive side effects
  - Combination therapy is useful for reducing side effects and improving patient adherence and outcomes

- Numerous agents already exist in tablet/capsule combinations

- Useful if the patient is concerned about the number of medications required

Considerations when Combing Agents

- ABCD Rule
  - The following provide additive effects if you combine an agent from column 1 with an agent from column 2

Column 1	Column 2
A ACEI ARB	**C** Long-acting CCB
B β-Blocker	**D** Thiazide Diuretic

  - Caveats
    - It has now been proven that C + D also provides some synergy
    - A + B combinations are often used for other indications (e.g. coronary artery disease), so this rule is not definitive
      - Small hypotensive effects, so compelling indication is the main reason for this combination
- Combine first line agents before moving onto other options
  - Caution should be used when combining a non-DHP-CCB with a β-blocker
    - Risk of additive negative inotropic & chronotropic effects (bradycardia or heart block)
- Creatinine and potassium should be monitored when combining K^+-sparing diuretics, ACEIs, and/or ARBs
- If a diuretic is not used as first- or second-line therapy, it should be included in triple therapy unless contraindicated
- Caution should be used when initiating 2 drugs in patients whom adverse events are more likely (e.g. frail elders, those with postural hypotension, dehydration)
- The use of dual therapy with an ACEI and ARB should only be considered in selected and closely monitored people with advanced heart failure or proteinuric nephropathy
  - This combination reduces proteinuria, but not yet shown to improve outcomes, thus CHF is the only indicated use
- If a potassium wasting diuretic is being used, consider using a potassium-sparing agents

Other Considerations

- β-Blockers are not recommended in patients > 60 years old without another compelling indication
- Erectile Dysfunction
  - Epidemiology
    - General population = 8-10%
    - Men with hypertension = 15-46%
  - Risk predictor of CV
    - Though not sure if ED is due to drug or disease/other risk factors
    - Possible Causes
      - Drugs: β & α-blockers; CCBs and ACEIs/ARBs to lesser extent
      - Disease: vascular diseases
      - CV Risk factors: smoking
- African Americans
  - Higher prevalence of hypertension
  - Also tend to have lower plasma renin concentrations
  - Thiazide diuretics are especially effective and well-tolerated
  - If there are no compelling indications, thiazides are CCBs are common first line agents
  - Combining the first-line agents with ACEIs/ARBs or β-blockers is synergistic
    - Remember the increased risk of angioedema

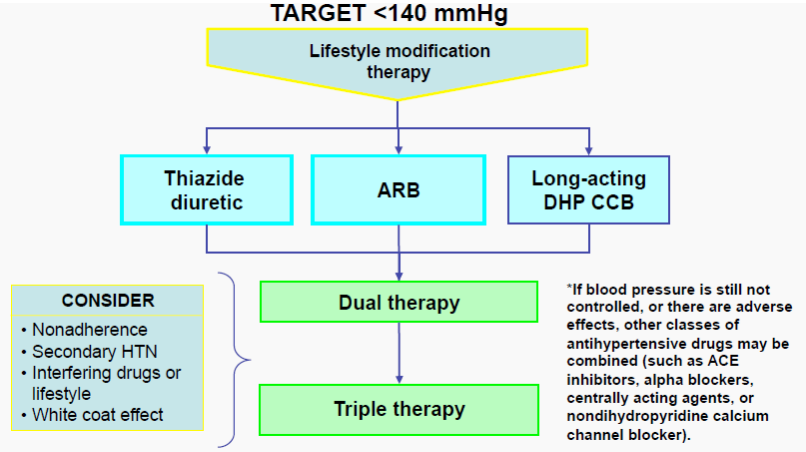
- ACEIs are not recommended as monotherapy in black patients without a compelling indication due to risk of angioedema

Improving Patient Adherence

- Assess adherence to both pharmacological and non-pharmacological therapy at every visit
- Teach patients to take their medication on a regular schedule associated with a routine daily activity (e.g. brushing teeth)
- Simplifying medication regimens using long-acting once-daily dosing and combination therapies (e.g. ones with diuretics combined)
- Utilize compliance packaging
- Encourage greater patient responsibility/autonomy in regular monitoring their blood pressure
- Educate patients and patients' families about their disease/treatment regimens verbally and in writing
- Use an interdisciplinary care approach coordinating with work-site health care givers and pharmacists if available

Treatment Algorithms

Management of Systolic Hypertension (Without Compelling Indication)



- Drugs recommended are limited due to limited trials

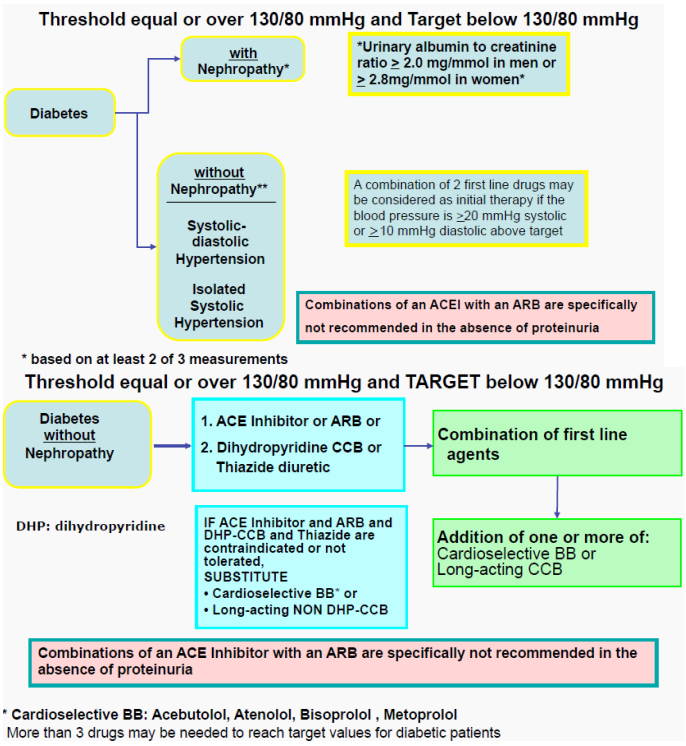
Refractory Hypertension

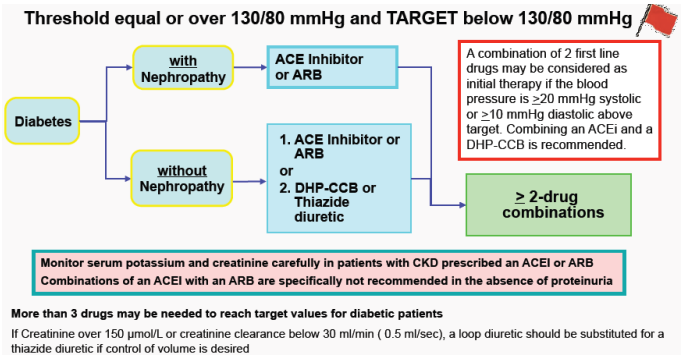
- If all the ABCD drugs/combinations are considered and BP is still not at target, use one or more of the following:
  - α-blocker (doxazosin 2-12mg/day)
    - Can lower BP significantly
    - Best to start low and at bedtime
  - Low-dose spironolactone (12.5-50mg/day)
    - If not hyperkalemic and sufficient renal function
    - Very effective agent
  - Direct Renin Inhibitors (Aliskiren 150-300mg/day)
  - Furosemide (if patient in renal failure or experiencing fluid retention)
  - Nitroglycerine patch (0.2-0.8mg/hr)
    - Evidence not known
  - Clonidine (0.1-0.3mg BID)
    - Risk of withdrawal effects with stopping
  - Hydralazine (10-50mg QID)
    - Requires frequent dosing
  - Minoxidil (5-20mg BID)
    - Can cause pulmonary edema and other adverse effects
  - Methyldopa (250-500mg BID-TID)

Summary of Treatment Compelling Indications/Special Populations

Options	Stable Ischemic Heart Disease	STEMI NSTEMI	Heart Failure	Acute Stroke (<72 hours)	Non-DM Chronic Kidney Disease
First Line	β-blocker Long-acting CCB	β-blocker & ACEI/ARB	β-blocker & ACEI (or ARB)	ACEI + thiazide preferred	ACEI or ARB (to treat proteinuria)
Second Line/ Add-on	ACEI/ARB (first line with CAD)	Long-acting CCB	Diuretic (thiazide or loop)		Diuretic (thiazide or loop) β-blocker or CCB
Notes	Caution if combining β-blocker with non-DHP CCB ACEI + non-DHP CCB preferred Avoid short-acting nifedipine	If heart failure, use DHP-CCB over non-DHP	3rd line: aldosterone antagonist 4th line: DHP CCB (avoid non-DHP) 5th line: ACEI/ARB combo	Treat extreme BP elevations with a 15-25% reduction over 24 hours and gradually thereafter, especially if eligible for thrombolytic therapy Excessive BP drops can exacerbate ischemia, reduce perfusion to brain	Avoid ACEI/ARB in bilateral renal artery stenosis Monitor K^+ as renal function declines Monitor closely if patient is not at target with 3 or more agents, has deteriorating function, recurrent edema
	Left Ventricular Systolic Dysfunction	**Left Ventricular Hypertrophy**	**Preeclampsia**		
First Line	ACEI/ARB & β-blocker	Any combination of ABCD drugs	Methyldopa Labetalol and/or DHP-CCB Hydralazine		
Second Line/ Add-on	Diuretic (aldosterone in CHF Class III-IV)		Thiazide (evaluate risk vs. benefit)		
Notes	Hydralazine + ISDN if ACEI/ARB contraindicated If further BP reduction needed: ARB/ACEI combo or long-acting DHP-CCB	**Avoid use of vasodilators**	Defined as BP > 140/90mmHg with proteinuria after 20 weeks gestation ACEIs/ARBs are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential		

Treatment of Hypertension in Association with Diabetes Mellitus





Considerations

- ACEIs and ARBs are first line in all cases (with or without nephropathy)
- If no nephropathy, any other first line agents are good in combination

Elderly > 80 Years Old

- Few studies in this population
  - HYVET Trial

Population	**N = 3845** **SBP > 160mmHg**
Intervention/Comparison	Indapamide SR 1.5mg & perindopril 2-4mg vs. Placebo Target < 150mmHg
Outcome	Stopped early due to significant reduction in any CVD (7.1% vs. 10.1%; NNT = 34) and total mortality (10% vs. 12; NNT = 47)

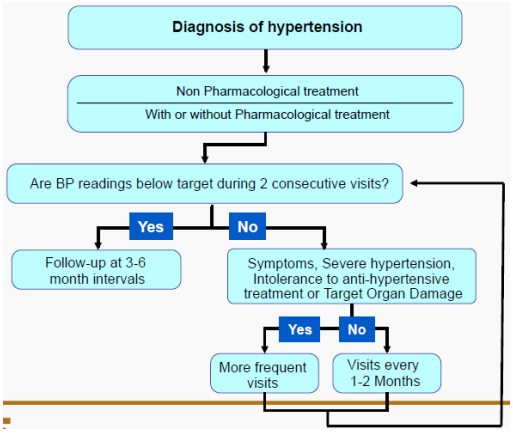
- "Start low and go slow"
- More sensitive to adverse effects of drugs

Global Vascular Protection

- Statin therapy if patient has 3 or more additional cardiovascular risks
- ASA once blood pressure is controlled

Follow up and Monitoring

Recommended Follow Up



Less follow up is required when targets are met

Patients with blood pressure at target are recommended to be followed at least every second month to improve adherence and assess response to therapy

Monitoring

- What do you monitor and when?
  - Four Questions to Evaluate Therapy
    - Indication
    - Efficacy
    - Safety
    - Adherence
  - Safety depends largely on the agents used and may require lab values
    - See individual medication classes for specific of monitoring
- General Concepts
  - Ensure baseline parameters are known for comparison once treatment initiated
    - Need to know what is normal to evaluate therapy
    - If baseline information not available, check trends in therapy

Resources

Canadian Hypertension Education Program (CHEP)

http://www.hypertension.ca/chep-recommendations

- Goal
  - To reduce the burden of cardiovascular disease in Canada through optimized hypertension management
- Activities
  - Regularly updated evidence-based recommendations for the management of hypertension
  - Knowledge and translation and exchange of recommendations to support implementation
  - Regular evaluation and revision of the program
  - Assessment of patient outcomes

Dyslipidemia

Classifications & Definitions

Dyslipidemia

- Abnormal fats in the blood
- Elevation of ≥ 1 lipoprotein(s) or reduced HDL
- Four Primary Categories
    - LDL = Low-density lipoproteins (bad cholesterol)
    - HDL = High-density lipoproteins (good cholesterol)
    - TC = Total Cholesterol = all lipoproteins
    - TG = Triglycerides

Terminology

Dyslipidemia	Abnormal lipid levels in blood
Hyperlipidemia	High lipid levels in blood
Hypercholesterolemia	High cholesterol levels in the blood
Hypertriglyceridemia	High triglyceride levels in the blood
Isolated hyperlipidemia/dyslipidemia	Just one LP that is elevated (e.g. just LDL)
Mixed hyperlipidemia/dyslipidemia	e.g. high LDL, low TG

Epidemiology

[To be filled in at a later date]

Etiology

Primary (Genetic)

- Most common in children
    - Familial hypercholesterolemia
    - Genetic predisposition for this

Secondary (Other Causes)

- Most common in adults
- Sedentary lifestyle
- Excessive dietary intake of fat or alcohol
- Diseases (hypothyroidism, kidney, liver disease)
- Cigarette smoking
- Drugs
    - Amiodarone
    - β-blockers (non-ISA) (e.g. metoprolol)
    - Carbamazepine
    - Clozapine
    - Corticosteroids
    - Cyclosporine
    - Loop diuretics
    - Oral contraceptives

- Olanzapine
- Phenobarbital
- Phenytoin
- Protease inhibitors
- Retinoids
- Thiazide diuretics (>50mg/day)

Pathophysiology

- No direct risks associated with dyslipidemia on its own
- However, it is a major risk factor for almost all other cardiovascular diseases
  - Example: Dyslipidemia and CAD
    - As TC and LDL increases, risk of CAD increases
      - Almost a linear risk
    - As HDL increases, risk of CAD decreases
    - Relationship between TG and CAD has not been established

Risk Factors

Risk Assessment

Framingham Risk Score (FRS)

- Estimates 10-year risk of total CV disease
- CCS guidelines Programs
  - Dyslipidemia Tools and Resources
- Bias: study done predominately in white American males

Reynolds Risk Score (RRS)

- Similar parameters to FRS, but a bit more specific
- Includes 2 more categories
  - Family history
  - High sensitivity C-reactive protein (HSCRP)
- Cardiovascular Life Expectancy Model

UKPDS Risk Engine

- Used in diabetic patients

Risk Categories

Risk Level	FRS	Other
High	≥ 20%	RRS ≥ 20% Established CAD, PVD, DM
Moderate	10-19%	
Low	< 10%	

- Avoid referring to a patient's risk in terms of risk level (low, moderate, high), as patients do not know what this corresponds to
  - Use percentages or odds

Clinical Presentation & Complications

"Silent killer"

- Most patients are asymptomatic

Possible Signs

- Xanthoma/xanthelasma
- Corneal arcus (Arcus senilis)
- Carotid bruits

Metabolic Syndrome

- "Syndrome X"
    - People with this syndrome are at high risk than if you were a normal person with this risks added together
- Complications
    - Central obesity
    - High blood pressure
    - High triglycerides
    - Low HDL cholesterol
    - Insulin resistance
- No uniform classification system
    - Some studies show that these people are at higher risk than if you consider the individual risk factors
    - No clinical trials has demonstrated reduced CV events in treating patients with metabolic syndrome
    - Recommend using FRS for risk assessment

Assessment & Diagnosis

Screening

- Men ≥ 40
- Women ≥ 50 and postmenopausal women
- Children with family history of hyperlipidemia
- All patients with the following conditions, regardless of age
    - Diabetes mellitus
    - Hypertension
    - Current smoker
    - Inflammatory diseases (e.g. RA)
    - HIV infection treated with HAART
    - Overweight/obese patients (BMI > 27kg/m^2)
    - Family history of premature CAD (< 60 years in first degree relative)
      Chronic renal disease (eGFR < 60mL/min)
    - Evidence of atherosclerosis
    - Clinical manifestation of hyperlipidemia (xanthomas, xanthelasmas, corneal arcus)
    - Erectile dysfunction

Treatment/Prevention

Goals of Therapy

Treatment Targets

Primary vs. secondary Prevention

Primary	Secondary
No established CAD	Established CAD, PVD, diabetes
Utilize risk assessment tools (e.g. FRS)	All patients are high risk

Target Lipid Levels

Risk Level	Initiate Treatment If:	LDL Target	Alternative Targets
High	Consider treatment in all patients	< 2mmol/L or 50% reduction	apoB < 0.8g/L
Moderate	LDL > 3.5 mmol/L TC/HDL > 5.0 hsCRP >2mg/L*	< 2mmol/L or 50% reduction	ApoB <0.8g/L
Low	LDL ≥ 5.0 mmol/L	≥ 50% reduction in LDL	N/A

*Only for men > 50 and women > 60 who are moderate risk based on FRS, but LDL is < 3.6mmol/L (based on JUPITER trial)

Secondary Targets

- ApoB
  - Located on atherogenic lipoproteins (e.g. LDL)
  - New alternative primary target in 2009
  - Associated with CAD
    - May be better marker for risk of CAD than LDL
  - No outcome data linking targeted lowering of ApoB and reduced CV events
  - Now available as routine laboratory value
    - May have slow turnaround time in rural areas
    - Many people do not know how to interpret this value
- High sensitivity C-reactive protein (hsCRP)
  - Acute phase reactant
    - Elevated in response to inflammation
    - Associated with CAD
  - Multiple drugs will lower hsCRP
    - e.g. NSAIDs, statins, niacin, ezetimibe, fibrates
  - No outcome data linking targeted lowering of hsCRP and reduced CV events
  - Used for risk assessment
    - RRS
    - Intermediate risk patients with LDL < 3.5mmol/L
  - High inter- and intra-patient variability
    - Recommended measurement:
      - Two levels at least 2 weeks apart
      - In absence of acute illness
  - Not useful in patients with inflammatory disease (including infections)
- TC/HDL Ratio
  - TC/HDL ratio < 4.0
  - No specific target for HDL
    - Low HDL associated with CV events
    - High HDL associated with atherosclerosis regression
  - Interventions that raise HDL
    - Exercise
    - Alcohol (in moderation)
    - Smoking cessation
    - Drugs (e.g. niacin)

    - Increasing HDL with pharmacologic therapy has not been shown to reduce CV events (so far)
- Triglycerides
    - < 1.7mmol/L
        - Derived from epidemiologic data
        - Not supported by clinical trial data
    - Reducing TG does not reduce CV events
    - Causes of Hypertriglyceridemia
        - High dietary fat intake
        - Excessive alcohol intake
        - Poor DM control
    - High TG associated with pancreatitis
        - Recommended treatment if > 10mmol/L

Non-Pharmacological Treatment

Smoking Cessation

- Single most important health behaviour to reduce risk of CVD
- Reduces cholesterol more than drugs

Dietary Modifications

- Calorie restriction
- Low sodium and simple sugars
- Substituted unsaturated fats for saturated/trans fats
- Fruits and vegetables
- Referral to dietician

Exercise

- Moderate to vigorous exercise
- 30-60 minutes per day most days of the week

Alcohol Consumption in Moderation

- Targets
    - Women: ≤ 1 drink per day
    - Men: ≤ 2 drinks per day
    - Cannot "save up drinks" throughout the week
- In absence of metabolic/clinical contraindications
- We do not recommend people start drinking though

Psychological stress management

Pharmacological Treatment

Options

- HMG-CoA Reductase Inhibitors (Statins)
- Cholesterol Absorption Inhibitor (Ezetimibe)
- Fibrates
- Niacin
- Bile Acid Sequestrant

Relative Effects

Drug Class	LDL	HDL	TG

Statins	↓↓↓↓	↑	↓↓
Ezetimibe	↓↓	-	-
Niacin	↓↓	↑↑↑	↓↓↓
Fibrates	↓↓	↑↑	↓↓↓
Bile Acid Sequestrants	↓↓	-	-

- These values are not guaranteed
- Variations between patients, drugs, formulations
- References may report different values

Considerations for LDL Pharmacotherapy

- First Line Therapy
  - Statin monotherapy
- Second Line Therapy
  - Better to add another agent then increase dose
    - Rule of 6
    - This general rule applies to most medications in CVD
  - Good Combinations
    - Ezetimibe (20% decrease in LDL)
    - Niacin (20% decrease in LDL)
    - Bile Acid Sequestrant (10-15% decrease in LDL)
  - Bad Combinations
    - Avoid Statin and Fibrate combination
      - No study has demonstrated benefit
      - One study in diabetic patients demonstrated no additional benefit of fibrate/statin vs. statin alone
      - Gemfibrozil/statin contraindicated due to risk of rhabdomyolysis
      - Fenofibrate/statin increases risk of myopathies

Considerations for HDL Pharmacotherapy

- First Line Therapy
  - Statins (increases HDL by 5-15%)
  - Fibrates (increases HDL by 10-20%)
  - Niacin raises HDL has not demonstrated a reduction in CV events
    - Increases HDL by 15-35%
    - AIM-HIGH Trial

Population	N = 3,414 Men and women with established CVD All patients receiving simvastatin ± ezetimibe LDL target = 1.03-2.07mmol/L
Intervention/Comparison	Niacin 1500-2000mg PO daily vs. placebo x 3 years
Outcome	HDL 0.91mmol/L → 1.08mmol/L No statistically significant difference in CV events

Considerations for TG Pharmacotherapy

- Goal is to reduce risk of pancreatitis
- First Line Therapy
  - Fibrate monotherapy (reduces TG by 20-50%)
- Second Line Therapy
  - Niacin (reduces TG by 20-50%)
  - Statins have modest effect (reduces TG by 7-30%)

        - Most Potent: atorvastatin, rosuvastatin, and simvastatin
    - Omega-3 Fatty Acids are a "natural" alternative

Combination Therapy

- Most common: ezetimibe + statin
    - Used to achieve target LDL or for mixed dyslipidemia
    - Controversial
    - No outcome data demonstrating reduced CV events
- Ensure dose of statin is optimized before adding other therapies
    - Don't add another agent until maximum recommended or tolerated dose
        - While this contradicts the ideas behind the “rule of 6”, other agents generally do not yet have evidence behind them supporting improved patient outcomes with altered lipid levels
- Example Combinations

Dyslipidemia		
	Additional Drug (added to statin)	Considerations
To achieve target LDL	Ezetimibe	Generally well tolerated
	Niacin	Poorly tolerated
	Fibrate	Increased risk of myopathy
	Bile acid sequestrant	Poorly tolerated
Mixed Dyslipidemia		
	Additional Drug (added to statin)	Considerations
High LDL and High TG	Fibrate	Increased risk of myopathy
	Omega-3 Fatty Acids	Less potent, but better tolerated
High LDL and Low HDL	Niacin	No additional benefit

Treatment Algorithm

1) Identify and screen all appropriate patients
2) Assess **individualized** level of risk
3) Address all modifiable risk factors and reversible causes
4) Institute lifestyle modifications
    - Should be done in all patients
    - May be sufficient in treating low risk patients
5) Assess need for pharmacologic treatment and, if needed, initiate treatment
    - May be required in moderate risk patients
    - Should be initiated in all high risk patients
6) Monitor and follow-up

Monitoring & Follow Up

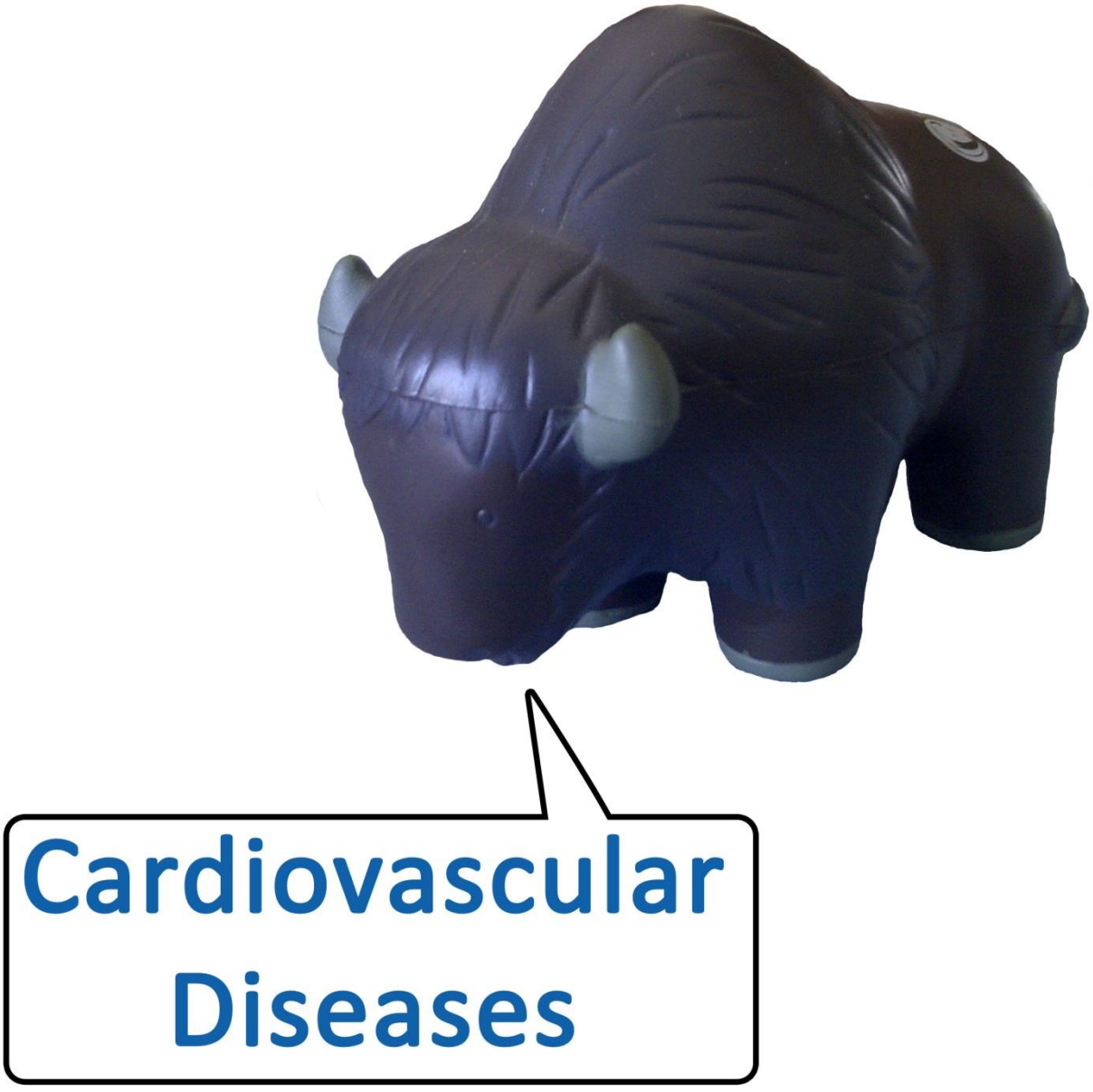
At Baseline

- Prior to initiating lipid-lowering therapy
    - Fasting lipid profile
    - TSH
    - ALT
    - CK
    - SCr
- Also recommended:
    - Fasting blood glucose (assessment for diabetes)
    - Uric acid (niacin)

        - Gout → side effect of niacin

Follow Up

- In 6-8 weeks
    - Fasting lipid profile
    - ALT
- Annually
    - Fasting lipid profile
- With Suspected Myopathy
    - CK
    - TSH
- Ongoing
    - Signs & symptoms of CV events
    - Signs and symptoms of adverse effects


Cardiovascular
Diseases

Atherosclerosis

Classifications & Definitions

Definitions

Sclerosis (pathology)	Hardening
Athero (Greek)	Gruel-like, soft pasty material
Arteriosclerosis	Disorder of hardening of the arterial wall, thereby thickening and losing elasticity
Atherosclerosis	Type of arteriosclerosis Disorder of progressive narrowing and hardening
Atherogenic (pathology)	Capacity to initiate or accelerate atherosclerosis (e.g. LDL)
Stenosis (pathology)	Narrowing or stricture
Thrombus (Greek)	Clot
Ischemia (physiology)	Low oxygen state, usually caused by reduced blood flow leading to tissue hypoxia

Epidemiology

Etiology & Pathophysiology

1. Endothelial Injury and Dysfunction
    - Causes of Injury
        - Hypercholesterolemia
        - Smoking (free radical production)
        - Hypertension
        - Diabetes
        - Genetic alterations
        - Elevated homocysteine
        - Microorganisms (e.g. Herpes virus, C. *pneumoniae*)
    - Typically develops in response to alterations in blood flow
        - Turbulence, decreased shear stress
        - Usually develops at bifurcations, branches, curvatures where blood flow is most altered
    - Most prone vessels:
        - Coronary arteries
        - Lower abdominal aorta
        - Descending thoracic aorta
        - Popliteal arteries
        - Internal carotid arteries
        - Circle of Willis
2. Intimal infiltration
    - Deposition of LDL which forms a plaque (atheroma) in the inner layer of the arterial wall (intima)
        - Develops over decades
        - But may begin as early as 5 years old
    - LDL undergoes oxidation causing:
        - Increased plasminogen inhibition
        - Induces endothelin expression
        - Inhibits NO expression

        - Provokes inflammatory response
    - Inflammatory Response
        - Adhesion of leukocytes to endothelial cells
        - Migrate into intima
        - Monocytes mature into macrophages
        - Macrophages uptake lipids → become foam cells → fatty streak
    - Fatty Streak Promotes:
        - Coagulation
        - Platelet inhibition
        - Vasoconstriction
        - Inflammation
3. Cell proliferation
    - Smooth muscle cell proliferation and migration
        - Migrate from media to intima and proliferate
    - Extracellular matrix accumulation
        - Smooth muscle cells
        - Proteoglycans
        - Elastin fibres
        - Collagen
    - Repeated injury and repair → more fatty streaks → more fibrofatty lesions → formation of plaque and central core
4. Plaque progression
    - Core = lipids, collagen, calcium, inflammatory cells
    - Continued macrophage accumulation
    - Injury and repair leads to fibrofatty lesion
    - Formation of acellular fibrous cap
        - Fibrosis → calcification
        - Calcification → smooth muscle cell death
    - Formation of necrotic core
5. Stenosis ± plaque rupture
    - Rupture of plaque fibrous cap
        - Vulnerable Plaque Characteristics
            - Large lipid core
            - Rich in cholesterol
            - Rich in macrophages
            - Thin fibrous cap
            - Poor in smooth muscle cells
            - Low grade stenosis
            - NB: plaques are more susceptible to rupture early **on**
    - Tissue factors in plaque exposed to blood coagulants
    - Formation of occlusive thrombus

Risk Factors

- Older age
- Male
- Hypertension
- Smoking
- Diabetes
- Family history
- Diet
- Hypercholesterolemia

- High cholesterol identified as risk factors for MI
- Correlation between lipoproteins and risk of atherosclerosis
- Atherogenic lipoproteins:
  - ApoB → measure of total atherogenic particle burden
  - ApoB molecules → LDL, VLDL, HDL
    - Two primary sources: endogenous (liver) and exogenous (liver)
  - HDL
    - Protective lipoprotein
      - Decreases inflammation
      - Decreases oxidation of LDL
      - Promote cholesterol efflux from foam cells
    - Inverse correlation between HDL and risk of atherosclerosis
    - However, increasing HDL pharmacologically has not been shown to provide a benefit in CAD morbidity and mortality
  - Correlation between diet (high fat consumption) and risk for atherosclerosis
    - Example: Chimpanzees
      - Primarily vegetarian diet
      - Low dietary fat intake
      - LDL level: 1.0-1.8mmol/L
      - Do not develop atherosclerosis

Clinical Presentation & Complications

Location	Symptom	Definitive Investigation
Coronary	Angina, ACS	Angiogram
Cerebral	Stroke	CT scan
Carotid	Syncope, stroke	Carotid ultrasound
Abdominal Aortic Aneurysm	± abdominal pain	Abdominal ultrasound
Peripheral	Calf pain with walking	Ankle-brachial index

- Primarily Asymptomatic
  - Usually lesions with >70% stenosis will induce ischemia
- Atherosclerosis can develop into numerous other cardiovascular illnesses
  - Arrhythmia
  - MI
  - PAD
  - Stroke

Assessment & Diagnosis

Depends on the location and presentation; refer to specific sections for further detail.

Treatment/Prevention

General Treatment – Vascular Protection

- Pharmacological mechanisms of Action
  - Plaque stabilization
  - Improve endothelial function
  - Reduce inflammatory mediators
  - Reduce platelet aggregation
  - Fibrinolysis

- Therapeutic Agents
    - Statins ("pleiotropic effects")
    - Antiplatelet agents
    - ACEIs and ARBs

Other Treatments

Depends on the location and presentation; refer to specific sections for further detail.

Coronary Artery Disease

Classifications & Definitions

Definitions

Ischemia	Tissue hypoxia (low O_2)
Ischemic Heart Disease (IHD)	Myocardial hypoxia (Demand > Supply)
Coronary	Arteries that supply the myocardium From corona (Latin): "encircling like a crown"
Coronary Artery Disease or Coronary Heart Disease	IHD caused by atherosclerosis Lots of times, people use CAD and CHD synonymous with IHD
Angina (Latin)	"infection of the throat" Now defined as a disease marked by spasmodic attacks of suffocative pain
Ankhon (Greek)	"strangling"
Pectus (Latin)	"chest"
Angina Pectoris	A clinical syndrome due to myocardial ischemia characterized by precordial cardiac discomfort, typically precipitated by exertion/stress and relieved by rest/NTG
Prinzmetal's Angina (angina inversa)	Coronary vasospasm that causes chest pain at rest (typically overnight) Not associated with the common risk factors
Ludwig's Angina (angina ludovici)	Bacterial infection of the floor of the mouth Treated as infection, not angina
Vincent's Angina (necrotizing ulcerative gingivitis/ periodontitis, trench mouth)	Bacterial infection of the gingiva or periodontium Treated as infection, not angina

Epidemiology

[To be filled in at a later date]

Etiology

Coronary Artery Obstruction

- Atherosclerosis (CAD)
  - Angina pectoris
- Coronary Spasm
  - Prinzmetal's Angina
  - Cocaine
- Other
  - Aortic regurgitation or stenosis
  - Cardiomyopathy (e.g. dilated, hypertrophic)

Pathophysiology

- Coronary artery disease is the atherosclerosis of the coronary arteries

Myocardial Economics

Imbalance in Supply vs. Demand

- Myocardial oxygen consumption= MVO_2
- Balance between O_2 deliver and MVO_2
- Imbalance where demand > supply → angina

Factors Affecting Supply

- Size of coronary artery
- Time of diastole
    - Myocardial perfusion during diastole
    - ↑ HR = ↓ time in diastole = ↓perfusion time

Factors Affecting Demand

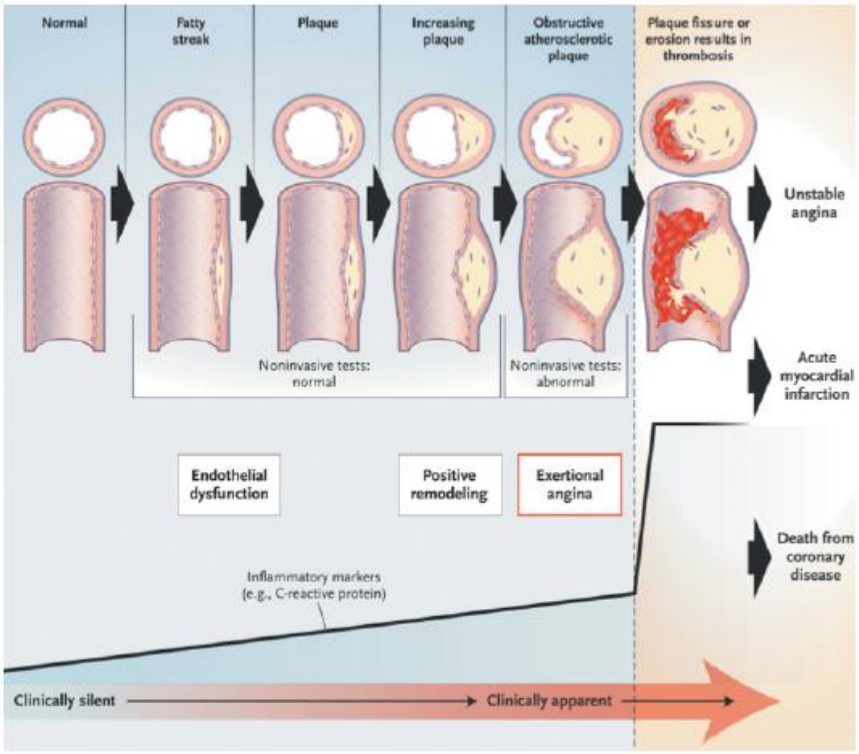
- Contractility
- Heart rate
- Myocardial wall stress
    - Preload
        - Volume of blood returned to heart
        - ↑ preload = ↑ MVO_2
    - Afterload
        - Pressure which the heart has to pump against
        - ↑ afterload = ↑ work = ↑ MVO_2

Risk Factors

[To be filled in at a later date]

Clinical Presentation & Complications

Spectrum of Coronary Artery Disease



- Plaque → flow limiting stenosis → stable angina
- Plaque rupture → temporary thrombus → unstable angina
- Plaque rupture → permanent thrombosis → MI

Signs

- 60% of patients with CAD will experience angina

Assessment & Diagnosis

Evaluating Chest Pain

- Location
- Duration
- PQRST
    - P → Provoking/Palliating factors
    - Q → Quality
    - R → Radiation
    - S → Severity
    - T → Timing

Differentiating Causes of Chest Pain

Causes of Chest Pain

CNS	Panic/anxiety attack
CVS	Angina, pericarditis, aortic dissection
GI	GERD, esophagitis, cholecystitis, pancreatitis
RESP	PE, pneumothorax, pneumonia

MSK	Costochondritis, intercostal myalgia, rib fracture

Chest Pain Caused by Angina

Location	Substernal or retrosternal
Duration	Usually minutes (usually < 10 minutes)
Provoking Factors	Exertion/exercise or emotional stress Others Sudden exposure to hot/cold environment Exertion after large meal Exertion in early morning Drugs: sympathomimetics, ergot alkaloids, cocaine
Palliating Factors	Rest or NTG
Quality	Crushing, squeezing, pressure, heavy
Radiation	Neck, jaw, left arm, back
Severity	Often severe (≥ 8/10)
Timing	After exertion, at night
Associated Symptoms	CNS: dizziness, fatigue, fear RESP: Dyspnea CVS: palpitations, change in BP or HR GI: Nausea ± vomiting DERM: diaphoresis

- Atypical presentation more likely in women, diabetics, and the elderly

Classification of Chest Pain

"Typical" Angina (High Probability)

- Characteristics, quality match typical presentation
- Provoked by exertion or emotional stress
- Relieved by rest or NTG

"Atypical" Chest Pain (Intermediate Probability)

- Any two of the above

"Non-Cardiac" Chest Pain (Low Probability)

- ≤ 1 of above
- Could still be angina

Functional Classification of Angina

Canadian Cardiovascular Society (CCS) for Stable Angina

Class	Activity Evoking Angina	Limits to Physical Activity
I	Prolonged exertion	None
II	Walking rapidly, uphill, after meals, in the cold, in the wind, under emotional stress, or only in a few hours after waking	Slight
III	Occurs on walking 1-2 blocks or 1 flight of stairs in normal conditions at normal pace	Marked
IV	Minimal of at rest	Severe

Criteria for Unstable Angina

Rest Angina	Occurs at rest or with minimal exertion with prolonged duration (usually lasting > 10 min)

New Onset Angina	Severe angina (CCS Functional Class III or IV) within 2 months of presentation
Increasing Angina	Previously diagnosed angina that is occurring more frequently, longer in duration, or with lower threshold of activity over a period of time < 4 weeks

Diagnosis

- History
- ECG Changes
    - ST elevation/depression
    - T wave inversion
- Diagnostic Tests
    - Exercise stress test
        - Patient walks on a treadmill at differing speeds and elevation
    - Heart rate and ECG is monitored and patient monitored for pain
    - Myocardial Perfusion Imaging
        - Nuclear medicine scan
        - 99mTc-sestamibi: radioactive lipophilic cation
        - Image heart at rest and during stress
    - Stress Echocardiography
        - Transthoracic echocardiography (ultrasound)
        - No radiation exposure
        - Image heart at rest and under stress
    - Coronary Angiography
        - Gold standard
        - Inject contrast dye into body via femoral or radial artery
        - Invasive procedure

Treatment/Prevention

Goals of Therapy

- Prevent mortality
- Prevent morbidity (e.g. Major Adverse Coronary Event)
- Reduce/eliminate symptoms
- Prevent symptoms
- To improve quality of life

Non-Pharmacological Therapy

Avoid precipitating factors

- See provoking factors in “Chest Pain Caused by Angina”
- Examples: exercise, strenuous work, drugs, etc.

Lifestyle Modifications

- Smoking cessation
- Healthy diet
- Daily exercise
- Weight management

Coronary Revascularization

- Coronary Artery Bypass Graft (CABG) Surgery

- An additional blood vessel is grafted onto the coronary artery to bypass the blockage
- Three Types
  - Internal artery
  - Saphenous vein graft
  - Arterial graft

Percutaneous Coronary Intervention (PCI)

- Process
  - Catheter is inserted into blockage to break it up
  - Balloon is inflated to expand stent
  - Balloon deflates and catheter is removed; stent remains in place
- Types of Stents
  - Bare-metal stent
  - Drug-eluting stent
- Efficacy – COURAGE Trial

Patient	N = 2,287 with CAD
Intervention/Comparison	PCI vs. medical management
Outcome	No difference in survival between medical management vs. PCI

Pharmacological Therapy

Summary of Recommendations

	Antiplatelets	ACEI/ARB	Statin	βB	CCB	Nitrate
Agents	ASA 75-162mg daily	Perindopril 2-8mg daily Coversyl 1.25-20mg daily Telmisartan 80mg daily*	See dyslipidemia guidelines	Atenolol 12.5-100mg daily bisoprolol 2.5-10mg daily Metoprolol 12.5-100mg BID	Any agent except IR nifedipine	Short acting for acute treatment Long acting for prevention
Prevent Mortality	X	X	X	X**	-	-
Prevent MACE	X	X	X	X**	-	-
Symptoms of Angina **Prevention** **Reduce frequency** **Improve activity** **Improve QoL**	-	-	-	X	X***	X***

*if intolerant to first line therapy
**only indicated in patients with previous MI or HF
***if intolerant to β-blocker therapy, symptoms persist despite β-blocker, or Prinzmetal's angina

Agents for Prevention of Mortality/MACE

Antiplatelets

- Recommendation
  - **ASA 75-162mg should be used indefinitely in patients with CAD**
  - Clopidogrel only should be used if patient is allergic/intolerant to ASA
  - There is no indication for dual antiplatelet therapy
- Evidence

Trial	Antithrombotic Trialists Collaboration (ATT)	CAPRIE	CHARISMA
Patients	Meta-analysis of 16 trials N = 17,000	N = 19,185 patients with vascular disease	N = 15,603 patients with CV disease or multiple CV risk factors
Intervention/ Comparison	ASA vs. placebo	Clopidogrel 75mg daily vs. ASA 325mg x 2 years	Clopidogrel 75mg daily + ASA 75-162mg daily

			vs. ASA 75-162mg daily x 2.3 years
Outcome	20% reduction in major coronary events 19% reduction in all strokes 19% reduction in any serious vascular event 10% reduction in total mortality Increase in major extracranial bleeds (RR 2.69) No statistical difference in hemorrhagic stroke	PO (MI, stroke, vascular death): ARR 0.51% (NNT = 196) Severe rash higher with clopidogrel (0.16%) Severe GI bleeding higher with ASA (0.22%)	PO (MI, stroke, CV death): NSS Moderate bleeding increased by 0.8%

Angiotensin Converting Enzyme Inhibitors

- Recommendation
  - **Perindopril 2-8mg daily or ramipril 1.25-20mg daily**
  - No other agents have been studied and have shown a benefit
- Benefits (Beyond BP Effects)
  - Decreases progression towards atherosclerosis
  - Plaque stabilization
  - Fibrinolysis
  - Improve endothelial function
  - Prevent ventricular remodelling
- Evidence

Trial	HOPE	EUROPA	PEACE
Patients	> 55 years of age History of CAD, stroke, PAD, or DM + 1 other risk factor N = 9.297	Previous MI, revascularization, evidence of CAD on angiography, or men with a history of CP and positive test for CAD N = 12,218	≥ 50 years of age Previous MI, revascularization, or evidence of CAD on angiography N = 8,290
Intervention/ Comparison	Ramipril 10mg vs. placebo x 5 years	Perindopril 8mg vs. placebo x 4.2 years	Trandolapril 4mg vs. placebo x 4.8 years
Outcome	PO (MI, stroke, CV death) ARR = 3.8% (NNT = 27)	PO (CV death, MI, cardiac arrest) ARR = 1.9% (NNT = 52)	PO (CV death, MI, revascularization) ARR = NSS

Trial	Angiotensin-Converting Enzyme Inhibitors in Coronary Artery Disease and Preserved Left Ventricular Systolic Function
Patients	Meta-analysis of 6 trials N = 33,500
Intervention/ Comparison	ACEI vs. Placebo x 4.4 years (mean follow up)
Outcome	16% reduction in non-fatal MI 17% reduction in CV mortality 13% reduction in all-cause mortality Overall: ACEI indicated in all patients with CAD, in particular those with HTN, CKD, DM, or HF

Angiotensin Receptor Blockers

- Evidence

Trial	ONTARGET
Patients	N = 25,620 Vascular disease or DM with end-stage organ damage
Intervention/ Comparison	Telmisartan 80mg daily vs. ramipril 10mg daily vs. telmisartan + ramipril 10mg daily x 4.7 years
Outcome	PO (CV death, stroke, HF, hospitalizations) AR = 16.7% vs. 16.5% (p = 0.006 for non-inferiority) No difference in adverse events

Overall: Telmisartan may be appropriate in patients intolerant to ACEI therapy

HMG-CoA Reductase Inhibitors

- Indicated as per dyslipidemia guidelines (all patients with CAD are considered high risk and should receive treatment to dyslipidemia targets)

Agents for Preventing/Treatment of Angina

Treatment Algorithms

- Prevention

First Line	β-blocker
Second Line Intolerance to first line	CCB or long-acting nitrate
Prinzmetal's/Vasospastic Angina	CCB or long-acting nitrate

- Treatment

Acute Symptoms	Short-acting nitrate
Persistent Symptoms (First Line)	β-blocker + CCB or long-acting nitrate ± analgesics
Persistent Symptoms (Second Line)	β-Blocker + CCB + long-acting nitrate ± analgesics

- Evidence

Trial	**Meta-analysis of Trials Comparing β-Blockers, Calcium Antagonists, and Nitrates for Stable Angina**
Patients	Patients with stable angina
Intervention/ Comparison	β-blocker vs. CCB vs. nitrate
Outcome	β-blocker vs. CCB • No difference in cardiac death or MI • No difference in angina episodes per week, NTG use, or exercise tolerance • Fewer withdrawals due to adverse effects in β-blockers Nitrates vs. CCB or β-blocker • Insufficient evidence

β-Adrenergic Antagonists

- Recommendation
  - **Atenolol 12.5-100mg daily, bisoprolol 2.5-10mg daily, or metoprolol 12.5-100mg BID**
  - Indicated as first line for **prevention of angina** in patients with **prior MI, HF, or HTN**
  - Indicated for **secondary prevention** in patients with **IHD and prior MI or HF**
- Mechanism of Action
  - Decreases HR, BP, and contractility, thereby:
    - Decreasing MVO_2 (demand for O_2)
    - Prolongs diastole
    - Blunts HR and BP response during exercise

Calcium Channel Blockers

- Recommendation

Drug	**Dose**
Verapamil	40mg TID to 120mg BID 120-240mg SR daily
Diltiazem	30-60mg TID 120-300mg CD daily 120-360mg ER daily 240-360mg XR daily
Amlodipine	2.5-10mg daily

Felodipine	2.5-10mg ER daily
Nifedipine	30-120mg XL daily

- Indicated for treatment of angina in patients with:
  - β-blocker contraindication or intolerance
  - Persistent symptoms despite β-blocker
  - Prinzmetal's or vasospastic angina
- Mechanism of Action
  - Smooth muscle relaxant and vasodilation
  - Non-DHP
    - Decreases force of contraction, HR, conduction velocity (decreased demand)
    - Coronary and peripheral vasodilation (increase supply)
  - Long-Acting-DHP
    - Coronary and peripheral vasodilation (increase supply)

Nitrates

- Recommendations for Treatment (Short Acting)

Generic Name	Dose	Onset	Duration
NTG Spray	0.4mg	3-4min	10-30min
NTG SL tablets	0.3-0.6mg	1-3min	10-30min
ISDN	5-10mg	2-5min	1-3 hours

  - All patients with IHD should carry a short-acting nitrate
  - If no relief after 1 dose, or not resolved after 3 doses → seek medical attention
  - If some relief provided, use every 5 minutes until EMS arrives
- Recommendations for Prevention (Long Acting)

Generic Name	Usual Dose
NTG Patch	0.2-0.8mg/hr daily (for 12-14 hours)
ISDN	10-30mg TID (last dose at 7pm)
ISMN	30-240mg daily (QAM)

  - Indicated in β-blocker tolerance or persistent symptoms despite β-blocker
  - Important to ensure nitrate free period of 10-12 hours every day to prevent tolerance
  - May also be used as an ointment or IV
- Mechanism of Action
  - Vasodilation
    - Converted to NO by vascular endothelium
    - NO activated cGMP → decreases cellular Ca^{2+}
    - Results in smooth muscle relaxation
  - Primary anti-anginal effect: venous vasodilation
    - Decreases volume returned to heart (preload)
  - Also causes coronary artery vasodilation
    - Increased blood flow to myocardium

Monitoring & Follow Up

[To be filled in at a later date]

Acute Coronary Syndromes

Classifications & Definitions

Definitions

ACS	Any constellation of clinical symptoms that are compatible with acute myocardial ischemia
Myocardial infarction	Any amount of myocardial necrosis caused by ischemia
NSTEMI	Partial occlusion of infarct related artery resulting in necrosis
STEMI	Total occlusion of infarct related artery resulting in necrosis

Epidemiology

[To be filled in at a later date]

Etiology

[To be filled in at a later date]

- Occlusion of coronary artery typically occurs as a result of atherosclerosis/CAD

Pathophysiology

[To be filled in at a later date]

- Occlusion may be the result of growing atherosclerotic plant or thromboembolism from a ruptured plaque

Risk Factors

[To be filled in at a later date]

Clinical Presentation & Complications

Presentation

Elderly patients, women, diabetics my present with other symptoms not typical of myocardial ischemia

Chest pain or discomfort

- "A fist clenching my heart"
- Central or substernal, upper abdominal, or epigastric pain
- Pain radiating to the neck, jaw, shoulders, back, one or both arms
- Sensation of pressure, crushing, tightness, heaviness, cramping, burning, aching
- Accompanying dyspnea, indigestion, nausea, vomiting, diaphoresis
- Associated hypotension or ventricular arrhythmias

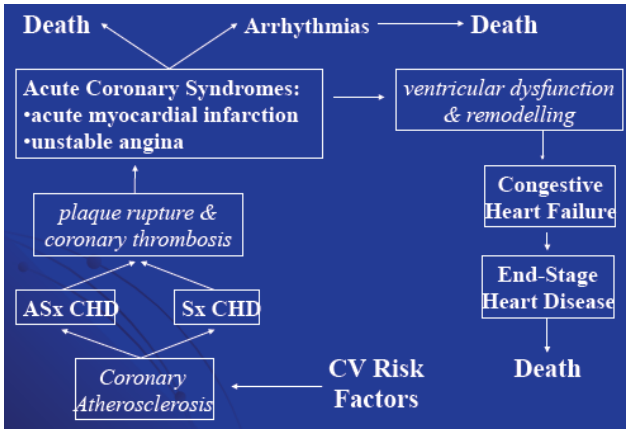
Other Symptoms

- Isolated dyspnea
- Weakness

- Diaphoresis
- Light-headedness and/or syncope
- Nausea

Outcomes of ACS

Medical Outcomes



A proportion of people will die before they ever make it to hospital → this is why it is better to go to the hospital if you have symptoms, even if it is something more minor (e.g. GERD)

Survivors may develop arrhythmias and die

Survivors may get ventricular dysfunction and remodeling with CHF and inevitably death

Hospital Statistics

- Hospital Discharge Status

	STEMI	NSTEMI	UA
Death	7%	4%	3%
Home	77%	78%	87%
Transfer (to acute care)	10%	12%	9%
Other	6%	6%	2%

  - Elderly patients > 75 are more likely to die
- Six-Month Follow Up

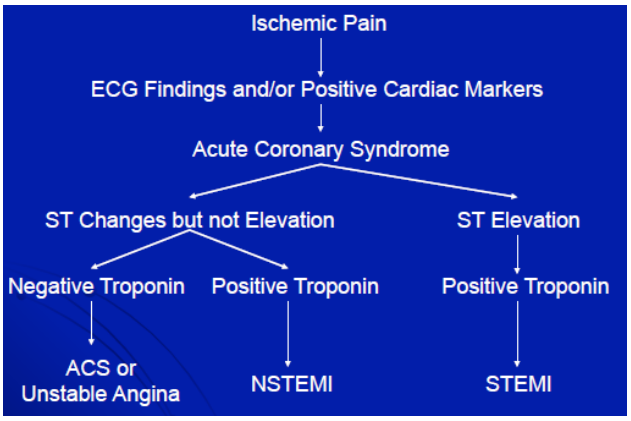
	STEMI	NSTEMI	UA
Death	5%	6%	4%
Stroke	1%	1%	1%
Hospitalized	18%	19%	19%

Assessment & Diagnosis

Evaluating Ischemic Pain

- Anyone coming in with plausible ischemic pain (with a clinical history supporting it) will get an ECG
  - Guidelines say within 10 minutes of presentation
  - Either classified as ST elevation or ST changes without elevation
    - ST changes without elevation → partial occlusion (less urgent)
    - ST elevation → coronary artery is entirely occluded (more urgent)
  - Then a troponin test is run
    - Must be done in lab, so can't be done instantly
    - Therefore treatment starts after the first two categories (ischemic pain + ECG findings/Cardiac markers)

Diagnostic Algorithm



Treatment/Prevention

Goals of Therapy

- Rapid Reperfusion to limit infarct size and reduce mortality (want to reduce amount of necrosis and salvage tissue)
    - Prompt identification of STEMI
    - Initiate reperfusion within recognized timeframe
    - Use of agents to maintain arterial patency, prevent recurrent infarction, and limited adverse ventricular remodelling
        - Breaking up a clot releases a lot of pro-thrombotic components → need to stop them from clotting elsewhere
    - Optimize long-term measures to reduce cardiovascular risk

Managing Bleed Risk

- Major bleeding is the most frequent complication of ACS
    - Increases risk of in-hospital mortality by 60%
    - 5-fold increase in 1 year rate of death or MI

Risk Factors

- Older age
- Female gender
- Low body weight
- History of bleeding
- Hypertension
- Hemodynamic instability
- Increased risk of ischemic events
- Renal insufficiency
- CrCl <60mL/min

Scoring Risks

Low Risk	Absence of risk factors (see above), other antiplatelet, coagulant agents
Moderate risk	1-2 risk factors
High risk	≥ 3 risk factors
Very high risk	Prior ulcer disease with history of complications

Factors to Manage

- Use of glycoprotein IIb/IIIa inhibitors
- PCI within first 24 hours
- Femoral access site
- Excessive antiplatelet and/or antithrombotic dosing
- Triple therapy (ASA, clopidogrel, warfarin)

Prevention

- Careful patient history, physical examination, and assignment to therapy
- Appropriate selection of antithrombotic drugs
- Shortened duration of exposure to antithrombotic drugs
- Consider renal function
- Use of PPIs in high risk patients

Treatment of STEMI

Fibrinolysis vs. Primary PCI

Fibrinolysis Preferred	PCI Preferred

• Treatment within 3 hours of symptoms onset
• If PCI is not an option (e.g. due to geographical barriers)
• When used to delay need for invasive strategies
• Absolute Contraindications
  ○ High bleed risk, particularly intracranial bleed
  ○ Any prior ICH
  ○ Known structural cerebrovascular lesion
  ○ Known malignant intracranial neoplasm
  ○ Ischemic stroke in past 3 months, but > 3 hours
  ○ Suspected aortic dissection
  ○ Active bleeding
  ○ Significant closed head or facial trauma in past 3 months
• Relative Contraindications
  ○ History of chronic, severe, or poorly controlled hypertension
  ○ SBP > 180mmHg or DBP > 110mmHg
  ○ History of prior ischemic stroke, dementia, or known intracranial pathology
  ○ Traumatic or prolonged CPR or major surgery (less than 3 weeks prior)
  ○ Recent (2-4) weeks internal bleeding
  ○ Non-compressible vascular punctures
  ○ Pregnancy
  ○ Active peptic ulcer
  ▪ Current use of anticoagulants (higher INR = higher risk)
	• Treatment after 3 hours of symptoms onset
	• High risk STEMI with cardiogenic shock or Killip class ≥ 3
	• Fibrinolysis contraindicated
	• Diagnosis is in doubt (fibrinolysis carries a 0.7% risk of intracranial hemorrhage)

Antiplatelet Therapy Post-PCI

- Recommendation
  - ASA 75-162mg daily indefinitely
    - Clopidogrel may be used in place of ASA if patient is intolerant to therapy
  - Dual Antiplatelet Therapy
    - Duration

- Bare Metal Stent: minimum of 1 month and up to 12 months (if clot risk is high or bleed risk does not limit use)
- Drug Eluting Stent: at least 1 year and beyond if risk of stent thrombosis is considered higher than risk of bleed

▪ Clopidogrel 75mg daily
▪ Prasugrel 10mg daily may be used in place of clopidogrel patients who are at an increased risk of stent thrombosis (e.g. prior history of STEMI, DM, or stent thrombosis)
▪ Ticagrelor 90mg BID may be used in place of clopidogrel for 12 months (if increased bleed risk is not a problem)

- Considerations

	Clopidogrel	Prasugrel	Ticagrelor
Prodrug	X	X	
Individual variability	X		
Speed of onset		X	X
Potency		X	X
Reversibility			X (shorter $t_{1/2}$)

- Contraindications and Warnings

	Ticagrelor	Prasugrel
Contraindications	• History of intracranial hemorrhage • Moderate of severe hepatic impairment • Concomitant therapy with strong CYP3A4	• Patients with a known history of transient ischemic attack (TIA) or stroke • Patients with severe hepatic impairment (Child-Pugh Class C)
Warnings	• Patients at risk of bradycardia events • Patients reporting new, prolonged, or worsened dyspnea should be investigated and if not tolerated treatment should be stopped	• In patients ≥ 75 years of age, prasugrel is not recommended because of the increased risk of fatal and intracranial bleeding • In patients with body weight < 60kg, prasugrel is not recommended because of increased risk of major bleeding • Due to an increased exposure to the active metabolite of prasugrel

- Evidence

Trial	Antithrombotic Trialists Collaboration (ATT)	COMMIT	CLARITY
Patients	Meta-analysis of 16 trials N = 17,000	N = 45,852 STEMI patients after 12 hours of symptoms onset	N = 3,491 STEMI patients after 12 hours of symptoms onset
Intervention/Comparison	ASA vs. placebo	Clopidogrel 75mg daily + ASA 162mg daily vs. ASA 162mg daily	Clopidogrel 75mg + ASA vs. ASA
Outcome	20% reduction in major coronary events 19% reduction in all strokes 19% reduction in any serious vascular event 10% reduction in total mortality Increase in major extracranial bleeds (RR 2.69) No statistical difference in hemorrhagic stroke	Death RRR = 9% (p=0.002) Death, MI, stroke RRR = 7% (p=0.03)	Occluded artery, death or MI OR reduction = 0.36

Trial	PLATO	TRITON-TIMI 38
Patients	N = 18,624 ACS patients with symptoms in past 24 hours ACS without ST elevation or STEMI, but intention for primary PCI	Patients with ACS undergoing PCI
Intervention/ Comparison	Clopidogrel 300mg LD, then 75mg daily + ASA 75-100mg daily vs. Ticagrelor 180mg LD, then 90mg BID	Clopidogrel 300mg LD, then 75mg daily + ASA 75-162mg daily vs. prasugrel 60mg LD, then 10mg daily + ASA 75-162mg daily
Outcome	Ticagrelor showed lower mortality, stent thrombosis Increased fatal ICH in some patients and SOB	PO (death, non-fatal MI, non-fatal stroke) HR = 0.81 Decreased stent thrombosis Increased rate of major bleeding (including life-threatening bleeding)

Antiplatelet Therapy Post-Fibrinolysis

- Recommendation
  - ASA 75-162mg daily indefinitely
    - Clopidogrel may be used in place of ASA if patient is intolerant to therapy
  - Clopidogrel 75mg daily for 14 days
    - May be continued for up to 12 months in the absence of excess bleed risk
  - Prasugrel and ticagrelor are not studied in this population and not recommended

Discharge Therapy

Anticoagulation

- Only indicated in large anterior STEMI or visualized clot
- Consider bleed risks of triple therapy (dual antiplatelet + oral anticoagulation)

Nitrates

- Indications as per coronary artery disease

β-Adrenergic Antagonists

- Indicated in all patients, excluding those with contraindications, cannot tolerate therapy or low risk patients
- Therapy should continue indefinitely

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

- Indicated for short term reduction in mortality (4-6 weeks), started immediately after initial management
- May be continued indefinitely for cardiovascular protection if no contraindications
- ARBs can be used in place of ACEI if patient is intolerant to ACEI has clinical signs of heart failure (or LVEF < 40%)

HMG-CoA Reductase Inhibitors

- Early and intensive high-dose statin therapy is shown to reduce death, MI, cardiac arrest, and recurrent ischemia in **NSTEMI**
- Results have been extrapolated to STEMI
- Fasting lipid profiles should be obtained within 24 hours post-ACS due to a false depression of LDL following ACS

NSTEMI Treatment

Fibrinolysis vs. Primary PCI vs. Revascularization

- Choice of therapy depends on risks
  - Recurrent Ischemic Event
    - Determined by an interaction between patient's pre-event status and impact of the acute event
  - Bleeding
    - Increased by intensive antithrombotic therapy and invasive management

        - Risk can be assessed by GRACE Risk Model
    - Outcomes of Low Risk Patients
        - *Presentation with UA in the absence of dynamic ECG changes, no troponin elevation, no arrhythmia, no hypotension*
            - Abnormal ECG in 38%
            - 27% stress test, 37% echo, 52% angio
            - 6 Month Outcomes
                - 23% readmission
                - 12% revascularized
                - 3% death
        - **Low risk ≠ no risk**

Dual Antiplatelet Therapy Post-Medical Treatment

- Recommendation
    - ASA 75-162mg continued indefinitely
        - Clopidogrel may be used in place of ASA if patient is intolerant to therapy
    - Clopidogrel 75mg daily for 14 days
        - May be continued for up to 12 months in absence of excess bleeding risk
    - Ticagrelor 90mg BID may be used in place of clopidogrel

Dual Antiplatelet Therapy Post-PCI

- Recommendation
    - ASA 75-162mg continued indefinitely
        - Clopidogrel may be used in place of ASA if patient is intolerant to therapy
    - Clopidogrel 75mg daily for 14 days
        - May be continued for up to 12 months in absence of excess bleeding risk and patient is high risk of thrombosis
    - Prasugrel 10mg daily may be used in place of clopidogrel for 12 months
        - Consider in patient who have an increased risk of stent thrombosis
        - Avoid in patients who at high risk of bleeding, **likely to undergo CABG within 7 days**, history of stroke/TIA, age ≥ 75 years old, or weight < 60kg
    - Ticagrelor 90mg BID may be used in place of clopidogrel for 12 months

Discharge Therapy

Glycoprotein IIb/IIIa Receptor Antagonists

- May be initiated in patients who have undergone PCI

Nitrates

- Indications as per coronary artery disease

β-Adrenergic Antagonists

- Indicated in all patients, excluding those with contraindications, cannot tolerate therapy or low risk patients
- Therapy should continue indefinitely

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

- Indicated for short term reduction in mortality (4-6 weeks), started immediately after initial management
- May be continued indefinitely for cardiovascular protection if no contraindications
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HMG-CoA Reductase Inhibitors

- Early and intensive high-dose statin therapy is shown to reduce death, MI, cardiac arrest, and recurrent ischemia in NSTEMI

Secondary Prevention

- All patients with ACS should be assessed for willingness to quit smoking (if applicable)
- All patients with ACS should be referred to a comprehensive outpatient cardiovascular rehabilitation program
- It is reasonable to screen patients with recent MI for depression
- Patients with cardiovascular disease should have an annual influenza vaccination

Monitoring & Follow Up

[To be filled in at a later date]

Heart Failure

Classifications & Definitions

- Heart Failure (HF) is a complex clinical syndrome characterized by the inability of the heart to provide sufficient blood to meet the body's metabolic demands
    - Structural or functional disorder that impairs ventricular filling or ejection of blood (typically decreasing cardiac output)
    - Characterized by dyspnea, fatigue, and fluid retention
    - Formally known as "Congestive Heart Failure"
        - "congested" because of fluid overload

Two Types of Heart Failure

Systolic Dysfunction

- Classic form of heart failure
- Reduced "pump" function
- Left ventricular ejection fraction (EF) < 40%
    - Normal EF ~65%

Diastolic dysfunction

- Abnormal ventricular filling
- "HF with preserved systolic function"
- EF > 50%
- ***Majority of cases refer to systolic dysfunction, but treatment of the two are very similar (differences are noted where applicable)***

Epidemiology

Prevalence

- 1.5% and increasing
    - Aging population
    - More post MI survivors (60-70% of patients)
    - Uncontrolled hypertension
- Approximately evenly split between systolic and diastolic dysfunction
    - Diastolic heart failure more common in the elderly and females

Etiology

HF is likely the final common pathway for a variety of cardiac disorders

Possible Causes

- Loss of viable myocardial tissue: slowly due to hypertension or coronary artery disease or quickly due to MI
    - Left ventricle shape changes → doesn't pump properly
- Iatrogenic myocardial damage
    - Radiation
    - Drugs
        - Anthracyclines (doxorubicin), trastuzumab
        - Negative inotropic drugs: β-blockers (at high initial doses), CCBs, antiarrhythmics

        - Fluid retention: NSAIDs, COX-2 inhibitors, thiazolidinediones
- Valvular disease - reversible and irreversible
    - Heart muscle works properly, but the valves don't properly open and close (e.g. backflow into previous chambers/vessels would prevent proper ejection and filling)
- High output failure
    - The metabolic demands on the heart exceed the output
- Atrial fibrillation
    - Atrium doesn't fill well → ventricle doesn't fill well
    - Heart failure can also cause atrial fibrillation
- Viral myocarditis
    - Scarring and dysfunction of heart muscle due to viral infection

Pathophysiology

A Progressive Condition

- Index event produces decline in pumping capacity
- Asymptomatic and symptomatic phases

Normal Physiology

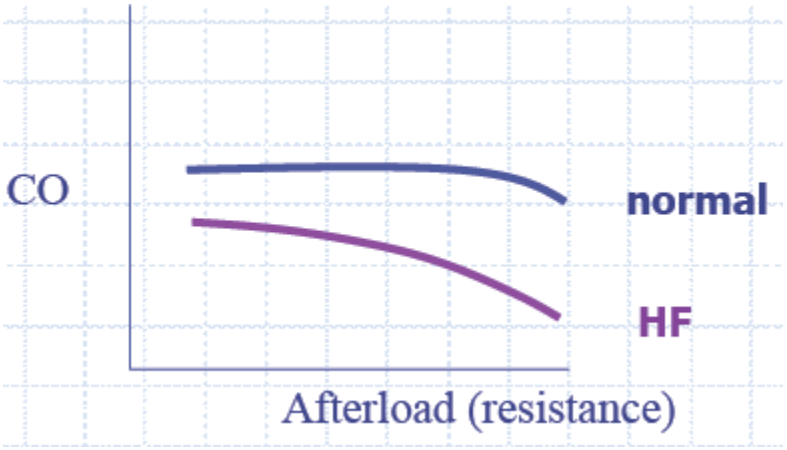
$$CO = HR * SV$$

- Heart Rate (HR) controlled by:
    - ANS
- Stroke Volume (SV) affected by:
    - Afterload (Systemic Valvular Resistance, Total Peripheral Resistance)
    - Afterload is the resistance against which the heart must work to pump blood (resistance to blood exiting the heart)
        - Related to arteriolar tone and is reflective of, but not the sole determinant of BP

$$BP = CO * SVR$$

Heart Failure Pathophysiology

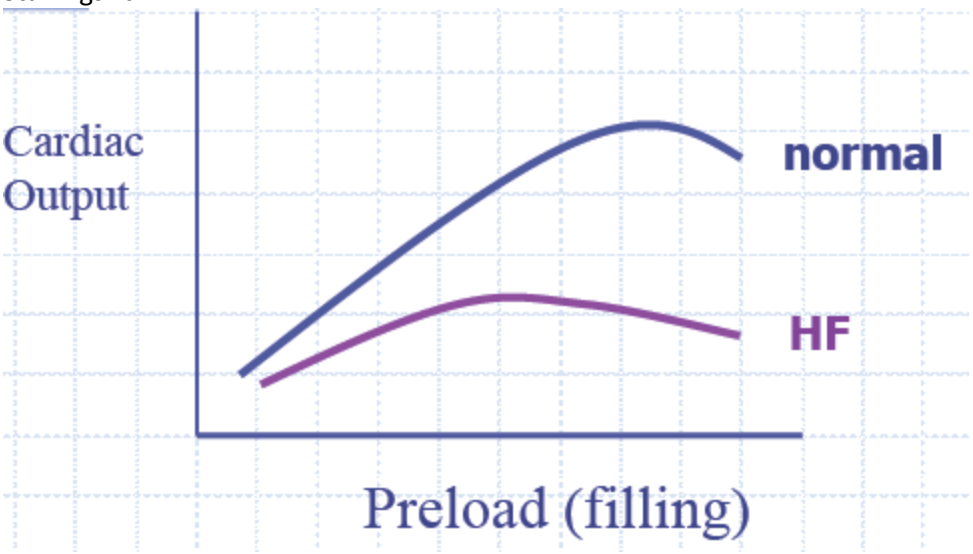
Increasing afterload increases myocardial work



- Normal Heart → increasing the afterload doesn't change CO much
- **HF Heart → increased afterload makes the already weakened heart work harder, and will actually decrease CO**
- NB: Increase in afterload can cause HF, or can occur as a result of HF

Preload (LVED Pressure, Pulmonary Capillary Wedge Pressure)

- Amount of blood presented to the heart for pumping at the end of diastole (left ventricular end diastolic volume [LVEDV])
- Influences the initial stretching of the cardiac myocytes (sarcomere length)
- Starlings Law

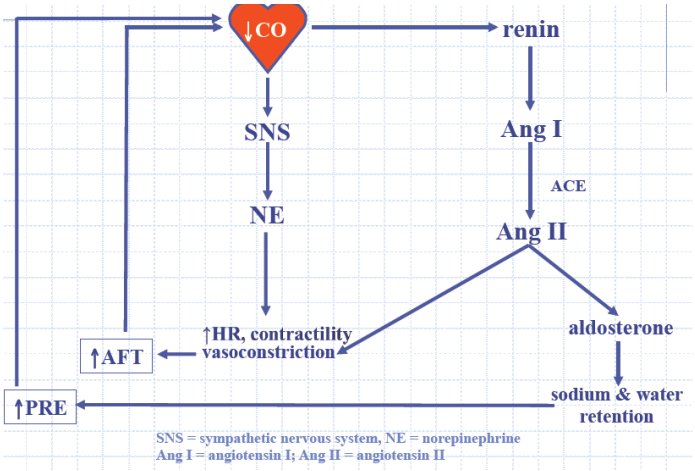


  - Normal Heart → increasing preload increases cardiac output
  - **HF Heart → increasing the preload doesn't increase cardiac output, and in fact, will decrease it by overwhelming the pumping capacity of the heart**
  - NB: Increase in preload is both the cause and an effect of heart failure

Contractility (inotropy)

- Decreased inotropy (i.e. strength of contraction)
- Can be due to numerous causes (e.g. loss of viable myocardial tissue from MI)

Compensatory Mechanisms in Heart Failure



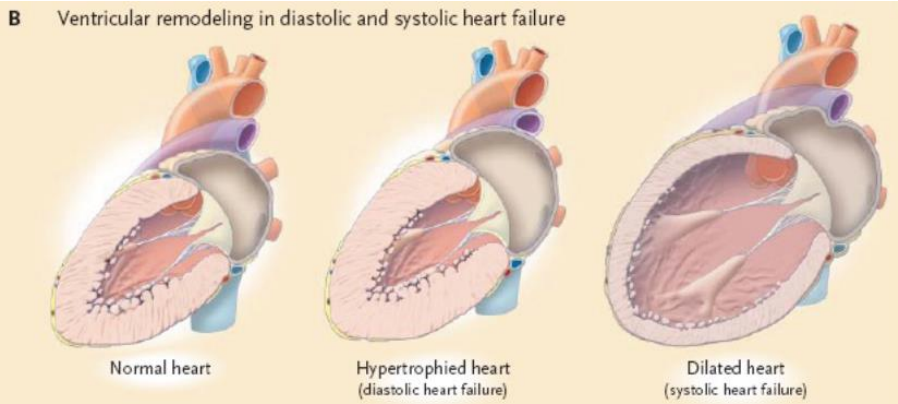
1. The body senses a decrease in perfusion (low BP), and the sympathetic nervous system releases norepinephrine in an attempt to increase BP
   - However, this system is only good for short term compensation
2. Norepinephrine causes an increase in afterload (the vascular resistance), but this has a detrimental effect on cardiac output (increases the force against which the heart must eject blood)
   - The increase in afterload causes a decrease in CO (instead of an increase) because it overwhelms the heart
3. The decrease in perfusion also makes the body think that it is low on fluid, so the RAAS system is activated
   - Angiotensin II (a potent vasoconstrictor) is produced, which increases afterload (via vasoconstriction)

    - Aldosterone is produced, leading to water, sodium and fluid retention which increases the preload
    - Once again these both overwhelm the capacity of the heart and decrease CO further
4. Overall, the cardiac output is not improved, and is, in fact, worse because of the raised afterload and preload
5. Also, the left ventricle dilates in a feeble attempt to increase the cardiac output, but this is unsuccessful

Ultimately: The primary disturbance in HF is a decrease in CO, and, in an attempt to compensate for the decreased perfusion, the body makes itself sicker by creating a vicious cycle

Ventricular Remodeling

- Activation of neurohormonal compensatory responses promote remodeling process
- Angiotensin II, norepinephrine, aldosterone, vasopressin, endothelin, inflammatory cytokines exert direct toxic effect on cardiac cells
- Results in changes to the structure (size, shape, composition) and function of ventricle
- Remodeling responsible for progression of HF
    - Can't pump as effectively anymore
- Different Types of Remodeling



    - Our normal heart size is ideal for pumping
    - Changing in either direction reduces effectiveness

Risk Factors

Systolic Dysfunction

- Atherosclerotic disease
- Hypertension (70% of the cases of heart failure)
- Diabetes
- Obesity
- Metabolic syndrome
- Cardiotoxins (smoking, alcohol, cocaine, etc.)

Diastolic Dysfunction

- Comorbidities more common
    - Obesity
    - Hypertension
    - Atrial fibrillation
    - Diabetes

Drugs that Worsen HF

- Negative Inotropic Drugs
    - Antiarrhythmics

    - β-blockers
        - Initially may worsen symptoms of HF, but provides benefit in the long term
    - CCB (verapamil, diltiazem)
        - Due largely to inotropic effects (which occur in a greater degree than β-blockers)
    - Itraconazole
- Cardiotoxic
    - Doxorubicin
    - Daunorubicin
    - Cyclophosphamide
    - Alcohol
    - Cocaine
- Sodium/Water Retention
    - NSAIDs
    - Glitazones
    - Glucocorticoids
    - Androgens
    - Estrogens
    - High dose salicylates
    - Sodium containing drugs
        - Ticarcillin
        - IV penicillin

RESOLVD Trial

- Measured the most common precipitants of HF exacerbations
    - Excessive salt intake (22%)
    - Other, non-cardiac causes (20%)
    - Two-thirds were pulmonary infectious processes
    - Study medications (15%)
    - Antiarrhythmic agents (15%)
    - Development of arrhythmias (13%)
    - Calcium channel blockers (13%)
    - Inappropriate reductions in CHF therapy (10%)

Clinical Presentation & Complications

Poor Prognosis

- High mortality & morbidity
    - 5-year survival 50%
    - Death due to pump failure or sudden cardiac death (typically due to arrhythmia)
- Poor quality of life
    - Extremely low exercise tolerance

Signs & Symptoms of HF

General	Rapid weight gain, fatigue, weakness
CV	Tachycardia, jugular venous distension (>4cm), hepatojugular reflux, S3 gallop rhythm
RESP	Congestion, hypoperfusion Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough, rales
GI	Ascites, hepatomegaly, abdominal pain, nausea, bloating

GU	Nocturia, increased SCr
MSK/EXT	Pitting edema, cool extremities
Labs	B-type Naturetic Peptide (BNP) > 500pg/mL, CBC BNP released when ventricle myocytes stretched to limit • Work to counter RAAS • Decreases fluid load in the body
Diagnostics	X-ray: cardiomegaly, pleural effusion, pulmonary edema, ECG **Echocardiogram: LV function, structure**

Economic burden

- High costs for frequent hospitalizations
- Also on a personal level → medications, not able to work

Hospitalizations

- One of the most common reasons for hospitalizations
- Over 106,000 hospitalizations and 1.4 million hospital days in fiscal year 2000
- 20-30% readmission rate
- Second and third most common reason for admission to hospital

Assessment & Diagnosis

Classifications

NYHA	Symptoms
I	No symptoms with physical activity
II	Symptoms with ordinary activity Slight limitations in physical activity
III	Symptoms with less than ordinary activity Marked limited of physical activity Comfortable at rest
IV	Symptoms at rest

Treatment/Prevention

Goals of Therapy

- Reduce mortality
- Improve quality of life (reduce symptoms)
- Reduce morbidity
    - Particularly hospitalizations
- Slow progression of the disease

Non-Pharmacological Therapy

Sodium and Fluid Restriction

- Very strict limits → a bag of chips contains enough sodium to fluid overload a HF patient

Device Therapy

- Implantable Cardioverter Defibrillator (ICD)

- Monitors rhythm, paces or delivers electrical shock
- Primary prevention indications
  - Ischemic HF: optimal medical therapy for 3 months and EF < 35%
  - Non-ischemic HF: optimal medical therapy for 9 months and EF < 35%

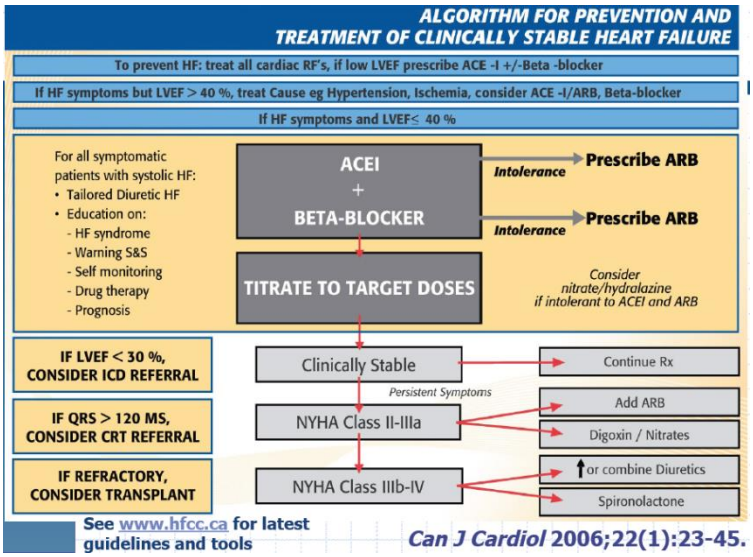
- Cardiac Resynchronization therapy (CRT)
  - Dyssynchronous ventricular contraction impairs cardiac function
  - Biventricular pacemaker
    - Improves symptoms, survival, EF, decreased hospitalizations
  - Indications
    - NYHA-FC III/IV
    - EF < 35%
    - QRS > 120msec despite optimal medical therapy

Other Considerations

- Physical activity
- Patient/family education
  - Adherence to diet and medications
  - Home monitoring of HF (symptoms, daily weights)

Pharmacological Therapy

Treatment Algorithm



All patients should receive

- ACEI
- β-Blocker
- Diuretics if needed

If symptoms continue to be poorly controlled:

- Digoxin
- Aldosterone antagonist
- ARBs

- Efficacy

	Mortality (RRR)	Hospitalization (RRR)	NNT (hospitalizations)
ACEI	28%	26%	10/3.5y
β-blockers	38-32%	34-46%	9/1y
Spironolactone	30%	35%	4/2y
Digoxin	0	27%	13/3y

- Diastolic Heart Failure
  - Very little data specifically regarding DHF
  - Non-Pharmacological Therapy
    - As per SHF
  - Pharmacological Therapy
    - ACEI, B-blockers, digoxin, CCB
      - Small trials or inconclusive results
    - ARB

        - CHARM-Preserved Trial: candesartan, trend towards reduced CV death or HF hospitalizations
        - I-PRESERVE (Irbesartan): no difference in CV hospitalizations & mortality
    - CCS Recommendations
        - Diuretics for volume overload (risk of hypotension)
        - Treat comorbidities - HTN, CAD, atrial fibrillation

Diuretics

Loop Diuretics

- Indications
    - Acute and chronic treatment of pulmonary and peripheral edema in heart failure
- Recommendation
    - Furosemide 20-160mg (40mg average) QAM
        - Larger doses may be given QAM
        - If needed, can be given IV (40-80mg daily as a 20-40mg/h infusion)
    - Adjust dosage based on fluid retention of patient and use lowest possible dose
        - Absorption is variable in heart failure

Thiazide and Thiazide-Like Diuretics

- Recommendation
    - Metolazone 2.5-10mg daily in combination with loop diuretics
    - Hydrochlorothiazide and chlorthalidone may be used in combination with other agents as well

Angiotensin Converting Enzyme Inhibitors

- Indication
    - First-line therapy in HF and asymptomatic left ventricular dysfunction
- Dosage

Drug	Initial Dose	Target Dose
Captopril	6.25-12.5mg TID	50mg TID
Enalapril	2.5mg BID	10mg BID
Lisinopril	2.5-5.0mg daily	20-35mg daily
Ramipril	2.5 BID	5mg BID
Trandolapril	1-2mg daily	4mg daily
Perindopril	Not studied	Not studied

    - Titrate dose slowly and titrate up to target dose

β-Adrenergic Antagonists

- Indication
    - First-line therapy for HF (NYHA-FC II-IV)
- Dosage

Drug	Dose
Metoprolol	12.5-75mg BID 100-200mg SR daily
Carvedilol	3.125-25mg BID
Bisoprolol	2.5-10mg daily

  Other β-blockers have not been studied
- Considerations
    - Even more important than ACEI to titrate dose
    - Patient will feel worse when starting therapy (e.g. worsening fluid retention), but this will resolve with time
    - If patient has an exacerbation stop titration or reduce dose

- May increase dose of diuretic to treat worsening HF symptoms

- Evidence

Trial	COMET
Patient	N = 3,029 Stable NYHA-FC II-IV One or more CV hospitalization in past 2 years EF < 0.35, HR ≥ 60BPM, SBP ≥ 85mmHg Most patients were on ACEI
Intervention/Comparison	Metoprolol 5-50mg BID vs. Carvedilol 3.125-25mg BID x 58 months
Outcomes	Metoprolol mortality HR = 0.83 No significant difference in combined hospitalizations and death

Digoxin

- Indications
  - Adjunctive therapy for HF
  - Used after patient stable on β-blocker and ACEI
- Dosage
  - Maintenance dose (IV/oral) = 0.0625-0.25mg daily
  - Lower doses for renal disease
  - Important: narrow therapeutic index

Aldosterone Receptor Antagonists

Spironolactone

- Indications
  - Use with ACEI and B-blockers in patients with NYAH-FC III or IV symptoms (i.e. those who remain symptomatic despite ACEI and BB)
- Dosage
  - 12.5-25mg once daily (can increase up to 50mg daily)
- Evidence

Trial	RALES
Patient	N = 1,633 NYHA-FC III-IV EF < 35%
Intervention/Comparison	Spironolactone 25-50mg daily vs. placebo x 2 years
Outcomes	Total mortality RRR = 30% (NNT = 9) Hospitalization RRR = 35% (NNT = 3)

Eplerenone

- Indication
  - Alternative to spironolactone (if patient cannot tolerate)
    - Costs much more than spironolactone
- Evidence

Trial	EPHESUS	EMPHASIS-HF
Patient	EF < 40%, HF or DM within 14 days of MI	N = 2,737 EF < 35%, CV hospitalization within 6 months, or increased BNP Excluded if K^+ > 5mmol/L, GFR < 30mL/min
Intervention/ Comparison	Eplerenone 25-50mg daily vs. placebo x 1.3 years	Eplerenone (up to 50mg daily) vs. placebo x 21 months
Outcomes	All-cause mortality RRR = 15% (NNT = 50/year)	Stopped early All-cause mortality HR = 24% (NNT = 51) CV Mortality and HF Hospitalizations HR =37% (NNT = 19)

Hydralazine & Nitrates

- Indication
  - African-Americans, in addition to standard therapy (ACEI, B-blockers, etc.)
  - Patients unable to tolerate ACEI/ARB due to hyperkalemia, renal insufficiency
- Evidence

Trial	VHeFT & VHeFT2	A-HeFT
Patient		N = 1,050 Self-identified as African descent NYHA-FC III or IV Already receiving first line therapy EF < 0.35 or EF < 0.45 with ventricular dilation
Intervention/ Comparison		Hydralazine 37.5mg TID + ISDN 20mg TID (increased up to 75mg + 40mg TID) vs. Placebo
Outcomes	VHeFT found that combination was superior to placebo VHeFT2 found that combination was inferior to enalapril	Stopped early Mortality RRR = 39% Hospitalization RRR = 33%

Angiotensin Receptor Blockers

- Indications
  - May represent an alternative in patients unable to tolerate ACEI (mostly due to severe cough)
  - May be combined with ACEI in patients who remain symptomatic despite all other therapies, but be aware of increased ADRs
- Dosage

Drug	Usual Dose
Candesartan	4-32mg daily
Valsartan	40-160mg BID

Other ARBs have not been studied

- Evidence

Trial	ELITE II	CHARM	ValHeFT	CHARM-Added
Patient				
Intervention/ Comparison	Captopril vs. Losartan	Candesartan vs. Placebo	Valsartan + ACEI vs. ACEI	Candesartan + ACEI vs. ACEI
Outcomes	Losartan not better or equivalent	Candesartan better than placebo	Reduced hospitalizations No effect on mortality	Reduction in mortality and hospitalizations Increased risk of ADRs

Monitoring & Follow Up

Improvement of Heart Failure Symptoms

- Improvements in exercise tolerance
  - Can measure using NYHA-FC classifications
- Improvement in fluid retention
  - Patient can measure weight daily
    - Large shifts in weight may be an early sign of a HF exacerbation
  - Measuring of peripheral edema
  - Resolution of dyspnea, orthopnea, or edema following diuretic therapy

Important Medication Concerns

- Patients may develop a cough as a symptom of HF; it is important to differentiate a cough due to heart failure from one due to an ACEI
    - You do not want to discontinue an ACEI on a patient if you can avoid it

Arrhythmia

Classifications & Definitions

Any disturbance in normal rhythm or conductance

Common Arrhythmias

- Atrial flutter, fibrillation
- Ventricular tachycardia, fibrillation
- Heart block
- Ventricular pre-excitation
    - Slight delay between atrial and ventricular contraction
- Torsades de pointes (Long QT)

Etiology

- Heart failure
- Mitral disease
- Wolfe-Parkinson-White Syndrome (WPW)
    - An extra electrical pathway in the heart

Treatment/Prevention

- Treatment of the underlying disease
- Surgical interventions
- Implantable pacemakers and defibrillators
- Pharmacological Therapy

Atrial Fibrillation

Classifications and Definitions

Classification of Atrial Fibrillation

These classifications will affect therapy choices

Classified By:

- Presence of structural heart disease
  - Determines risk of stroke
  - Determined by echocardiogram
- Duration of AF

Structural Disease

Non-Valvular AF (NVAF)	AF without presence of mitral valve disease Risk of stroke ≈ 4.5%/year Over half of these patients will suffer death or permanent disability NVAF + previous stroke or TIA ≈ 12%/year
Valvular AF (VAF)	AF and presence of mitral valve disease or prosthetic mitral valve Risk of stroke ≈ 17%/year
Lone AF	AF in the absence of any cardiac disease AF in the absence of any precipitating factors Low incidence (0.8%) Risk of stroke ≈ 1%

Duration of Atrial Fibrillation

Newly diagnosed AF	Initial diagnosis, duration unknown
Paroxysmal	Terminates spontaneously within 7 days of onset
Persistent	May alternate between NSR and AF Does not terminate spontaneously; may be terminated electrically or pharmacologically
Permanent	Does not terminate

NB: This is important if you are going to choose rate or rhythm control; does not affect need to anticoagulate

Epidemiology

- The most common cardiac arrhythmia
  - Other ones mostly seen in emergency cases
- 750,000 Canadians affected
- Prevalence and incidence increases with age
  - < 50 years old: 0.1% of population
  - > 80 years old: 10-15% of population
- A single episode of atrial fibrillation will promote future ones
- Associated with 3-6 fold increase in stroke
- Symptoms may lead to decreased quality of life and increased morbidity and mortality

Etiology

Overview

- Increased adrenergic tone leads to enhanced automaticity and may cause abnormal impulse generation
- Inflammation or atrial stretch may cause damage to the heart tissue and lead to re-entry loops
- Increase automaticity may initiate the arrhythmia, but re-entry loops sustain the arrhythmia

Causes of Adrenergic Tone

- Obesity
- Obstructive sleep apnea
- Pulmonary disease (pneumonia, COPD, pulmonary embolism)
- Hyperthyroidism
- Anemia
- Drugs:
    - Alcohol
    - Caffeine
    - Sympathomimetics

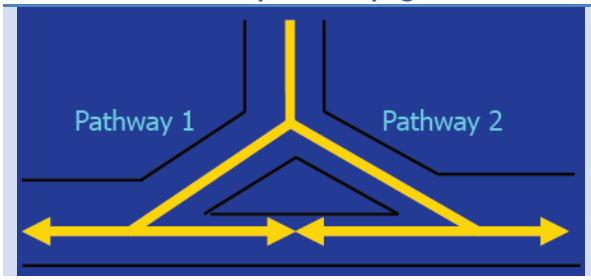
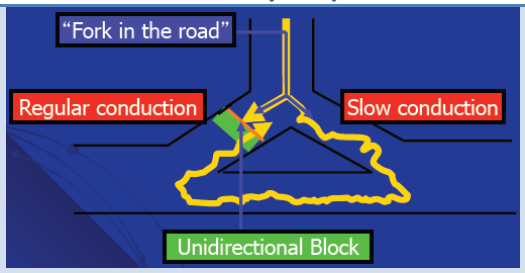
Causes of Atrial Stretch and Inflammation

- Hypertension → atrial stretch
- CAD with prior MI
- LV dysfunction → back flow of fluid → atrial stretch
- Valvular heart disease → problem with valve → regurgitation of fluid → back log of fluid → atrial stretch
- Cardiac surgery (CABG or valve) → cutting heart → inflammation
    - Can cause temporary or long term problems

Pathophysiology

Arrhythmia Mechanisms

- Abnormal Impulse Generation (Automaticity)
    - Rapid firing of ectopic foci initiates arrhythmia
- Abnormal impulse propagation
    - Re-entry Loop

Normal Impulse Propagation	Re-Entry Loops
	
Normally when a signal bifurcates it cannot loop back around because it encounters depolarized tissue	If there is damage to the tissue that blocks the impulse in a single direction (unidirectional block) you can development of re-entry loops. These impulses are self-propagating and can continue to travel throughout the heart.

Consequences of Atrial Fibrillation

- Atria
  - Multiple re-entry loops in the atria cause disorganized atrial activity
  - Atria can beat at a rate of 400-600BPM
  - Ineffective atrial contraction can cause stasis of blood and red clot formation
    - Blood not being removed from atria to ventricle → stasis!
  - Thrombus usually occurs in left atria (LA) or left atrial appendage (LAA)
    - Appendage has naturally low blood flow → more likely to clot
- Ventricular
  - Impulse from the atria are irregular and reach the AV node at varying times
  - AV node acts as a gatekeeper and does not allow all impulses through
  - The impulses pass through the AV node and irregular and cause the ventricles to contract at an irregular rhythm
  - Ventricular rate may reach 120-180BPM
    - Ventricular arrhythmia = death
- Loss of Atrial Kick
  - Normal Sinus Rhythm
    - Atria contract in a synchronized rhythm, pumping blood from the atria to the ventricles
    - Atrial kick can account for up to ~20% of cardiac output in NSR
  - Atrial Fibrillation
    - Atrial contract in a very rapid and irregular rhythm impairing emptying of blood into ventricles
  - Ejection Fraction
    - Normal ≈ 60%
    - Atrial Fibrillation ≈ 48%
    - Slight reduction in exercise tolerance maybe, but overall not symptomatic
    - However any further reduction may cause severe problems → e.g. Heart failure will decrease from 20% to 16% → will definitely notice this

Risk Factors

[To be filled in at a later date]

Clinical Presentation & Complications

Signs and Symptoms

- Patients with AF may be completely asymptomatic to highly symptomatic
- Initial presentation can be AF symptoms, heart failure symptoms, cardioembolic stroke, or systemic embolism
- Example
  - Palpitations, chest pain, hypotension
  - Heart failure symptoms: dyspnea, fatigue, syncope, decreased exercise tolerance

Complications

- Decreased functional capacity and quality of life
- Thrombus formation in left atria or left atrial appendage
- Morbidity and mortality
  - Tachycardia-induced cardiomyopathy
    - Heart works too fast → induces MI
  - Stroke or systemic thromboembolism
  - ER visits and hospitalizations

Assessment & Diagnosis

Diagnosis

ECG

- Main mechanism of diagnosis
- "Irregularly irregular supraventricular tachyarrhythmia"
- Irregular absence of P waves
- Irregular intervals of QRS of complexes

Holter Monitor

- Patients may have NSR as their predominant rhythm with brief bouts of AF
- Holter monitor allows for 24 hour monitoring of ECG because patients may fall in and out of atrial fibrillation

Echocardiogram

- Transthoracic Echocardiogram (TTE) recommended in all patients
- Transesophageal Echocardiogram (TEE) usually needed to: identify LA size, LV hypertrophy or dysfunction, valvular heart disease, and possibly LAA thrombus
    - TEE → ultrasound within the esophagus
    - These findings would suggest AF

Blood Work

- CBC, coagulation profile, electrolytes, renal, thyroid, and LFTs
- Determine if underlying cause
- Prepare for possible therapy

Assessing Risks of Atrial Fibrillation

Risk of Thromboembolic Stroke

$CHADS_2$ Score

- Scoring

C	**C**ongestive Heart Failure	1
H	History of **H**ypertension	1
A	**A**ge > 75	1
D	**D**iabetes	1
S_2	**S**troke/TIA	2

- Risk of Stroke

$CHADS_2$ Score	Stroke Rate/Year
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.9%
5	12.5%
6	18.2%

- Validity
    - Most validated stroke risk scheme
        - Tested in > 1700 patients with NVAF (age: 65-96)
    - Limitations
        - Congestive heart failure has not been consistently demonstrated as a risk factor for stroke
        - Risk associated with hypertension is going to vary greatly depending on degree of control

- Risk increases with age and likely is increasing prior to 75
- Other risks: female sex, presence of vascular disease

CHA_2DS_2-VASc

- Scoring

C	**C**HF/LV dysfunction	1
H	**H**ypertension	1
A_2	**A**ge ≥ 75	2
D	**D**iabetes	1
S_2	**S**troke or **S**ystemic embolism	2
V	**V**ascular disease (MI, PAD, aortic plaque)	1
A	**A**ge 65-74	1
Sc	**S**ex **c**ategory - Female	1

- Risk of Stroke

CHA_2DS_2-VASc	Stroke Rate/year
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

- Used in patients with a $CHADS_2$ score < 2 to ensure consideration of all stroke risk factors

Evaluate Bleed Risk

HAS-BLED Score

- Scoring

H	**H**ypertension	1
A	**A**bnormal renal and liver function	1 or 2 (1 for each)
S	**S**troke	1
B	**B**leeding	1
L	**L**abile INRs	1
E	**E**lderly (Age > 65)	1
D	**D**rugs (antiplatelets/NSAIDs) or alcohol	1 or 2

- Bleed Risks

Risk Factor Score	Major Bleed %
0	1.13%
1	1.02%
2	1.88%
3	3.74%
4	8.70%
5	12.5%

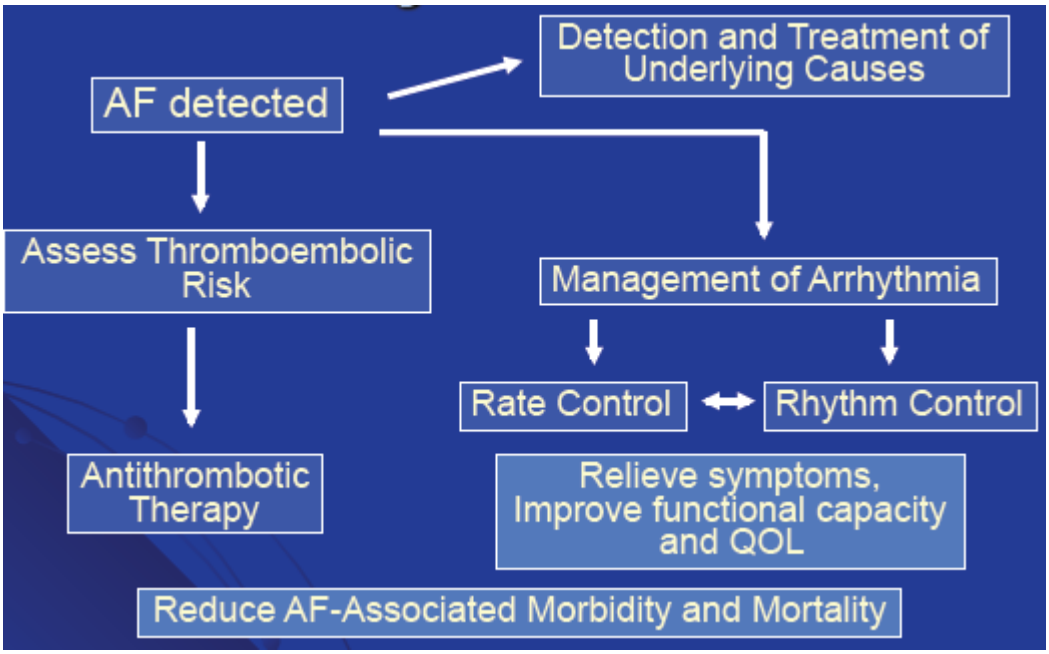
  - Should not be sole criterion for deciding to initiate therapy
  - HAS-BLED ≥ 3 suggests increased bleeding risk and warrants caution and/or regular review

Treatment/Prevention

Goals of Therapy

- Relieve symptoms
  - Palpitations, chest pain, dyspnea, fatigue, syncope, hypotension, decreased exercise tolerance
  - Reduce AF-associated morbidity and mortality
- Prevent stroke or systemic thromboembolism
  - Prevent tachycardia-induced cardiomyopathy
  - Reduce ER visits and hospitalizations
- Improve functional capacity and quality of life

Treatment Algorithm



Prevention of Thromboembolic Stroke

Evaluating Benefits and Risks

1. Determine risk of stroke
   - $CHADS_2$ Score
   - CHA_2DS_2VASc
2. Determine risk of bleed
   - HASBLED
3. Balance the risks with evidence
4. Select, implement, monitor

Guidelines for Prevention of Stroke (CCS 2012)

$CHADS_2$ Score	Suggested Antithrombotic	Comments
0	ASA	No antithrombotic may be chosen in selected young patients with no stroke risk factors
1	Warfarin or Dabigatran*	ASA reasonable alternative in some based on risk-benefit
≥ 2	Warfarin or Dabigatran*	

*Dabigatran is preferred over warfarin

CHEST Guidelines (2012)

$CHADS_2$ Score	Recommendation	Suggestion
0	No therapy	Presence of multiple non-CHADS2 risk factors may favor OAC For patients who choose antithrombotic therapy suggest ASA 75-325mg/day rather than OAC or ASA + Clopidogrel
1	OAC	Dabigatran 150mg PO BID is preferred over warfarin
≥ 2	OAC	For patients who are unsuitable for or choose not to take OAC (for reasons other than concerns about major bleed), suggest ASA + clopidogrel rather than ASA

Cardiac Condition	Recommendation	Suggestion
AF + Mitral Stenosis	Warfarin (target INR 2-3)	For patients who are unsuitable for or choose not to take OAC (for reasons other than concerns about major bleed), suggest ASA + clopidogrel rather than ASA (17% risk of thrombosis)
AF+ Stable CAD (no ACS within last year)	Warfarin (target INR 2-3)	Warfarin (target INR 2-3), rather than Warfarin + ASA Higher risk of MI with dabigatran in this population

Cardiac Condition	$CHADS_2$ Score	Suggestions
AF + Stent	0-1	<u>0-12 Months After BMS or DES</u> ASA + Clopidogrel > 12 months <u>> 12 Months</u> As per AF + Stable CAD
	2	<u>Initial Period: 1 Month After BMS or 3-6 Months After DES</u> Warfarin + ASA + Clopidogrel <u>After Initial Period until 12 months</u> Warfarin + single antiplatelet <u>> 12 Months</u> As per AF + stable CAD (warfarin)
AF + ACS without Stent	0	<u>0-12 Months After ACS</u> ASA + Clopidogrel <u>> 12 Months</u> As per AF + stable CAD
	1-2	<u>0-12 Months</u> Warfarin + single antiplatelet <u>> 12 Months</u> As per AF + stable CAD

Acetylsalicylic Acid Evidence

Trial	Canadian Cardiovascular Society atrial fibrillation guidelines 2010
Population	Meta-analysis of several large trials using ASA for AF stroke prevention NVAR
Intervention/Comparison	ASA vs. Placebo
Outcomes	RRR = 19% AR of major hemorrhage: ASA = 1.1%, placebo = 0.7%

Clopidogrel Evidence

Trial	ACTIVE-W	ACTIVE-A
Population	N = 6,706 AF + $CHADS_2$ ≥ 1, PAD, or age = 55-74 years old DM or CAD Mean $CHADS_2$ = 2, Mean Age = 70	N = 7,554 AF with ≥ 2 episodes in last 6 months + $CHADS_2$ ≥ 1, PAD, or CAD Patients "unsuitable for warfarin" (50% due to physician judgement, 25% due to specific risk, 25% due to patient preference) Mean $CHADS_2$ = 2, Mean age = 71
Intervention/ Comparison	Clopidogrel 75mg daily + ASA 75-100mg daily vs. warfarin (INR = 2-3)	ASA 75-100mg daily + Clopidogrel 75mg daily vs. ASA 75-100mg daily
Outcomes	Ended early due to superiority of warfarin PO (stroke, embolism, MI, vascular death) RR = 1.44 (1.18-1.76)	Major vascular events RR = 0.89 (0.81-0.98) Risk of major bleeding = 1.57 (1.29-1.92)

Warfarin Evidence

Trial	Warfarin for AF Stroke Prevention	Warfarin vs. ASA for Stroke Prevention
Population	NVAR	NVAR
Intervention/Comparison	Warfarin vs. placebo	Warfarin vs. ASA
Outcomes	Incidence of ischemic stroke ARR = 3.1%/year Rate of hemorrhage ARI = 0.3%	Stroke RRR = 39%

Dabigatran, Rivaroxaban, Apixaban Evidence

	Dabigatran	Rivaroxaban	Apixaban
Trial	**RE-LY**	**ROCKET**	**ARISTOTLE**
Design	Blinded dabigatran, open-label warfarin, non-inferiority	DB, non-inferiority	DB, non-inferiority
Population	N = 18,113 AF + additional risk factor	N = 14,264 NVAF with $CHADS_2$ score of ≥ 2	N = 18,201 NVAF or Atrial flutter + ≥ 1 $CHADS_2$ risk factor
Exclusion Criteria	Valvular AF CrCl < 30mL/min Condition increasing bleed risk Stroke < 14 days Severe stroke < 6 months	Valvular AF CrCl < 30mL/min Hemorrhagic related concerns GI bleed < 6 months BP > 180/100mmHg Stroke < 3 months TIA < 3 day ASA > 160mg/day Chronic NSAID use	Mechanical heart valves, Severe renal insufficiency (SCR > 221µmol/L) Stroke in past 7 days ASA > 165mg/day ASA + Clopidogrel
Warfarin Naïve	50%	40%	43%
Current ASA Use	40%	35%	30%
Intervention	Dabigatran 150mg vs. warfarin (INR 2-3) Dabigatran 110mg vs. warfarin (INR 2-3)	20mg Daily 15mg for CrCl 30-49mL/min	5mg BID 2.5mg BID (if ≥ 2 of: age ≥ 80, weight ≤ 60kg, SCr ≥ 133µmol/L)
Mean Age	71	73	70
Mean $CHADS_2$	2.1	3.5	2.1
Time in Therapeutic Range	64%	55%	66%
Conclusions	Dabigatran 150mg BID is superior to warfarin with a similar rate of major bleeding 110mg is non-inferior with lower bleed rate	Rivaroxaban is non-inferior to warfarin with similar rates of bleeding	Apixaban is superior to warfarin with a significantly lower rate of major bleeding

Other Considerations	Higher rate of MI with both strengths – should be combined with ASA Contraindicated in CrCl < 30mL/min, valvular AF, active bleeding stroke in past 14 days, or major stroke in past 6 months No antidote exists 110mg BID should be used in patient > 80 years old or > 75 years + 1 risk factor for bleeding	Approval in Canada for treatment of AF and for DVT Awaiting approval for PE No antidote exists	Approval in Canada for prevention of VTE; not yet approved for treatment of AF or VTE No antidote exists Available as 2.5mg; 5.0mg strength waiting for NOC

Symptomatic Treatment

Rate vs. Rhythm Control

Rate Control	Patient remains in AF; heart rate control used to decrease symptoms and prevent heart failure
Rhythm Control	Strives to achieve NSR

- Recommendation

Favors Rate Control	Favors Rhythm Control
Persistent AF	Paroxysmal AF (Better chance of success)
	Newly detected
Less symptomatic	More symptomatic
Aged ≥ 65	Aged < 65 (young people tend to be more intolerant of impact of symptoms)
Hypertension	No hypertension
No history of CHF	CHF exacerbated by AF (if you can't live in AF you need to get out)
Previous antiarrhythmic failure	No previous antiarrhythmic failure
Patient preferences	Patient preferences

  - Usually rate control tried before rhythm control due to side effect profile of antiarrhythmics
  - Rhythm control will be tried if rate control does not successfully controls symptoms, arrhythmia progresses, or patient's condition changes
  - Patient should be referred to cardiologist for arrhythmia management
- Evidence

Trial	AFFIRM	
Population	N = 4,060 Patients > 65 years old + AF + ≥ other risk factor Mean age = 70, half hypertensive, 23% CHF, 5% valvular disease Must be able to tolerate either treatment option 70% received warfarin	
Intervention/ Comparison	Rate Control • β-blocker (68.1%) • Non-DHP CCB (62.9%) • Digoxin (70.6%) • Combination of any of the above	Rhythm Control • Amiodarone (39%) • Sotalol (33%) • Propafenone (10%) • Procainamide (6%)
Outcomes	< 40% were in NSR with rate control and > 60% were in NSR with rhythm control Overall Mortality: rate control: 25.9%, rhythm control: 26.7% (p = 0.08)	

  - Other Studies: RACE, STAF, PIAF, HOT CAFÉ
  - No study showed survival benefit with rhythm control; RACE and AFFIRM showed slight risk with rhythm control
  - All studies show that both option may have similar efficacy in some populations
  - Symptomatic control has no impact on risk of thromboembolic stroke; patients must still be anticoagulated

Rate Control

- Pharmacological Therapy

Class	Dose	Adverse Effects	Indications
β-Blockers			
Atenolol	50-150mg PO daily	Bradycardia, fatigue, depression	AF with no other heart disease AF with hypertension AF with CAD AF with heart failure
Bisoprolol	2.5-10mg PO daily		
Metoprolol	25-200mg PO BID		
Nadolol	20-160mg PO daily-BID		
Propranolol	80-240mg PO TID		
CCB			
Diltiazem	120-480mg PO daily	Bradycardia, ankle swelling	AF with no other heart disease AF with hypertension AF with CAD
Verapamil	120-240mg PO BID	Bradycardia, constipation	
Other			
Digoxin	0.125-0.25mg PO daily	Bradycardia, nausea/vomiting, visual disturbances	AF with no other heart disease AF with hypertension AF with heart failure

  - Target dose is based on symptom control (typically occurs at HR < 100BPM) and before side effects (typically < 50BPM)
  - Start dose low and titrate up slowly
    - Can use IV and titrate more quickly if needed
  - If one agent does not work, may use combination therapy
    - Be aware of bradycardia and hypotensive effects
  - Amiodarone does have rate control properties, but toxicity makes it a last line agent compared to these agents
  - Dronedarone no longer recommended in any situation

Trial	PALLAS
Population	N = 3,236 ≥ 65 years old with at least 6 month history of permanent AF and risk factors for major vascular events
Intervention/ Comparison	Dronedarone 400mg vs. placebo
Outcomes	Trial ended early due to safety concerns Death from CV causes HR = 2.11 Death from arrhythmia HR = 3.26 Stroke HR = 2.32

- Non-Pharmacological Therapy
  - AV Node Ablation
    - AV node is destroyed
    - Pacemaker is installed to control heart rhythm of the ventricles
  - Re-Entry Loop Ablation
    - Sites of re-entry loops are destroyed
    - May result in decreased ventricular rate or even restoration of sinus rhythm

Rhythm Control

- Pharmacological Therapy

Antiarrhythmic Class	Drug	Dose	Indication	Considerations
I	Flecainide	50-150mg PO BID	AF with normal ventricular function (first line)	Toxicity: ventricular tachycardia, decreased heart rate Must be combined with an AV node blocker Contraindicated in CAD and LVD

III	Propafenone	150-300mg PO TID	AF with normal ventricular function (first line)	Toxicity: rapid ventricular response Must be combined with an AV node blocker Contraindicated in CAD and LVD
	Sotalol	40-160mg PO BID	AF with normal ventricular function (first line) AF with abnormal ventricular function	Toxicity: Torsades de Pointes, tachycardia, β-blockers side effects Avoid in patients at risk of QT elongation (patients at risk of hypokalemia [e.g., diuretics, especially women > 65, renal insufficiency], patients using drugs known to cause QT elongation)
	Amiodarone	100-200mg PO daily (after 10G load)	AF with normal ventricular function (second line) AF with abnormal ventricular function	Toxicity: photosensitivity, bradycardia, thyroid dysfunction, hepatic toxicity, pulmonary toxicity, neuropathy, tremor, GI upset, rarely torsades de pointes Low risks of arrhythmia generation Most effective agent for rhythm control (all other agents are probably equally effective)

- Non-Pharmacological Therapy
  - DC cardioversion
    - Antiarrhythmic agents are very effective at preventing AF recurrences, but are unlikely to convert patients in AF to NSR at maintenance doses
    - DC cardioversion or higher doses of some antiarrhythmic agents can be used to convert rhythm to NSR
      - DC cardioversion is much more effective (initially effective in targeting > 80% of patients) without the added toxicity
    - DC cardioversion may be used to convert patient to normal sinus rhythm prior to initiating antiarrhythmic agents or antiarrhythmic agents may be initiated 1-4 weeks prior to cardioversion to decrease chance of early AF recurrence
    - Requires patient to be anticoagulated

For patients in AF > 48 hours	Anticoagulate at a target INR of 2-3 for 3 weeks prior to cardioversion
For patients in AF < 48 hours	Initiate anticoagulation at time of cardioversion
All patients post-cardioversion	Anticoagulation for at least 4 weeks

      - If INR every drops below 2 → Cardioversion is cancelled

Monitoring & Follow Up

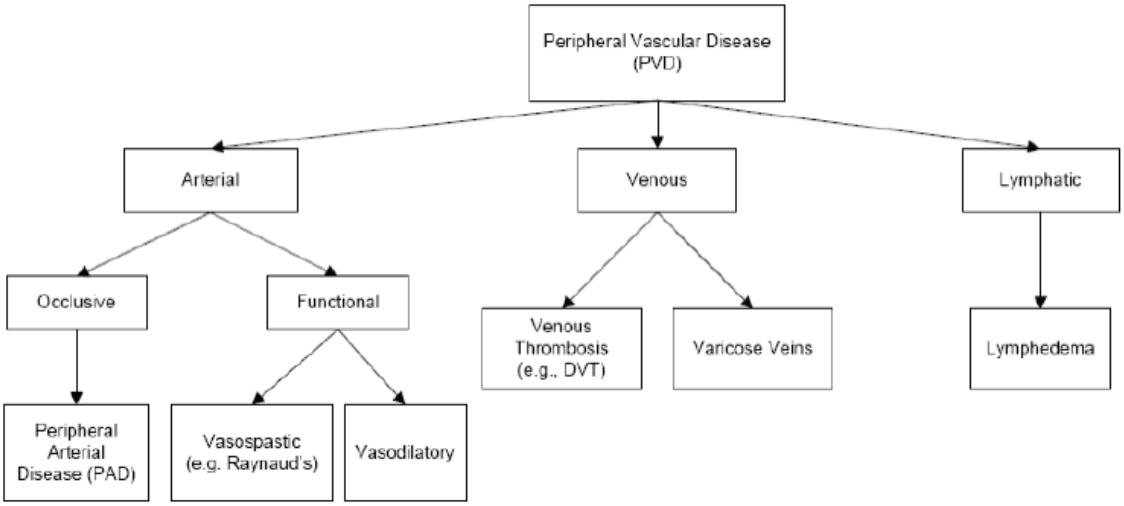
[To be filled in at a later date]

- Patients should be monitored on an ongoing basis for changes in arrhythmias and for signs of toxicity (especially those using rhythm control)

Peripheral Vascular Diseases

Classifications & Definitions

Peripheral Vascular Disease



- Disorders of the arteries, veins, and lymphatics of the extremities

Peripheral Arterial Disease

- PAD encompasses a range of non-coronary arterial syndromes caused by the altered structure and function of the arteries that supply the brain, visceral organs (e.g. kidneys, intestines, and the limbs)
    - This includes the:
        - Thoracic aorta
        - Carotid and vertebral arteries
        - Upper extremity arteries
        - Renal and mesenteric arteries
        - Abdominal aorta
        - Iliac and lower limb arteries

Etiology

[To be filled in at a later date]

Pathophysiology

[To be filled in at a later date]

Risk Factors

PAD shares risk factors with other forms of atherosclerotic disease

Traditional Risk Factors

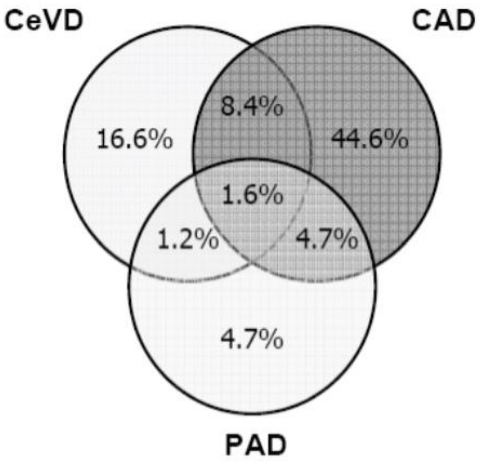
- Cigarette smoking
- Diabetes
- Dyslipidemia
- Hypertension
- Age
- Male gender

Emerging Risk Factors

- Elevated C-reactive protein
- Elevated homocysteine
- Elevated fibrinogen
- Lipoprotein A
- ApoB

Clinical Presentation & Complications

Co-existing Cardiovascular and Cerebrovascular Disease



More overlap with PAD and CAD than cerebrovascular disease, but there is still the possibility of concomitant disease

Morbidity and Mortality

- CV events are more frequent than ischemic limb events
- PAD is a "CHD Risk Equivalent" → High Risk
    - Patients with atherosclerosis are at higher risk of other cardiovascular events and death
    - Need to combine treatment of disease with cardiovascular risk reduction

Renal Artery Disease

Renal Artery Stenosis (RS) present in 20-60% of PAD patients

Clinical consequences

- Hypertension
- End Stage Renal Disease

Presentation

- New or worsening renal function after starting an ACEI or ARB
- Hypertension before the age of 30 years
- Severe hypertension before the age of 55 years

- Accelerated hypertension, resistant hypertension, malignant hypertension

Treatment

- Hypertension & unilateral RAS: ACEI, ARB, CCB, B-blocker & diuretics are all effective
- Revascularization → manage hypertension, preserve renal function, and manage heart failure or angina
- High CV Risk Management
    - Evaluate CV risk factors
    - Implement risk reduction strategies

Assessment & Diagnosis

[To be filled in at a later date]

Treatment/Prevention

[To be filled in at a later date]

Monitoring & Follow Up

[To be filled in at a later date]

Lower Extremity Peripheral Arterial Disease

Epidemiology

Prevalence

- 27 million people in North America and Europe
- ~60% are symptomatic
- Screening Study in Canada: ~4% over 40 years of age
    - None were aware they had a blockage of circulation in their limbs

Etiology

- Atherosclerosis is the most common cause of lower extremity PAD
- Symptoms result from the imbalance between supply and demand of blood flow that fails to meet metabolic demands
- Locations
    - Aorta and/or iliac artery blockage
        - Buttock, thigh, and hip pain
        - With continued ambulation claudication may progress to include the calf
    - Superficial femoral artery blockage
        - Causes intermittent Claudication (IC)
    - Popliteal and tibial arterial blockage
        - Causes critical limb ischemia (CLI)

Pathophysiology

[To be filled in at a later date]

Risk Factors

[To be filled in at a later date]

Clinical Presentation & Complications

Morbidity and Mortality

Disease Progression

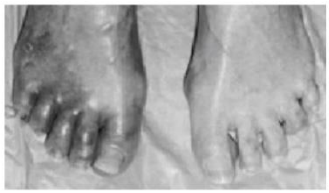
- Starts of asymptomatic
- Can then develop to:
    - Intermittent claudication
    - Critical leg ischemia
    - Acute limb ischemia
    - Amputation
    - At any point could also result in death through numerous causes, such as cardiac death or cerebral vascular death

Limb Morbidity

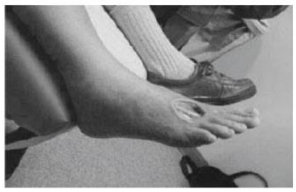
- Leg pain, wounds, gangrene, amputation, decreased quality of life
- Claudication usually remains stable over time
- Only 1-2% will ever require treatment
- Risk Factors for Deterioration
    - Diabetes (increased risk of CLI and major amputation by 7-15 fold)
    - Smoking
    - Low ankle brachial index
    - Hypertension

Clinical Presentation

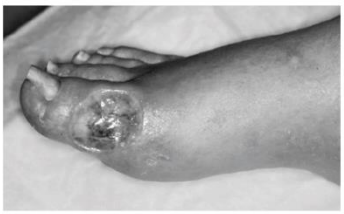
- Asymptomatic (60%)
- Symptomatic (40%)
    - Classic Intermittent Claudication (33%)
        - Painful aching or cramping in the calf caused by walking and relieved by rest
    - Atypical Leg Pain (> 50%)
        - Pain in the thigh or buttock without calf pain
    - Critical Limb Ischemia (≤ 5-10%)
        - 1 year mortality > 20%
        - 50% require revascularization for limb salvage
        - Patient may notice rest pain in the foot and ischemic ulcers or gangrene



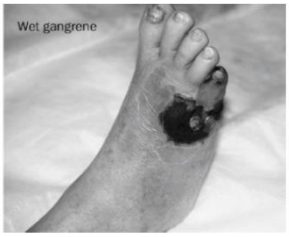
Dependent rubor, shiny, hairless skin, dystrophic nail changes in right foot



Ischemic ulceration of the dorsum of the foot



Ischemic Ulceration



Wet Gangrene

    - Acute Limb Ischemia
        - Rapid or sudden decreased in limb ischemia perfusion → threaten tissue viability
        - Plaque rupture, thrombosis of a bypass graft, or embolism
        - 6 P's (Pain, Paralysis, Paresthesias, Pulselessness, Pallor, Polar [cold])
- Other Manifestations/Findings
    - Reduced pedal pulses
    - Femoral bruit (turbulent blood flow)
    - Slow venous filling
    - Cold skin
    - Abnormal skin colours

Assessment & Diagnosis

Differential Diagnosis

- Nerve root compression (herniated disc)
- Spinal cord compression
- Hip arthritis
- Venous disease (e.g. after venous thrombosis)
- Nocturnal leg cramps

Screening

- The following individuals should be screened for PAD
  - Men > 40 years
  - Post-menopausal women or those > 50 years
  - Patients with ≥ 1 recognized cardiovascular risk factor
- Basic screening should include
  - Focused physical exam
    - Looking for femoral bruit & pedal pulses
  - A direct history for symptoms of claudication
    - e.g. Edinburgh Claudication Questionnaire

The Edinburgh Claudication Questionnaire

(1) Do you get a pain or discomfort in your leg(s) when you walk? Yes ☐ No ☐ I am unable to walk ☐

If you answered "Yes" to question (1)—please answer the following questions. Otherwise you need not continue.

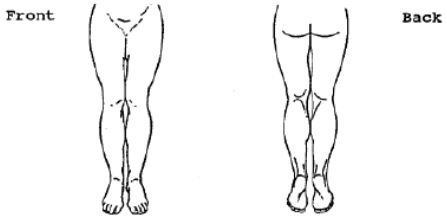
(2) Does this pain ever begin when you are standing still or sitting? Yes ☐ No ☐

(3) Do you get it if you walk uphill or hurry? Yes ☐ No ☐

(4) Do you get it when you walk at an ordinary pace on the level? Yes ☐ No ☐

(5) What happens to it if you stand still?
Usually continues more than 10 minutes ☐
Usually disappears in 10 minutes or less ☐

(6) Where do you get this pain or discomfort?
Mark the place(s) with "×" on the diagram below.



Definition of positive classification requires all of the following responses: "Yes" to (1), "No" to (2), "Yes" to (3), and "usually disappears in 10 minutes or less" to (5); grade 1 = "No" to (4) and grade 2 = "Yes" to (4). If these criteria are fulfilled, a **definite** claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of *atypical* claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain in the calf.

Ankle Brachial Index

- Simple, effective, non-invasive, inexpensive to predict PAD

When to Use ABI

- During basic workup when you suspect IC
- General screening
  - Asymptomatic patients with ≥ 1 CV risk factors after the age of 40 years in men and post-menopausal women and after 50 years in all women
  - Asymptomatic patients with arterial bruits or decreased leg pulse
- "Intermediate Risk" patients
  - ABI to detect potential subclinical atherosclerosis
  - If ABI < 0.9 → patients become "high risk"

Determining Resting ABI

- Calculation of the resting ABI

- With the patient in lying down, measure the ankle and brachial blood pressure (on the right and left) using a handheld Doppler device
- Doppler used to listen for blood flow in an artery
- Calculation

$$ABI = \frac{Ankle\ systolic\ pressure}{Brachial\ systolic\ pressure}$$

- As you get blockages in the artery you get lower blood pressure in the ankle

Interpreting Results

	ABI
Normal	> 0.9
Mild PAD	0.71-0.9
Moderate PAD	0.41-0.7
Severe PAD	≤ 0.40

- Further evaluation may be required if:
  - ABI > 1.30
  - Borderline ABI (i.e. 0.91-1.30)

Other Techniques

Non-invasive

- Toe brachial index
- Exercise ABI
- Continuous wave Doppler ultrasound
- Duplex ultrasound
- CT angiography
- MRI angiography

Invasive

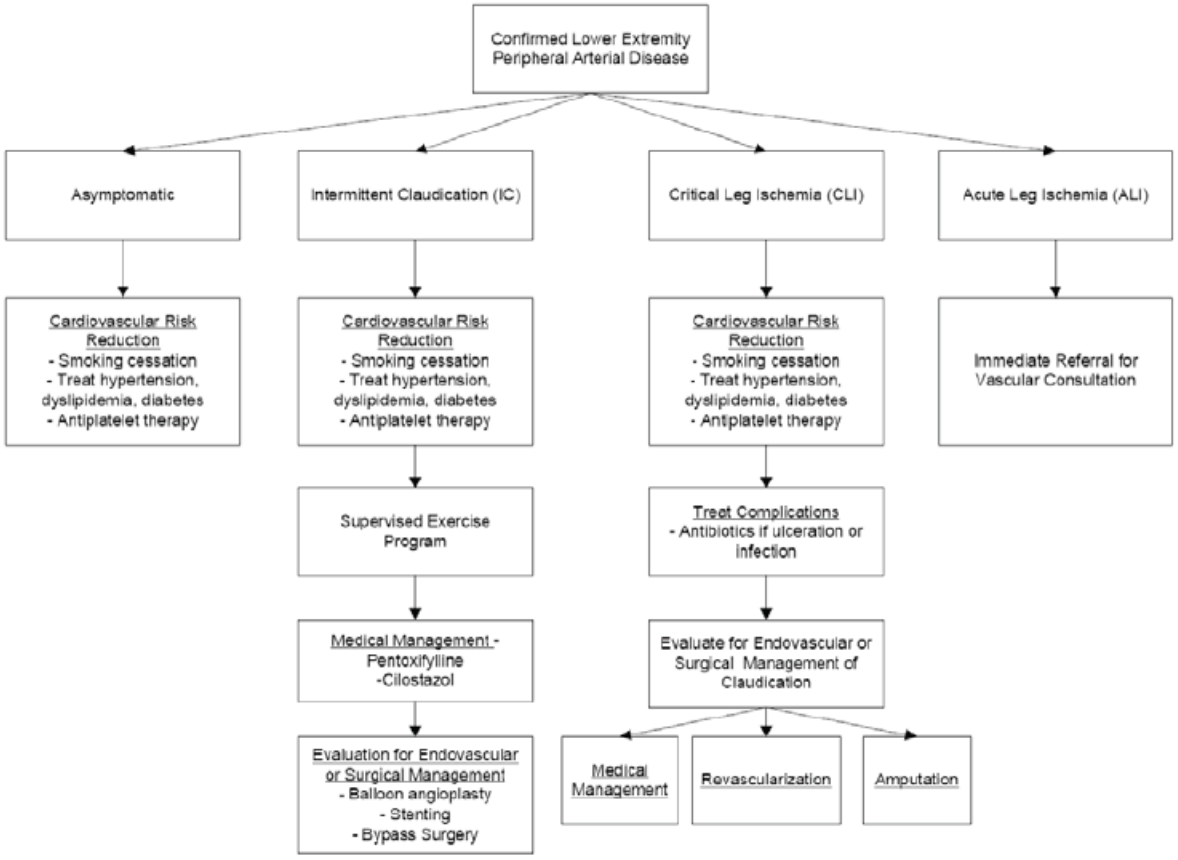
- Contrast angiograph

Treatment/Prevention

Goals of Therapy

Prevent adverse cardiac events
Treat leg symptoms
Improve quality of life
Prevent/minimize adverse effects of drug therapy

Treatment Algorithm



Prevention

Cardiovascular Risk Reduction

- ABCDE

A	**A**CEI, **A**ntiplatelets
B	**B**lood Pressure
C	**C**holesterol, **C**essation (smoking)
D	**D**iet, **D**iabetes
E	**E**xercise

Smoking Cessation

- Smoking is an important risk factor
- Quitting smoking will:
    - Decrease risk of death, MI, and amputation
    - Increase exercise tolerance
- All patients should be offered smoking cessation interventions

Management of Hypertension

Antihypertensive therapy decreased CV events & mortality in patients with hypertension
Impact on progression of claudication is unknown

Recommendations

- Treatment occurs as per normal treatment of hypertension

- Considerations
  - β-blockers
    - Theoretically may worsen intermittent claudication
    - Meta-analysis found that β-blocker therapy had no adverse impact on walking capacity
    - β-blockers are NOT contraindicated in PAD
  - ACEI
    - HOPE trial suggested ramipril decreased CV risk by ~25%
    - Totality of evidence suggests ACEI benefits due to BP lowering
    - Caution → PAD patients likely have more RAAS activation

Management of Hyperlipidemia

- In patients with CAD, statins decrease non-fatal MI and CV death by 24-34%
- Goals remain the same as regular patients (LDL < 2.0mmol/L, TC/HDL < 4.0)
- Statin therapy may decrease intermittent claudication symptoms
  - Simvastatin decreases the risk of new/worsening IC
  - Atorvastatin increased time walked to the onset of IC

Management of Diabetes

- Retrospective analysis of DCCT found intensive insulin had no impact on IC symptoms, revascularization, amputation
- Aggressive treatment of diabetes
  - Decreased microvascular complications (retinopathy, nephropathy)
  - Metformin in overweight diabetics (decreased DM endpoints, mortality, and MI)
- Foot care is very important
  - 7-15 fold increase risk of chronic limb ischemia & major amputation in DM
- Glucose target is normal (A_1C < 7%)

Antiplatelet Therapy

- ASA
  - Decreased MI, stroke, death in patients with PAD
  - Dose
    - 75-325mg once daily
  - Evidence
    - 3 Recent studies show disappointing results for ASA in the areas of:
      - Low ABI (AAA)
      - Patients with type 2 diabetes (JPAD)
      - Diabetes and asymptomatic PAD
- Clopidogrel
  - Decreased risk of ischemic stroke, MI, or vascular death in patients with established CV disease (vs. ASA)
  - Indication
    - Alternative for ASA intolerance/allergy
  - Evidence

Trial	CAPRIE	CHARISMA
Population		N = 15,603 CAD, CeVD, PAD, or multiple CV risks
Intervention/ Comparison	Clopidogrel vs. ASA	Clopidogrel + ASA vs. ASA
Outcomes	PAD patients showed larger reduction in RRR of stroke and MI (RRR = 23.8% vs. 8.7%)	PO (Death, MI, stroke) = NSS Increased risk of bleeding

- Warfarin

- WAVE Trial
  - Warfarin + antiplatelet provides no benefit over antiplatelet therapy alone

Treatment of Intermittent Claudication

Exercise Training

- Supervised exercise programs
  - Most effective intervention
  - Increased speed, distance, and duration walked
- Benefits in 4-8 weeks
- Exercise training improves
  - Pain-free walking time ~180%
  - Maximal walking time ~120%
- Predictors of Success
  - Session > 30 minutes
  - ≥ 3 times monthly
  - ≥ 6 months
  - Walking at near maximal pain
- Exercise improves:
  - Blood pressure
  - Lipid profile
  - Glycemic control
- Efficacy

Comparison	Increase in Maximal Walking Distance (vs. Placebo)
Exercise	120%
Pentoxifylline	20-25%
Cilostazol	40-60%

Pentoxifylline

- Indications
  - Effectiveness marginal and not well established
  - ACC Guidelines: Second-line alternative to cilostazol
  - Canadian Guidelines: not recommended
- Dose
  - 400mg TID as CR formulation
  - Dose adjustments for renal dysfunction
    - CrCl ≥ 50mL/min = no dose adjustment
    - CrCl = 10-50mL/min = reduced interval to BID
    - CrCl < 10mL/min = reduced interval to daily
- Efficacy
  - Maximal walking distance: 20-25%
  - Two meta-analysis have shown
    - Increased pain free walking distance (21-29 meters)
    - Increased maximal walking distance (43-48 meters)
    - No more effective than placebo in relieving other IC symptoms (cramping, tiredness, tightness, and pain during exercise)

Cilostazol

- Not Available in Canada
- Mechanism of Action

- Platelet aggregation inhibitor
- Efficacy
  - Comparison

Comparison	Maximal Walking Distance (difference from mean)
Cilostazol vs. Placebo	42 metres (14-70)
Cilostazol vs. Pentoxifylline	43 metres (15-71)
Pentoxifylline vs. Placebo	1 metre (-24-26)

  - Meta-analysis of 8 placebo controlled RCTs
    - Increased maximal walking distances (50%)
    - Increase pain free walking distances (67%)
    - Increased quality of life
    - Increased headache, bowel complaints, and palpitations

Ineffective Therapies

- Vitamin E
- Testosterone
- Homocysteine lowering therapies
- Garlic
- Gingko biloba
- Vasodilator prostaglandins (beraprost, iloprost)

Endovascular & Surgical Management

- Revascularization
  - Endovascular: balloon angioplasty ± stenting
  - Surgical: bypass (Femoral-popliteal most common)
- Successful revascularization can effectively reduce or eliminate symptoms of claudication
- Therapy Following Revascularization
  - Cardiovascular risk reduction is essential
    - Surgical approach only addresses symptoms
    - Requires continued non-pharmacological and pharmacological management
  - Maintaining Patency After Lower Extremity Angioplasty ± Stenting
    - ASA - all patients
    - ASA + warfarin - no benefit, increased risks
    - ASA + clopidogrel - under investigation
  - Maintaining Graft Patency After Bypass Surgery
    - ASA - all patients
    - Warfarin - more effective, but increased bleeding and not recommended for routine use
    - ASA + warfarin - only high risk patients

Treatment of Critical Leg Ischemia (CLI)

- Pharmacotherapy
  - IV pentoxifylline not effective for rest pain
  - Cilostazol not evaluated
  - IV prostaglandins (PGE-1) may decrease pain and increase ulcer healing
- Other Management Issues
  - Pain control
  - Wound care management
  - Infection

Monitoring & Follow Up

Drug Therapy

Pentoxifylline

- Efficacy
  - Pain free walking distance/time
  - Improvement may be seen in 2-4 weeks, but can take up to 8 weeks (assess at 4 week intervals)
- Toxicity
  - Symptoms, blood pressure, heart rate
  - May be administered with food to minimize GI irritation
  - May decrease dosage to 400mg BID

Abdominal Aneurysm

Classifications & Definitions

Definition

- Abnormal enlargement or outward ballooning of a blood vessel

Epidemiology

Etiology

Pathophysiology

Risk Factors

Clinical Presentation & Complications

Most abdominal Aortic Aneurisms (AAA) are asymptomatic

Complications

- Rupture
- Thromboembolic ischemic events
- Compression of adjacent structures

Assessment & Diagnosis

Treatment/Prevention

Monitoring & Follow Up

Approach to Management

- Management of risk factors
- Endovascular therapies
    - Endovascular and surgical management

- β-blockers may decrease the rate of aneurysm expansion in patients

Raynaud's Syndrome

Classifications & Definitions

Classification

Primary

- No evidence of any associated disorder

Secondary

- Associated disorder (e.g. systemic lupus, scleroderma)
- Other Factors (e.g. drugs)

Epidemiology

Etiology

- Abnormal vasoconstriction of the digital arteries due to a local defect

Pathophysiology

- Exaggerated vascular response to cold or emotional stress

Risk Factors

- More Common In:
    - Young females
    - Younger age groups
    - Patients with family history

Clinical Presentation & Complications

Symptoms

- Sharply demarcated colour changes in the skin of the digits

Clinical Manifestations

- Attacks occur in fingers and toes
    - Starts with a single finger and spreads to other digits symmetrically in both hands
- With re-warming the ischemic phase lasts 15-20 minutes
- Erythema occurs with reperfusion

Assessment & Diagnosis

Treatment/Prevention

Non-Pharmacological Therapy

- Education regarding causes and general measures to terminate an attack
- Avoidance of sudden cold exposure, stress reduction
- Dressing warmly
- Mittens
- Avoidance of smoking and sympathomimetic drugs

Pharmacological Therapy

- Calcium Channel Blockers
    - First Line therapy
    - Moderately efficacious (reduce frequency and severity of attacks)
    - Long-acting nifedipine (30mg), amlodipine (5mg) used 60 minutes prior to cold exposure
- Direct Vasodilators
    - Nitroglycerine
- Indirect Vasodilators
    - Fluoxetine, ACEI, PDE5 Inhibitors (sildenafil)
- Sympatholytic agents
    - Prazosin
- Prostaglandins
- Antiplatelet Agents
    - ASA + Dipyridamole

Monitoring & Follow Up

Varicose Veins

Classifications & Definitions

Epidemiology

- Most common manifestation of chronic venous disease

Etiology

Primary

- Superficial venous insufficiency

Secondary

- Venous hypertension, from vein valvular incompetence or venous obstruction

Pathophysiology

Risk Factors

Clinical Presentation & Complications

- Visible palpable, dilated, tortuous, elongated subcutaneous veins

Assessment & Diagnosis

Treatment/Prevention

Goals of Therapy

- Improve symptoms and appearance

Non-Pharmacologic Management

- Leg elevation
- Compression stockings
- Sclerotherapy
- Surgery

Monitoring & Follow Up

Chronic Venous Insufficiency

Classifications & Definitions

Epidemiology

Etiology

Pathophysiology

- Persistent elevation of venous pressures
    - Caused by valvular incompetence or obstruction
- Morphological changes in the capillaries and lymphatic system → tissue hypoxia → edema → hyperpigmentation, subcutaneous fibrosis, ulcer formation

Risk Factors

Clinical Presentation & Complications

- In contrast to arterial ulcers, venous ulceration is usually located above the ankle

Assessment & Diagnosis

Treatment/Prevention

Monitoring & Follow Up

Goals of Therapy

Reduce edema
Heal ulcers

Non-Pharmacological Treatment

Mechanical Therapies

- Leg elevation
- Compression stockings

    - Compression stockings are good for venous conditions
    - NB: will make arterial conditions worse
- Intermittent pneumatic compression pumps

Dressings

- Wet or dry non-adherent dressings
- Occlusive hydrocolloidal or gel dressings
- Zinc paste impregnated bandages

Pharmacological Treatment

Diuretics

- Hydrochlorothiazide, furosemide

ASA

- May accelerate healing of venous ulcers

Systemic antibiotics

- If ulcer has become infected

Topical steroids

- Treatment of symptoms of infection, disease

Pentoxifylline

- May improve ulcer healing


Medications

β-Adrenergic Antagonists

Formulations & Dosages

Generic Name	Trade Name	Dosages	Selectivity	Other Properties/Notes
Acebutolol	Sectral	200-400mg BID	Cardioselective	ISA Class II antiarrhythmic
Atenolol	Tenormin	12.5-100mg daily	Cardioselective	ISA
Bisoprolol	Monocor	2.5-10mg daily	Cardioselective	
Carvedilol	Coreg	3.125-25mg BID	Non-selective	ISA Class II antiarrhythmic Partial α-blocker
Labetalol	Trandate	100-400mg BID	Non-selective	Partial α-blocker
Metoprolol	Lopressor	12.5-100mg BID 100-200mg SR daily	Cardioselective	
Nadolol	Corgard	40-160mg daily	Non-selective	
Pindolol	Visken	5-20mg BID to TID	Non-selective	ISA (strong)
Propranolol	Inderal	10-80mg BID	Non-selective	Class II antiarrhythmic
Sotalol	Sotacor	40-160mg BID	Non-selective	Class III antiarrhythmic
Timolol	Timoptic	1 drop in affected eye BID	Non-selective	Eye Drop

Mechanism of Action and Pharmacodynamics

Classes and Activity of β-Adrenergic Receptors

- In general
  - β_1 = cardioselective
  - β_2 = vasoselective, bronchoselective
- Complete List

Organ	Receptor	Effect
Heart		
Sinus Node	β_1, β_2	Heart rate increase
Atria	β_1, β_2	Increase in contractility and conduction velocity
AV Node	β_1, β_2	increase in AV conduction velocity
His-Purkinje	$\beta_1 > \beta_2$	Automaticity increases
Ventricle	$\beta_1 > \beta_2$	Increase in contractility and conduction velocity
Vessels	β_1, β_2	Constriction
Arterioles and veins	β_2	Relaxation
Coronary arteries	β_1	Relaxation
Lung	β_2	Bronchial muscle relaxation

Pharmacological Effect of β_1-Adrenergic Antagonists

- Negative inotropy (decreased contractile strength of heart)
  - One of the main effects
- Negative chronotropy (decrease heart rate)
  - Other main effect
- Negative lusitropy (decrease rate of relaxation)
- Negative dromotropy (decrease conduction rate)
- Increased bathmotropy (increased action potential threshold)

Pharmacological Effect of β_2-Adrenergic Antagonists

- Vasoconstriction
- Bronchoconstriction

Secondary Properties

Intrinsic Sympathomimetic Activity (ISA)

- Occurs as a result of a β-blocker that is a partial agonist (instead of full antagonist)
- Generally results in β-antagonism to a lesser degree

Membrane Stabilizing Activity

- Also known as Class II antiarrhythmic activity
- Mainly work by blocking activity through AV node (through β receptor antagonism)
    - Also known as Class II anti-arrhythmic
    - Unknown clinical significance
    - Examples

α-Receptor Antagonism

- Works by blocking activity at α-adrenergic receptors
- Results in peripheral vasodilation

Indications

- Numerous indications, largely depending on the type of β-blocker used
    - Examples
        - Hypertension
        - Ischemic Heart Disease
        - Acute Coronary Syndromes
        - Cardiomyopathies (e.g. MI)
        - Heart Failure
        - Arrhythmias
    - NB: very important to consider the evidence to support the use of a β-blocker in a certain indication (e.g. only certain β-blockers are appropriate for heart failure)
    - Specific agents used for a condition can be found under the individual condition

Adverse Effects

System	Signs & Symptoms
CNS	Fatigue, lethargy Dizziness Insomnia, vivid dreams Depression
CVS	Bradycardia/bradyarrhythmias Hypotension Heart/AV block Worsening of peripheral arterial disease symptoms
RESP	Bronchoconstriction/bronchospasm Reduced exercise tolerance
GI	
GU	

MSK/EXT	
DERM/EENT	
HEME	
Endocrine	Sexual dysfunction, impotence, decrease libido Masking hypoglycemic symptoms, increased blood glucose Increased TG, lowered HDL
Electrolytes	
Other	Cold extremities

Contraindications & Warnings

Warnings

- Concomitant therapy with other agents with negative chronotropic of inotropic effects due to additive effects

Relative Contraindications

- Concomitant therapy with Non-DHP calcium channel blockers (i.e. verapamil, diltiazem) due to risk of extreme bradycardia/heart block

Absolute Contraindications

- Severe heart block (2° or 3°)
- Non-selective β-blockers in patients with asthma or COPD
- Decompensated heart failure
- Pheochromocytoma in absence of α-blockade
- Severe PAD
- Poorly controlled diabetes
- β-blockers with ISA should not be used in patients with angina or post-MI

Drug Interactions

Pharmacokinetics

Absorption	Typically high intestinal absorption Bioavailability varies due to metabolism • Processes can be saturated
Distribution	Lipophilic β-blockers will have large Vd and concentrate in lipid-rich tissue Protein binding is highest in lipophilic β-blockers Lipophilic β-blockers are more likely to sequester in brain • Potential for higher risk of CNS side effects
Metabolism	Lipophilic agents are highly metabolised → shorter $t_{1/2}$ • Depends on hepatic blood flow Most do not form active metabolites • Exceptions: propranolol and acebutolol Genetic polymorphisms may account for different effects of β-blockers in certain individuals • Possibility for both extensive and poor metabolizers
Elimination	Mainly through biliary or renal elimination Renal: atenolol and sotalol Can occur as unchanged molecules or metabolites

Monitoring and Follow Up

Adverse Effects Monitoring

- Blood Pressure and Heart Rate
    - Important in patients at risk of suffering adverse effects from hypotension/bradycardia, such as those prone to orthostatic hypotension
- Withdrawal Effects
    - Rapidly withdrawing a β-blocker will cause a rebound hypertension, thus patients should be monitored and doses titrated down slowly (over 2-4 weeks)

Counselling & Considerations

- Lipophilic β-blockers cause more CNS adverse effects
- Do not avoid discussing sex-related adverse effects

Angiotensin Converting Enzyme Inhibitors

Formulations & Dosages

Generic Name	Trade Name	Dosages
Benazepril	Lotensin	5-40mg daily
Captopril	Capoten	6.25-50mg TID
Cilazapril	Inhibace	2.5-10mg daily
Enalapril	Vasotec	2.5mg daily to 10mg BID
Fosinopril	Monopril	10-40mg daily
Lisinopril	Zestril/Prinivil	5-35mg daily
Perindopril	Coversyl	2-8mg daily
Quinapril	Accupril	5-40mg daily
Ramipril	Altace	1.25-20mg daily 1.25-10mg BID
Trandolapril	Mavik	0.5-4mg daily

Mechanism of Action and Pharmacodynamics

Renin-Angiotensin-Aldosterone System (RAAS)

Triggers of RAAS

- Low atrial blood pressure
- Decreased sodium reabsorption in distal tubule
- Decreased blood volume
- Increases sympathetic activity

Role of Angiotensin Converting Enzyme

- Last enzyme in the activation of angiotensin I to angiotensin II (the active enzyme)

Role of Angiotensin II

- Corrects states of hypotension
- Occurs through fluid retention (kidney, adrenal glands), vasoconstriction (vasculature), and remodeling (kidney, heart, and vasculature)

Sites of Action & Effects of Angiotensin Converting Enzyme Inhibitors

Kidney	Sodium excretion Prevention of fibrosis Vasodilation of efferent arteriole of glomerulus
Adrenal Gland	Inhibition of aldosterone release (decreased sodium retention)
Heart	Negative inotropy Negative chronotropy Prevention of hypertrophy and fibrosis
Vasculature Smooth Muscle	Vasodilation Prevention of hypertrophy and fibrosis
Brain	Inhibition of vasopressin Inhibition of sympathomimetic activity

Indications

- Hypertension
- Ischemic Heart Disease
- Acute Coronary Syndromes
- Heart Failure
- Chronic Renal Dysfunction

Adverse Effects

System	Signs & Symptoms
CNS	Light headedness, dizziness, orthostatic hypotension Fatigue
CVS	Hypotension
RESP	Dry cough (5-15%)
GI	Nausea/vomiting Taste disturbance
GU	Renal dysfunction (AKI)
MSK/EXT	
DERM/EENT	Angioedema Rash
HEME	
Endocrine	
Electrolytes	Hyperkalemia
Other	

Contraindications & Warnings

Warnings

- Any condition or drug that can cause acute kidney injury (dehydration, NSAIDs, ARBs, CNIs)

Contraindications

- History of angioedema
- Bilateral renal artery stenosis or aortic stenosis
- Hypersensitivity
- Pregnancy
  - Due to teratogenicity

Drug Interactions

Drug	Interaction
K^+-sparing diuretics, K^+ supplements	Hyperkalemia
ARBs	Hyperkalemia Hypotension
Lithium	Increased lithium levels
NSAIDs	Renal dysfunction Increased BP

Pharmacokinetics

Absorption	Peak effects occur 2-4 hours after oral administration
Distribution	Lipophilicity determines tissue penetration
Metabolism	Activated from prodrug by ester hydrolysis in liver, which increases absorption • Exceptions: captopril and lisinopril
Elimination	Mostly kidneys, as active compounds

Monitoring and Follow Up

Drug Adverse Effects

Dry Cough

- Important to determine cause of cough
- May occur up to 1 year after initiation
- Especially important if there is an underlying disease that can also cause cough (e.g. infection, COPD, heart failure) because you do not want to stop an ACEI without a proper indication

Kidney Injury & Hyperkalemia

- Important to monitor SCr and serum potassium during initiation and with dose changes
- Increases in SCr by ~35% should warrant further inspection
- Start monitoring within ~3 days of initiation of therapy/changes in dose

Counselling & Considerations

- Want to titrate dose with most patients to avoid adverse effects from rapid change in blood pressure/fluid status
    - Especially important in conditions like heart failure
- Compensation
    - Build ups of angiotensin I reduces negative feedback on RAAS which may trigger increased production of ACEI and other enzymes that produce angiotension II (e.g. chymase)

Angiotensin Receptor Antagonists

Much of this information is similar to ACEIs; will fill in the blanks at a later date

Formulations & Dosages

Generic Name	Trade Name	Dosages
Candesartan	Atacand	4-32mg daily
Irbesartan	Avapro	75-300mg daily
Losartan	Cozaar	25-100mg daily
Olmesartan	Olmetec	20-40mg daily
Telmisartan	Micardis	40-80mg daily
Valsartan	Diovan	40-160mg BID

Mechanism of Action and Pharmacodynamics

- In theory should be the same as ACEIs

Kidney	Sodium excretion Prevention of fibrosis Vasodilation of efferent arteriole of glomerulus
Adrenal Gland	Inhibition of aldosterone release (decreased sodium retention)
Heart	Negative inotropy Negative chronotropy Prevention of hypertrophy and fibrosis
Vasculature Smooth Muscle	Vasodilation Prevention of hypertrophy and fibrosis
Brain	Inhibition of vasopressin Inhibition of sympathomimetic activity

Indications

- Used almost exclusively as a replacement if patients cannot tolerate ACEI therapy
- Sometimes used in diseases with proteinuria (e.g. heart failure) in combination with ACEI

Dosage

Efficacy

Adverse Effects

System	Signs & Symptoms
CNS	Light headedness, dizziness, orthostatic hypotension

CVS	Hypotension
RESP	
GI	
GU	Renal dysfunction (AKI)
MSK/EXT	
DERM/EENT	Angioedema
HEME	
Endocrine	
Electrolytes	Hyperkalemia
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption	Unaffected by food intake • Exception: valsartan
Distribution	Highly protein bound
Metabolism	Many prodrugs (e.g. losartan, olmesartan, candesartan) Prodrugs increase risk of drug-drug and drug-disease interactions
Elimination	Generally eliminated unchanged by kidney (olmesartan, valsartan) and via feces $t_{1/2}$ = 9-18 hours

Monitoring and Follow Up

Drug Adverse Effects

Kidney Injury & Hyperkalemia

- Important to monitor SCr and serum potassium during initiation and with dose changes
- Increases in SCr by ~35% should warrant further inspection
- Start monitoring within ~3 days of initiation of therapy/changes in dose

Counselling & Considerations

- Want to titrate dose with most patients to avoid adverse effects from rapid change in blood pressure/fluid status
    - Especially important in conditions like heart failure
- Compensation
    - Occurs with ARBs, just like ACEI (except occurs via up regulation of angiotensin II or ATII receptors

Direct Renin Inhibitors

Formulations & Dosages

Generic Name	Trade Name	Usual Dosages
Aliskiren	Rasilez	150-300mg daily

Mechanism of Action and Pharmacodynamics

- Block renin, preventing production of angiotensin II at the beginning
  - Effects therefore are similar to ACEIs
  - However, effectiveness not entirely known

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption	Poor bioavailability (F ≈ 3%) P-gp substrate
Distribution	50% protein bound Vd = 135L
Metabolism	CYP3A4 (extent unknown)
Elimination	$t_{1/2}$ = 24 hours Excreted uncharged in urine and feces (via biliary excretion)

Monitoring and Follow Up

Counselling & Considerations

Calcium Channel Blockers

Formulations & Dosages

Class	Generic Name	Trade Name	Dosages
DHP	Amlodipine	Norvasc	2.5-10mg daily
DHP	Felodipine	Renedil, Plendil	2.5-10mg ER daily
DHP	Nifedipine	Adalat, Adalat XL	5-30mg TID 30-120mg XL daily
Non-DHP	Verapamil	Isoptin	40mg TID to 120mg BID 120-240mg SR daily
Non-DHP	Diltiazem	Cardizem Tiazac Tiazac XC	30-60mg TID 120-300mg CD daily 120-360mg ER daily 240-360 XR daily

Mechanism of Action and Pharmacodynamics

General Action of Calcium Channel Blockers

- Work by blocking the L-type calcium channels, thereby reducing intracellular calcium
    - May be found in the pacemaker cells and myocardium of the heart or the arterial vasculature
    - Heart
        - Main Effects: negative inotropy, negative chronotropy
        - Minor: positive bathmotropy, negative lusitropy, negative dromotropy
    - Arterial Vasculature
        - Vasodilation of vasculature

Specific Effects of Dihydropyridine Calcium Channel Blockers

Selectivity

- Favours the calcium channels within the vasculature
    - DHPs favour the inactivated state of L-type calcium channels, which is found in depolarized channels (i.e. more frequently in the vasculature)

Pharmacological Effects

- Promotes vasodilation and reduces vasculature resistance
- Selectivity is not 100%, but tends to be high enough that there is little cross-reactivity
    - Some cross-selectivity and may have minor effects on the heart (negative chronotropy and inotropy)
    - However, these effects are generally small and are compensated for rapidly by the body

Specific Effects of Non-Dihydropyridine Calcium Channel Blockers

Selectivity

- Non-DHPs favor rapidly depolarizing L-type calcium channels, thus binds preferentially to the calcium channels within the cardiac muscle and pacemaker cells of the heart

Pharmacological Effects

- Decreases heart rate and force of contraction in the heart
- Major Effects

- Negative inotropic effect
- Negative chronotropic effect
- Negative dromotropic effect

- Slightly less specific than DHP calcium channel blockers so you will get some vasodilation in the arterials, particularly the coronary arteries

Summary

Drug	AV Node	HR	Contractility	Coronary vascular resistance	Peripheral vascular resistance
Amlodipine	-	-	↑	↓	↓↓↓
Nifedipine	-	↑	↓	↓↓↓	↓↓↓
Felodipine	-	↑	↑	↓	↓↓↓
Verapamil	↓↓	↓	↓↓	↓↓	↓↓
Diltiazem	↓	↓	↓	↓↓	↓

Indications

- Angina
- Coronary spasm
- Hypertension
- Supraventricular tachycardia
- Post-infarct protection
- Vascular protection

Adverse Effects

System	DHP Signs & Symptoms	Non-DHP Signs and Symptoms
CNS	Dizziness Fatigue Headache	Dizziness Fatigue Headache
CVS	Hypotension Bradycardia, heart block Tachycardia Decreased exercise tolerance	Hypotension Bradycardia, heart block Tachycardia Decreased exercise tolerance
RESP		
GI		Constipation (verapamil)
GU		
MSK/EXT		
DERM/EENT	Flushing	Rash (diltiazem) Flushing (verapamil)
HEME		
Endocrine		
Electrolytes		
Other	Peripheral edema	Peripheral edema (less likely than DHPs)

Contraindications & Warnings

Warnings

- Use in caution with any drug that have a similar pharmacological action due additive effects (e.g. bradycardia, hypotension)

- Use caution in states of severe hypotension (SBP < 90mmHg)
- Avoid used of DHPs in ischemic heart disease as these may worsen disease due to reflex adrenergic stimulation

Contraindications

- Avoid combinations of β-blockers and Non-DHP CCBs due to risks of extreme bradycardia, hypotension, and heart block
- Avoid use of non-DHPs in diseases negatively affecting the AV or SA node (e.g. sick sinus syndrome, AV nodal disease)
- Avoid use of diltiazem in ventricular tachycardia as this may worsen the condition

Drug Interactions

Drug	Interaction
CYP3A4 Inhibitors	Increased CCB levels
CYP3A4 Substrates	Increased CYP3A4 substrates and CCB levels

Pharmacokinetics

	Amlodipine	Verapamil	Diltiazem
Absorption	Peaks in 6-12 hours	Peaks in 3 hours Activity begins in 2 hours	Peaks in 1-2 hours Activity begins in 30 minutes
Distribution			
Metabolism	First pass metabolism (via CYP3A4)	First pass metabolism (via CYP3A4)	First pass metabolism (via CYP3A4)
Elimination	$t_{1/2}$ = 35-48 hours	$t_{1/2}$ = 3-7 hours	$t_{1/2}$ = 4-7 hours

Monitoring and Follow Up

Monitoring

- Monitor DHPs (and uncommonly non-DHPs) for pedal edema

Counselling & Considerations

- Be aware of the formulation of diltiazem
    - ER and CD concentrations peak in 6-11 hours
    - XR concentrations peak in 11-15 hours

Nitrates

Formulations & Dosages

Indication	Generic Name	Trade Name	Dosages	Frequency
Rescue	Nitroglycerine (NTG)	Nitrolingual (SL spray) Nitrostat (SL tablet)	0.4mg 0.3-0.6mg	Up to three doses at 5-10 minute intervals
Rescue & Prevention	Isosorbide Dinitrate (ISDN)	Isordil	5-10mg 10-30mg	Rescue: as above for NTG Prevention: 10-30mg TID (last dose at 7pm
Prevention	Nitroglycerine (NTG)	Nitro-Dur Minitran Trinipatch	0.2-0.8mg/hr	Apply 1 patch daily in the morning and remove before bed
Prevention	Nitroglycerine (NTG)	Nitrol	0.2%	
Prevention	Isosorbide Mononitrate (ISMN)	Imdur	30-240mg	One tablet daily (QAM)
See below	Nitroprusside			

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- All agents work by releasing nitric oxide (NO), which exerts its effects on the vasculature muscle

Pharmacological Effects

- Nitrates
  - Vasodilation
  - Predominantly on the veins, but also on arteries and coronary arterioles
  - Decreases preload and afterload, which is important in prevention/treatment of IHD
- Nitroprusside
  - Also a vasodilator, but mostly works on the vasculature

Indications

- Ischemic Heart Disease
  - Short-acting formulations are indicated for rescue therapy
  - Long-acting formulations are indicated as second line agents for prevention (in patients unable to tolerate β-blockers)
- Nitroprusside is indicated for emergency situations
  - Hypertensive emergencies
  - Myocardial infarctions
  - During surgical procedures

Adverse Effects

System	Signs & Symptoms
CNS	Headache

	Dizziness
CVS	Postural hypotension Reflex tachycardia Palpitations Syncope
RESP	
GI	Nausea/vomiting Diarrhea
GU	
MSK/EXT	Weakness
DERM/EENT	Flushing Rash
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Contraindications

- Must not be used in combination with phosphodiesterase inhibitors (e.g. sildenafil) due to risk of severe, life threatening hypotension
    - Spacing Between Administration
        - Sildenafil and vardenafil should be separated by ≥ 24 hours
        - Tadalafil should be separated by ≥ 48 hours
    - If the patient requires rescue nitrate therapy, but falls within this time frame they should be informed to call EMS

Drug Interactions

Drug	Interaction
PDE_5 Inhibitors	Prevents breakdown of nitric oxide, resulting in severe hypotension
Alcohol	Hypotension
Ergot alkaloids	Counteracts vasodilation
Rosiglitazone	Myocardial ischemia
Heparin	Decreased anticoagulant effect

Pharmacokinetics

Absorption	
Distribution	
Metabolism	NO is rapidly metabolized by tissue phosphodiesterase enzymes (within minutes)
Elimination	

Monitoring and Follow Up

Counselling & Considerations

- Failure to Relieve Anginal Symptoms
    - If not relief occurs after 1 dose, or pain remains after 3 doses it is important for patient to contact EMS
    - They may continue to use a dose ever 5 minutes until medical attention arrives
- Nitrate Free Period
    - Patients using long-acting nitrates must have a 10-12 hour nitrate free period ever day
    - Failure to do so will cause a tolerance to the effects of both long and short-acting nitrates

α Adrenergic Antagonists

Formulations & Dosages

Generic Name	Trade Name	Dosages
Prazosin		1mg BID-TID Titrate to max of 20mg daily
Terazosin	Hytrin	Hypertension: 1-5mg daily (maximum of 20mg) BPH: 5-10mg daily
Doxazosin	Cardura	Hypertension: 1-16mg daily BPH: 1-8mg daily
Alfuzosin	Xatral	10mg daily

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Blocks binding of epinephrine and norepinephrine to α-adrenergic receptors
    - Drugs may be specific for a receptor subtype (α_1 or α_2) or be non-selective

Pharmacological Effects

α_1-Adrenergic Receptor Antagonists

- Inhibition of cAMP and cGMP phosphodiesterase in vasculature
    - Causes a decrease of peripheral vascular resistance (both arteries and veins)
    - Degree of effect depends on amount of sympathetic stimulation occurring
- Blockage of α stimulation in the brain
    - Reduces sympathetic outflow
- Body will undergo a baroreceptor reflex
    - Increased heart rate
    - Promotes fluid retention

α_2-Adrenergic Receptor Antagonists

- α_2-adrenergic receptors are important in providing negative feedback to α_1 receptors
    - Inhibition causes a net vasoconstriction
- Also inhibits the baroreceptor reflex

Non-Selective α-Adrenergic Receptor Antagonists

- Causes a net vasodilation
- Stronger baroreceptor reflex occurs

Indications

- Relief of urinary incontinence due to Benign Prostate Hyperplasia (BPH)
- Treatment of essential hypertension

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	Postural hypotension
RESP	
GI	
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Monitoring and Follow Up

Drug Adverse Effects

- First dose effect
    - Postural hypotension and syncope in 30-90 minutes after first dose
    - Patient should be under observation for this dose

Counselling & Considerations

α-Adrenergic Blockers – Clonidine

Formulations & Dosages

Generic Name	Trade Name	Dosages
Clonidine	Dixarit	0.25-2mg

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Prevents binding of epinephrine and norepinephrine to α2-receptors within the brain

Pharmacological Effect

- Prevents release of norepinephrine
    - Therefore reduces all the effects of norepinephrine throughout the body, most predominantly blood pressure

Indications

- Hypertension
- Suspected pheochromocytoma patients
- Improving symptoms of postural hypotension in patients with severe autonomic failure

Adverse Effects

System	Signs & Symptoms
CNS	Sedation
CVS	Bradycardia
RESP	
GI	
GU	
MSK/EXT	
DERM/EENT	Dry mouth
HEME	
Endocrine	Sexual dysfunction
Electrolytes	
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption

Monitoring and Follow Up

Counselling & Considerations

- Withdrawal symptoms can occur with abrupt discontinuation
    - Taper dose down if discontinuing

Hydralazine

Formulations & Dosages

Generic Name	Trade Name	Dosages
Hydralazine		50mg QID 25-150mg BID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Causes an increase in GMP within the cardiovascular system

Pharmacological Effects

- Recues Ca^{2+} release from the sarcoplasmic reticulum
- Causes a decrease in vascular resistance
    - Mainly occurs in the coronary, cerebral, and renal circulations
    - Preferentially dilates arterioles over veins

Indications

- Treatment of refractory hypertension
- Treatment of heartfailure in combination with nitrates in patients who do not tolerate ACEIs/ARBs
- Hypertensive emergencies in pregnant women

Adverse Effects

System	Signs & Symptoms
CNS	Headache
CVS	Hypotension Tachycardia Angina
RESP	
GI	Nausea
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	Drug-induced lupus syndrome

Contraindications & Warnings

Warnings

- Avoid parenteral administration in hypertensive patients with CAD, multiple cardiovascular risk factors, and older patients

Drug Interactions

Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Monitoring and Follow Up

Counselling & Considerations

Potassium Channel Openers

Formulations & Dosages

Generic Name	Trade Name	Dosages
Minoxidil	Loniten	2.5-20mg BID
Minoxidil	Rogaine	1-5% applied topically BID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Causes opening of K^+ channels in arteries

Pharmacological Effects

- Inhibits uptake of calcium into vascular muscle cells
- Results in vasodilation in skin, skeletal muscle, GI tract, and heart
    - Decreases cardiac output
    - Vasodilation in skin may promote hair growth

Indications

- Treatment of refractory hypertension
    - Used in combination with a diuretic and β-blocker
- Treatment of alopecia

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	Tachycardia
RESP	
GI	
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	Hypertrichosis
Electrolytes	Hypernatremia
Other	Fluid retention

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Monitoring and Follow Up

Counselling & Considerations

- If used orally, it must be used in combination with a diuretic (to avoid fluid retention) and a β-blocker (to control reflex cardiovascular effects)

Naturetic Peptides

Formulations & Dosages

Generic Name	Trade Name	Dosages
Nesiritide	Natrecor	IV bolus of 2 µg/kg then continuous IV infusion of 0.01 µg/kg/min

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Mimics activity of B-type natriuretic peptide

Pharmacological Effects

- Causes effects that in general oppose RAAS activation (diuresis and vasodilation)
- Decreases afterload and preload without affecting chronotropy or inotropy

Indications

- Treatment of acutely decompensated congestive heart failure

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	Hypotension
RESP	
GI	
GU	Renal failure
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption	
Distribution	

Monitoring and Follow Up

Counselling & Considerations

Carbonic Anhydrase Inhibitors

Formulations & Dosages

Generic Name	Trade Name	Dosages
Acetazolamide		125-250mg daily to BID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Inhibits the activity of carbonic anhydrase in the distal convoluted tubule

Pharmacological Effects

- Causes accumulation of HCO_3^- in the lumen of the nephron
- pH of urine increases and reduces activity of the Na^+/H^+ antiport
- Increases excretion of Na^+ in the urine

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	
GU	Urinary alkalinisation
MSK/EXT	
DERM/EENT	Skin rashes, toxicity
HEME	
Endocrine	
Electrolytes	Metabolic acidosis
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption	
Distribution	
Metabolism	

Monitoring and Follow Up

Counselling & Considerations

- There is a compensation further down the tubule so the effects of carbonic anhydrase inhibitors on their own is minimal

Loop Diuretics

Formulations & Dosages

Generic Name	Trade Name	Dosages
Furosemide	Lasix	20-80mg daily to BID
Bumetanide	Burinex	0.5-2mg daily
Ethacrynic Acid	Edecrin	50-100mg daily to BID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Inhibition of $Na^+/K^+/2Cl^-$ symport in the ascending loop of Henle
- Occurs on the luminal side of the transporter

Pharmacological Effects

- Causes accumulation of Na^+ in the urine
- Also causes decreased K^+ and Cl^- absorption
- The altered membrane potentials will cause a decrease in Ca^{2+} and M^{2+} reabsorption

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	
GU	
MSK/EXT	
DERM/EENT	Ototoxicity
HEME	
Endocrine	Hyperglycemia
Electrolytes	Hypokalemia Hyponatremia Hyperuricemia Hypocalcemia Hypomagnesaemia
Other	Metabolic acidosis

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption	
Distribution	Highly protein-bound to albumin
Metabolism	
Elimination	Excreted in urine via the organic anion transporter system

Monitoring and Follow Up

Counselling & Considerations

- There is a compensation to the effects of loop diuretics further down the tubule
    - However, still one of the most effective agents

Thiazide Diuretics

Formulations & Dosages

Generic Name	Trade Name	Dosages
Hydrochlorothiazide	Hydrazide	25-50mg daily
Chlorthalidone		25-50mg daily
Indapamide		1.25-2.5mg daily
Metolazone	Zaroxolyn	1.25-5mg daily

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Inhibits the Na^+/Cl^- symporter in the distal convoluted tubule
    - Works on the luminal side of the symport

Pharmacological Effects

- Causes accumulation Na^+ in the urine

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	
GU	
MSK/EXT	
DERM/EENT	Ototoxicity
HEME	
Endocrine	Impotence Increased LDL Hyperglycemia
Electrolytes	Hyponatremia Hypokalemia Hypocalcemia Hyperuricemia
Other	Metabolic acidosis

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption	
Distribution	Highly protein bound
Metabolism	
Elimination	

Monitoring and Follow Up

Counselling & Considerations

- Efficacy of Hydrochlorothiazide
    - Meta-analysis of 19 trials showed less BP lowering (measured via ABPM) with 12.5-25mg daily dose compared to other first-line drug classes
    - Chlorthalidone reduces BP better than hydrochlorothiazide at equivalent doses with similar effects on K+
    - Major trials using chlorthalidone have demonstrated CV event reduction whereas hydrochlorothiazide trials have mixed results
    - British Hypertension Society (NICE Trial)
        - If diuretic treatment is to initiated or changed, offer a thiazide-like diuretic (e.g. chlorthalidone or indapamide) in preference to a conventional thiazide diuretic like hydrochlorothiazide
    - Note: Hydrochlorothiazide is incorporated into numerous combos, so this may affect decision

Potassium-Sparing Diuretics

Formulations & Dosages

Generic Name	Trade Name	Dosages
Amiloride	Midamor	5-20mg daily
Triamterene (only in combination with hydrochlorothiazide)	Dyazide	75/50mg daily

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Inhibition of the sodium channels in the collecting ducts

Pharmacological Effects

- Less absorption of Na^+, which also decreases activity of the Na^+/K^+-ATPase antiport, thus increasing K^+ retention

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	
GU	Cholelithiasis, interstitial nephritis (triamterene)
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	Hyperkalemia Hyperuricemia (triamterene)
Other	

Contraindications & Warnings

Drug Interactions

Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Monitoring and Follow Up

Counselling & Considerations

- Only responsible for 1-2% of Na^+ reuptake, but can be very effective if used to stop compensatory mechanisms due to earlier acting diuretics

Aldosterone Antagonists

Formulations & Dosages

Generic Name	Trade Name	Dosages
Spironolactone	Aldosterone	12.5mg-100mg daily
Eplerenone	Inspra	25-50mg daily

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Blocks binding of aldosterone to mineralocorticoid receptors

Pharmacological Effect

- Decrease absorption of sodium
  - Decreased synthesis or insertion of Na^+ channels and Na^+/K^+-ATPase pumps
  - Increase permeability of renal tight junctions
- Increased reabsorption of potassium
  - Via effects on Na^+/K^+-ATPase pumps

Indications

- Spironolactone
  - Hypertension
  - Heart failure
- Eplerenone
  - Typically used in situations where spironolactone is not tolerated

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	Hypotension
RESP	
GI	
GU	Increased SCr
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	**Most of these are exclusive to spironolactone** Gynaecomastia Impotency Deepening of voice Hirsutism Menstrual irregularities
Electrolytes	Hyperkalemia
Other	Metabolic acidosis

Dehydration

Contraindications & Warnings

Warnings

- Use with caution in patients at risk of hyperkalemia (e.g. using K^+ supplements, other potassium sparing diuretics)
- Use with caution in patients on nephrotoxic drugs (e.g. NSAIDs, high dose ACEI)
- Use with caution in patients at risk of dehydration

Contraindications

- Baseline K^+ > 5mmol/L
- CrCl < 30mL/min, SCr > 220µmol/L

Drug Interactions

Pharmacokinetics

	Spironolactone	Eplerenone
Absorption	73% bioavailability • Increased with food	Bioavailability unclear • Not affected by food
Distribution	90% protein bound	50% protein bound
Metabolism	Deacetylation & deethiolation to active/inactive metabolites	CYP3A4 metabolism
Elimination	Parent $t_{1/2}$ = 1.5 hours Active $t_{1/2}$ = 3-24 hours Urinary and bile excretion	$t_{1/2}$ = 4-6 hours Urinary and bile excretion

Monitoring and Follow Up

Drug Adverse Effects

- Hyperkalemia and Kidney Injury
    - Monitor serum K+ and SCr at baseline, after 3 days, and with dose changes

Counselling & Considerations

Antiarrhythmic Agents – Class I

Most data is based on procainamide – will clarify other agents at a later date

Formulations & Dosages

Class	Generic Name	Trade Name	Dosages/Targets
IA	Quinidine		200-300mg TID-QID
	Procainamide	Procan SR Pronestyl SR	Serum Level: 4-10mg/L
IB	Lidocaine		
IC	Propafenone	Rhythmol	300mg BID-TID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Blocks sodium channels in the heart
  - Class IA = Moderate Na^+ block
  - Class IB = Mild Na^+ block
  - Class IC = Marked Na^+ block
- Occurs in a use-dependent manner

Pharmacological Effects

- Increased threshold for action potential
- Decreased automaticity

Indications

- Indicated for rhythm control in atrial fibrillation

Adverse Effects

System	Signs & Symptoms
CNS	Dizziness
CVS	Hypotension Bradycardia Prolongation of PR, QRS, QT intervals Cardiac arrest
RESP	
GI	Nausea/vomiting
GU	
MSK/EXT	Fatigue, weakness
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	Lupus-like syndrome (procainamide)

Contraindications & Warnings

Drug Interactions

Drug	Interaction
Procainamide + H_2RAs	20% decrease in procainamide clearance
Procainamide + digoxin	Increase in digoxin levels (25-50%)
Procainamide + amiodarone	Increase in procainamide and NAPA levels (50, 30% respectively) due to inhibition of p-gp
Procainamide + trimethoprim	47% decreased renal clearance of procainamide 13% decrease renal clearance of NAPA

Pharmacokinetics

	Procainamide
Absorption	Given as a HCl salt • S = 87% (i.e. 87% of the weight of procainamide HCl is procainamide) Bioavailability (F) varies depending on formulations • IR = 75-95% • SR = 68% Differences may exist between the different SR formulations t_{max} • Procan SR = 2.2 hours • Pronestyl SR = 3.8 hours • May be important in determining blood sampling times

Distribution	Extensively distributed
	• Two-compartment distribution
	• Vd_c = 0.1-0.9L/kg
	• Vd_β varies depending on medical conditions
	  ○ Normal renal and cardiac function = 2-2.5L/kg
	  ○ CHF or renal dysfunction can be as low as 1.5L/kg
	Limited distribution to adipose tissue
	• IBW useful in calculating Vd_β from weight
	Large unbound fraction in plasma
	• f_u < 20%
	Procainamide and N-acetyl-procainamide (NAPA) secreted into breast milk
	• Must monitor in breast-fed infants

Metabolism	Metabolized by CYP2D6
	• Some dealkylated metabolites
	Metabolized by N-acetyl Transferase II to N-acetyl-procainamide (active metabolite)
	• 2-3% reversible deacetylation
	Rate of acetylation varies in individuals
	• NAPA:PA ratio of AUC or C_{SS}
	  ○ Slow acetylators = 0.6
	  ○ Fast acetylators = 1.1
	Polymorphism follows racial lines
	• Blacks/Whites = 50:50 (fast:slow)
	• Asians/Orientals = 80:20 (fast:slow)
	Slow acetylators are at higher risk of lupus-like syndrome
	Hydroxylamine intermediate is formed prior to acetylation to NAPA
	Hydroxylamine intermediate is implicated in lupus syndrome

	Lupus syndrome is reversible (within a few weeks of discontinuation)

Elimination	Excretion products are made up of 50% procainamide and 50% metabolized
	• On average 16% of drug recovered in urine is NAPA
	Clearance (L/h for 70kg patient)
	• Fast acetylator = 38.5
	• Slow acetylator = 24.5
	Renal Excretion
	• Renally excreted by GFR and proximal tubular secretion
	• Best to avoid use of drug in patients with renal disease
	• Fraction excreted renally (50-65%)
	  ○ Fast acetylator = 0.5
	  ○ Slow acetylator = 0.65
	• Renal excretion decreases in kidney disease
	  ○ Normal $t_{1/2}$ = 3.5h
	  ○ Anephric $t_{1/2}$ = 10 h
	• NAPA particularly is extensively renally excreted (80%)
	  ○ Normal $t_{1/2}$ = 4-15 hours
	  ○ Anephric $t_{1/2}$ > 40 hours
	Hepatic Excretion
	• Low E drug (for both slow and rapid acetylators)
	Procainamide has more than one decline phase in plasma
	• Normal Elimination Organ Function:
	  ○ α phase $t_{1/2}$ = 6 minutes
	  ○ β phase $t_{1/2}$ = 3.5 hours → predominant phase
	  ○ γ phase $t_{1/2}$ = 10 hours
	• However, can use one-compartment dosing equations to estimate new dosing requirements based on plasma concentration

Monitoring and Follow Up

Therapeutic Drug Monitoring

- Most therapeutic effects occur between 4-10mg/L
- Minor adverse effects start occurring at 8mg/L and serious ones at 14mg/L
- Timing of Blood Samples
  - IV dosing regimen: LD followed by maintenance infusion
  - Sample at 2 hours
  - Then at 12 and 24 hours to establish CSS
  - Samples may be more widely spaced after that

ECG Monitoring

- If QT elongation prolongation > 25% of baseline consider reducing dose
- If QT elongation prolongation > 50% of baseline stop therapy

Counselling & Considerations

Dosing Recommendations

- Based on CrCl
  - GFR > 50mL/min → τ = 6-12 hours
  - GFR < 10mL/min → τ = 8-24 hours

Antiarrhythmic Agents – Class II

These agents are β-blockers; they are typically used with membrane stabilizing agents as adjunctive therapy in the treatment of arrhythmia

Antiarrhythmic Agents – Class III

Formulations & Dosages

Generic Name	Trade Name	Dosages/Targets
Amiodarone	Cordarone	200-400mg daily Trough: 0.5-2mg/L
Sotalol		80-160mg BID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Block activity K+ channels in myocardial tissue
- Amiodarone also blocks Na^+ channels, Ca^{2+} channels and β-adrenergic receptors
- Sotalol also blocks β-adrenergic receptors

Pharmacological Effects

- Prolongs refractory period of period, preventing another action potential from firing early
- Secondary properties of amiodarone and sotalol result in negative chronotropic effects (amiodarone more than sotalol)

Indications

- Prevention and treatment of atrial and ventricular arrhythmias
    - Sotalol is typically used in patients unable to tolerate amiodarone

Adverse Effects

System	Amiodarone Signs & Symptoms
CNS	
CVS	QT elongation Torsades de pointes
RESP	Pulmonary fibrosis
GI	Hepatotoxicity
GU	
MSK/EXT	
DERM/EENT	Ocular deposits Photosensitivity (due to deposition of iodine in skin)
HEME	
Endocrine	Thyroid dysfunction
Electrolytes	
Other	

Contraindications & Warnings

Warnings

- Use with caution when combing with other drugs that may prolong QT intervals or increase activity of the antiarrhythmic due to risks of torsades de pointes
- Use with caution when combining with negative chronotropic drugs due to additive bradycardia

Drug Interactions

Drug	Interaction
Amiodarone + warfarin	Increased warfarin levels – decrease warfarin dose by 50%
Amiodarone + digoxin	Increased digoxin levels – decrease digoxin dose by 50%
Sotalol + drugs increasing K^+	Potential for fatal hypokalemia (due to generation of arrhythmias)
Amiodarone + CYP/p-GP substrates	Amiodarone inhibits activity of CYP and p-gp Amiodarone levels may be affected by other CYP substrates

Pharmacokinetics

	Amiodarone
Absorption	Low and variable absorption • F = 65% ± 33% • F increases by 2.4x when administered with fatty food
Distribution	Binds strongly to lipoproteins • Rats with hyperlipidemia have significantly higher plasma Extensively distributed • Very high Vd (66L/kg)
Metabolism	Extensively metabolized • Mainly dealkylation to DEA followed by dethylated amiodarone • Other hydroxylated metabolites exist, but are though to be inactive Desethylamiodarone (DEA) → formed by CYP3A4, 1A1, and others • Active metabolite • $t_{1/2}$ > amiodarone • Same K^+ and Na^+ blocking activity • Less Ca^{2+} blocking activity • Possess significant electrocardiographic activity • May be implicated in pulmonary fibrosis ○ Patients with higher DEA:amiodarone ratios tend to have more pulmonary toxicity
Elimination	Clearance varies depending on plasma or blood measurements • CL_{plasma} = 8L/h • CL_{blood} = 11.6L/h Very long half-life • $t_{1/2}$ = 21-90 days • Large Vd → takes a long time for drug to leave the tissues

Monitoring and Follow Up

Amiodarone Drug Monitoring

- Try to keep amiodarone troughs between 0.5-2mg/L
- Due to long half-life, simple monitoring of concentration with empirical dose adjustments should suffice
    - Important early on in therapy (minimize risk of excessive concentrations)
    - Otherwise monitoring for drug interactions is typically sufficient

Counselling & Considerations

Antiarrhythmic Agents – Digoxin

Formulations & Dosages

Generic Name	Trade Name	Dosages/Targets
Digoxin	Toloxin Lanoxin	0.625-0.25mg daily Target = 0.5-2mg/L

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Inhibits the Na+/K+-ATPase pump in the cardiac cell membrane, causing an increase in cytosolic calcium

Pharmacological Effect

- Increased cytosolic calcium causes
  - Negative chronotropy (due to increases in vagal tone)
  - Positive inotropy
- Other Effect
  - Increased parasympathetic effects (results in toxicity)
  - Vasoconstriction

Indications

- Treatment of atrial fibrillation
  - Typically in patients unable to tolerate β-blocker therapy, when other therapies are contraindicated, or when symptoms remain despite other treatments
- Adjunctive therapy for treatment of heart failure
  - Used if patient is still symptomatic after optimizing β-blocker and ACEI therapy

Adverse Effects

System	Signs & Symptoms
CNS	Confusion Visual disturbances
CVS	Arrhythmias
RESP	
GI	Anorexia Nausea/vomiting
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Warnings

- Use caution in hypokalemic states or with drugs that affect potassium levels due to enhanced toxicity
- Use caution when combining with other negative chronotropic drugs due to additive effects

Contraindications

- Contraindicated in AV conduction disturbances

Drug Interactions

Drug	Interaction
Amiodarone, propafenone	Increased digoxin levels by up to 50%
Cholestyramine, antacids	Decreased digoxin absorption
Broad spectrum antibiotics	Increased bioavailability due to removal of digoxin metabolizing bacteria
Anticholinergics	Increased bioavailability due to reduce GI transit time
Metoclopramide	Decreased bioavailability due to increased GI transit time
Verapamil	Decreases renal and non-renal excretion (via p-gp inhibition)
Quinidine	Increased Vd and decreased renal clearance (25-40%) • Decrease digoxin maintenance dose by 50% when starting quinidine in a patient already receiving digoxin • Decrease digitizing dose (loading dose) by 30% when starting digoxin in a patient already receiving quinidine

Pharmacokinetics

Absorption	Passively absorbed from duodenum/upper jejunum Absolute F depends on formulation • Ranges from 75-95%

Distribution	Vd Large (7-8L/kg)
	• Little affinity for fat (water soluble)
	• Plasma protein binding = 20-25%
	• Binds predominantly to muscle tissue
	Myocardial:serum digoxin concentration ratio ranges from 20:1 to 155:1 (usually 30:1)
	• In children, similar ratios found (125-150:1)
	Clinical Factors Affecting Vd
	• Decreased renal function
	  ○ Decreased volume of extracellular fluid and decreased tissue binding
	• Pregnancy
	  ○ Increased Vd due to increased space
	  ○ Distributes to fetus via placenta
	  ○ Fetal concentrations may be 50% of maternal serum digoxin concentration
	  ▪ Close monitoring serum digoxin concentration and fetal and maternal ECGs
	• Thyroid Disease
	  ○ Hypo = decreased Vd
	  ○ Hyper = Increased Vd
	• Heart Failure
	  ○ HF initially decreases Vd (less perfusion of muscle tissues)
	  ○ As HF worsen, fluid movement into extracellular space and Vd increases

	• Alterations in K^+ Balance
	  ○ Decreased K+ increases binding of digoxin to Na+/K+-ATPase pump and potentiates toxicity
	  ○ Increased K+ reduces toxicity
	• Quinidine
	  ○ Displaced binding of digoxin from tissue proteins, increasing Vd and toxicity

Metabolism	Only 22% metabolized; mostly cleavage of sugar followed by conjugation Enterohepatic recycling (EHR) of digoxin occurs → 30% of AUC attributable to EHR • Some active metabolites formed by intestinal bacteria (e.g. *Eubacterium lentum*) via lactone reduction
Elimination	60-80% of bioavailable digoxin excreted via glomerular filtration and active tubular secretion Half-Life • Elderly require reduced daily dosing due to the decreased renal function • Healthy young patients = 38 hours • Elderly patients = 69 hours • Pregnancy increases renal excretion • CHF decreases renal excretion Effect of Renal Function • Normal renal function → 1.6 days • Anephric patients → 3.5-4.5 days ○ Dosage reduction required in patient with low renal function

Monitoring and Follow Up

Therapeutic Drug Monitoring

- Concentrations should be drawn at pseudoequilibrium
  - Normal Renal Function = up to 8 days
  - Renal Impairment = up to 23 days
- Take trough samples at least 12 hours after doses
  - Troughs of 0.5-2mg/L provides maximal therapeutic activity and 90% of patients have no toxicity

ECG Monitoring

- More important than blood levels

Counselling & Considerations

Toxicity

- Difficult to identify/diagnosis (causes arrhythmias, so can't tell if dose is toxic or ineffective)
- Toxic dose only 2-3x of therapeutic dose
- 5-25% of patients exhibit signs of toxicity
- Best treated with Class IB drugs

HMG-CoA Reductase Inhibitors

Formulations & Dosages

Chemical	Trade Name	Dosages
Rosuvastatin	Crestor	5-40mg daily
Atorvastatin	Lipitor	10-80mg daily
Simvastatin	Zocor	10-40mg* QHS
Lovastatin	Mevacor	20-80mg QHS
Pravastatin	Pravachol	10-40mg QHS
Fluvastatin	Lescol	20-80mg QHS

*Simvastatin 80mg daily provides no additional benefits and increases risk of myopathies

Mechanism of Action and Pharmacodynamics

Mechanism of Action

1) Inhibits the activity of HMG-CoA Reductase, preventing formation of endogenous LDL

Pharmacological Effects

- Reduced LDL production
- Up-regulation of LDL receptors (SREBP), which further reduces blood cholesterol levels
- Increased removal of TG (LDL precursor)

Pleiotropic Effects

- Endothelial Function: enhancement of NO production (vasodilation)
- Plaque Stability: inhibition of monocyte infiltration & macrophage secretion of ECM proteinases, inhibition of smooth muscle cells
- Inflammation: decrease in C-reactive protein
- Chicken or egg problem
- Coagulation: reduction in platelet aggregation and fibrinogen

Lipid Lowering Ability

Drug	20-25%	26-30%	31-35%	36-40%	41-50%	51-55%
Atorvastatin	-	-	10mg	20mg	40mg	80mg
Fluvastatin	20mg	40mg	80mg	-	-	-
Lovastatin	10mg	20mg	40mg	80mg	-	-
Pravastatin	-	1mg	2mg	4mg	-	-
Rosuvastatin	-	-	-	5mg	10mg	20, 40mg
Simvastatin	-	10mg	20mg	40mg	80mg	

- TG Reduction ≈ 30%
- HDL Increase = minimal (Rosuvastatin ~15-20%)

Indications

- Treatment of dyslipidemia for primary and secondary prevention of cardiovascular disease

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	Nausea/vomiting Diarrhea Elevated LFTs Hepatotoxicity (1-2%)
GU	
MSK/EXT	Myopathy
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Warnings

- Use with caution in chronic stable liver disease; monitor more frequently for adverse effects
- Use with caution in specialty populations such as HIV patients, transplant patients
- Use with caution in children, and only those will hereditary diseases such as familial dyslipidemia

Contraindications

- Avoid use in active liver disease, including unexplained, persistent elevations in ALT and AST, or non-alcoholic steatohepatitis
- Pregnancy and lactation

Drug Interactions

Drug	Interaction
CYP3A4 inhibitors or substrates	Increased levels of atorvastatin, lovastatin, or simvastatin
CYP3A4 inducers	Decreased levels of atorvastatin, lovastatin, or simvastatin
Amiodarone, cyclosporine, diltiazem, verapamil	Increased statin levels (non-CYP)

Pharmacokinetics

Absorption	Variable absorption = 30-85% Variable bioavailability = 5-30%
Distribution	f_u > 95% protein bound • Pravastatin = 50% Peak concentrations in 1-4 hours
Metabolism	Extensive first pass metabolism (often CYP450) with active metabolites • CYP3A4 substrates = atorvastatin, lovastatin, simvastatin • CYP2C9 = fluvastatin, rosuvastatin • Exception: pravastatin
Elimination	Excreted predominately in feces $t_{1/2}$ = 1-4 hours

- Exception: atorvastatin, rosuvastatin ≈ 20 hours

Monitoring and Follow Up

Baseline Monitoring

- CK
- TSH
- LFT

Monitoring for Liver Toxicity

- May monitor in 6-12 weeks following initiation and with dose changes
- Most often presents with ALT elevation
- Does not predict liver damage or failure and patients are generally asymptomatic to LFT changes
- Treatment Algorithm

ALT ≤ 3x ULN	ALT > 3x ULN
No routine monitoring required	1) Discontinue statin and reassess in 6-12 weeks 2) If ALT still elevated investigate etiology 3) If ≤ ULN restart at lower dose or switch statin and reassess in 3-6 weeks 4) Monitor for signs and symptoms of liver failure and discontinue and seek medication assistance if they present

Monitoring for Myopathy

- Follow up monitoring only done in patients who are symptomatic
- Treatment Algorithm

CK ≤ ULN	CK < 10x ULN	CK > 10x ULN
1) If symptomatic, discontinue statin and measure CK 2) Reassess symptoms and CK in 6-12 weeks 3) Resume statin once patient asymptomatic	1) Consider other causes 2) Follow until CK ≤ ULN and patient asymptomatic, then restart different statin or lower dose	1) Hydrate PRN 2) Follow until CK ≤ ULN and patient asymptomatic, then restart different statin or lower dose (If moderate to severe, consider alternative therapy)

Counselling & Considerations

Law of Diminishing Returns (Rule of 6)

% Decrease in LDL

Dose (mg/day)	Rosuvastatin	Atorvastatin	Simvastatin
10	46%	37%	28%
20	52%	43%	35%
40	55%	48%	39%
80	-	51%	46%

- Doubling the dose of a statin causes approximately a 6% additional drop in LDL

Time of Dosing

- Less potent statins: take with evening meal or QHS
    - This is the point of most endogenous cholesterol production
- Atorvastatin and rosuvastatin: take any time

Managing Drug Interactions

3) Assess level of risk based on interaction, patient, situation
    - If Low Risk: No additional monitoring required
    - If High Risk: Consider alternative
        - If no alternative exists, consider length of therapy

Counselling on Myopathy

Incidence

- Myopathy = 1.5-5.0%
- Rhabdomyolysis = 0.004% (1/23,000 patients)

Risk Factors

- History of myalgias with statins
- History of unexplained muscle aches or positive family history
- Hypothyroidism
- Renal or hepatic impairment
- Female
- Small body frame
- Advanced age
- Drug interactions
    - Increased risk with fibrate combination (risk of rhabdomyolysis increased by 5.5 times)

Signs & Symptoms

- Effects are dose related and usually occurs within first 6 months of therapy
- Myopathy
    - Pain usually presents in thighs or calves
    - Described as heaviness, stiffness, cramping
    - 40% of patients with myopathy will tolerate another statin
- Rhabdomyolysis
    - Can result in serum myoglobinemia
    - Myoglobin toxic to kidneys → precipitates AKI
    - Darkens urine
    - Not well predicted by myalgias

Bile Acid Binding Resins

Formulations & Dosages

Chemical	Trade Name	Dosages
Cholestyramine	Olestry	4 grams once to six times daily

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Bile acid sequestrants are highly positive charged and bind aggressively to bile acids

Pharmacological Effects

- Prevents reabsorption of bile and therefore cholesterol
- Results in decreased LDL as it is used to replaced the lost bile acids
- May get an increase in HMG-CoA reductase

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	
GI	Constipation Diarrhea Fat soluble vitamin deficiency
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	Hyperlipidemia (theoretically from increased HMG-CoA production)
Electrolytes	
Other	

Contraindications & Warnings

Drug Interactions

- Avoid administering with any other medications – cations and fat binding can severely inhibit absorption of numerous drugs

Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Monitoring and Follow Up

Counselling & Considerations

- Should be administered with a statin because of HMG-CoA reductase up-regulation

Fibrates

Formulations & Dosages

Chemical	Trade Name	Dosages
Bezafibrate	Bezalip	400mg daily
Fenofibrate	Lipidil	48-200mg daily
Gemfibrozil	Lopid	600-1200mg

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Fibrates artificially stimulate peroxisome proliferator-activated receptors (PPARs)

Pharmacological Effects

- Increased LPL synthesis
- Increased fatty acid oxidation
- Decreased TG levels
- Reduction in ApoC-III expression
    - Liver responds by increasing SREBP production → more LDL receptors → more uptake of LDL from circulation

Indications

- Treatment of hypertriglyceridemia for primary and secondary prevention of cardiovascular disease

Adverse Effects

System	Signs & Symptoms
CNS	Headache
CVS	
RESP	
GI	GI upset Elevated LFTs
GU	Renal dysfunction (gemfibrozil) Increased SCr (gemfibrozil, fenofibrate)
MSK/EXT	Myopathy
DERM/EENT	Rash Alopecia
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Contraindications

- Hepatic dysfunction
- Severe renal dysfunction
- Gallbladder disease
- Pregnancy and lactation
- Soy lecithin or peanut allergy
- Gemfibrozil in combination with:
    - Statin → risk of rhabdomyolysis
    - Repaglinide → hyperglycemia

Drug Interactions

Drug	Interaction
HMG-CoA reductase inhibitors	Increased levels of HMG-CoA reductase inhibitors
Ezetimibe	Increased levels of ezetimibe
Warfarin	Increased levels of warfarin
Cyclosporine	Increased fibrate levels
Bile acid sequestrants	Decreased fibrate levels

Pharmacokinetics

Absorption	Rapid absorption >90% absorption with meals
Distribution	95% plasma protein bound Peak plasma levels within 4 hours Concentrates in liver, kidney, and intestines
Metabolism	Metabolized by liver to glucoronide conjugates
Elimination	$t_{1/2}$ = 20 hours 60-90% excreted in urine

Monitoring and Follow Up

Counselling & Considerations

Evidence of Efficacy

- Modest reduction in coronary events, but no reduction in CV or all-cause motality
- Effective in the reduction of TG levels to prevent pancreatitis

Nicotinic Acid

Formulations & Dosages

Formulation	Trade Name	Dosage	Notes
Crystalline (IR)		1-3g daily (in divided doses)	OTC
ER	Niaspan		Prescription
Flush-Free			OTC; no absorption

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Mechanism unknown
- Possibilities
    - Activation of G-Protein Coupled Receptor (GPCR)
    - Inhibits cAMP production
    - Decreases hormone-sensitive lipase activity
    - Decreased TG lipolysis and less free fatty acid formation

Pharmacological Effect

- Decreased HDL reuptake by level, thereby increasing blood HDL levels
- Decreased hepatic VLDL production
- Enhanced clearance of chylomicrons and VLDL

Indications

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	Postural hypotension
RESP	
GI	Increased LFTs Hepatotoxicity GI upset
GU	
MSK/EXT	
DERM/EENT	Flushing Pruritus
HEME	Thrombocytopenia
Endocrine	Hyperglycemia
Electrolytes	
Other	Hyperuricemia, gout

Contraindications & Warnings

Contraindications

- Active liver disease, including unexplained elevations of liver enzymes
- Active peptic ulcer disease
- Arterial hemorrhage

Drug Interactions

Drug	Interaction
HMG-CoA reductase inhibitors	Increased risk of myopathy
Bile acid sequestrants	Decreased absorption of niacin

Pharmacokinetics

Absorption	Completely absorbed Peak plasma levels in 30-60 minutes
Distribution	Extensive distribution to liver
Metabolism	Metabolized by the liver to nicotinuric acid
Elimination	$t_{1/2}$ = 1 hours Mainly excreted in urine as metabolites

Monitoring and Follow Up

Counselling & Considerations

Titration Schedule

Week	Breakfast	Lunch	Supper
1	-	-	250mg
2	250mg	-	250mg
3	250mg	250mg	250mg
4	250mg	250mg	500mg
5	500mg	250mg	500mg
6	500mg	500mg	500mg

- For crystalline niacin (regular release)
- Target dose: 1-3g/daily

Recommendations for Flushing

- Flushing is prostaglandin mediated (not histamine)
    - ASA 30min prior to dose could theoretically reduce flushing
- Take after meals or at bedtime with food
- Avoid items which will worsen symptoms
    - Hot beverages
    - Alcohol
    - Spicy food
- Loss of tolerance to flushing will occur after missing doses for 2-3 days

Ezetimibe

Formulations & Dosages

Chemical	Trade Name	Dosages
Ezetimibe	Ezetrol	10mg daily

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Inhibits luminal cholesterol uptake by jejunum enterocytes by inhibiting NPCILI receptors

Pharmacological Effects

- Reduces incorporation of cholesterol into chylomicrons and therefore reduces remnant chylomicrons
- Stimulates LDL receptor expression which reduce blood LDL
- Stimulation of LDL receptor expression
- Reduced blood LDL may stimulate HMG-CoA reductase expression
- Lowers LDL by 15-20%

Indications

- Treatment of dyslipidemia in combination with a HMG-CoA reductase inhibitor
    - May be used as monotherapy if patient is intolerant to statins

Adverse Effects

System	Signs & Symptoms
CNS	
CVS	
RESP	Upper respiratory tract infections
GI	Cholelithiasis Diarrhea Elevated LFTs
GU	
MSK/EXT	Arthralgia Fatigue
DERM/EENT	Sinusitis
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Contraindications

- Avoid combination with statins in patients with active liver disease, unexplained elevation in liver enzymes
- Pregnancy and lactation

Drug Interactions

Drug	Interaction
Cyclosporine, fibrates	May increase ezetimibe levels
Bile acid sequestrants	May decrease ezetimibe levels

Pharmacokinetics

Absorption	Highly water soluble
Distribution	Most remains in the gut, some intestinal absorption
Metabolism	Glucuronidated by intestinal epithelium
Elimination	70% excreted in feces, 10% in urine

Monitoring and Follow Up

Counselling & Considerations

Evidence

- No current evidence shows that reductions in LDL by ezetimibe correlate with reduced cardiovascular events

Pentoxifylline

Formulations & Dosages

Chemical	Trade Name	Dosages
Pentoxifylline	Trental	400mg SR BID-TID

Mechanism of Action and Pharmacodynamics

Mechanism of Action

- Thought to decrease blood viscosity & increased red blood cell flexibility

Indications

Adverse Effects

System	Signs & Symptoms
CNS	Headache Dizziness Nervousness Agitation
CVS	Flushing Palpitations
RESP	
GI	Dyspepsia Nausea/vomiting Bloating
GU	
MSK/EXT	
DERM/EENT	
HEME	
Endocrine	
Electrolytes	
Other	

Contraindications & Warnings

Contraindications

- Avoid in acute MI as it may worsen condition via myocardial stimulation
- Avoid in acute hemorrhage as it may worsen bleeding
- Avoid in severe liver disease

Drug Interactions

Drug	Interaction
Warfarin	May enhance anticoagulation
Oral hypoglycemics	May enhance hypoglycemia • Monitor blood glucose for 2-3 days and adjust doses as necessary

Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

Monitoring and Follow Up

Counselling & Considerations