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|  |
| Book of Cardiology |
| A STUDY BUFFALO STUDY GUIDE |



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| Joshua Torrance  4/9/2012 |



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# C:\Users\Joshua\Desktop\Cardiovascular Risk Factors.jpg

Hypertension

# 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

|  |  |
| --- | --- |
| Machine generated alternative text: • New hypertension (%) YEAR 1 YEAR 2 YEAR 3 YEAR 4 | 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

Machine generated alternative text: Risk of Hypertension % Risk of Hypertension %
.•• loo oOO°
•Women • OMen
••• 80 000
•• 60 0
. 0
.
. 4° 0
. 0
20
0
o
0 2 4 G 8 lO 12 14 16 18 20 0 2 4 6 8 10 12 14 16 18 20
Years to Follow-up Years to Follow-up

* Nearly everyone will become hypertensive if they live long enough

## Blood Pressure Distribution

Machine generated alternative text: 150
130
110
80
70
Men
Women
pp
150
130
110
80
70
I I I I I I
30-39 40.49 50-59 60-69 70-79  60 30.39 40-49 50-59 60-69 70-79 80
Age PPPuIse Pressure Age

* 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
  + 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

Machine generated alternative text: CAD Death Rate per 10,000 Person-years
90-99 80-89 75-79 70-74
Diastolic BP (mmHg)
160+
140-159
120-1 39
Systolic BP
(mmHg)

* + - 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/1.73m2)
    - 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

Machine generated alternative text: Elevated Out of the
Office BP
measurement
Elevated Random
Office BP
Measurement
BP: 140-1 79 ¡90-109
Clinic BP
ABPM (If available) I
HBPM I
Hypertension visit 3
? 160 SBP or
? loo DBP
<1601100
¿or
Hypertension visit 4-5
 140 SBP or
90 DBP
Continue to
follow-up
Awake BP
<135/85 and
24-hour
<130/80
<135/85
or
Hypertension Visit I
BP Measurement,
History id Physical exaninatiori
Diaioshc tests
at isit 1
ordering
or 2
Hypertension Visit 2
within I month
Hypertensive
Urgency ¡
Emergency
j
BP? 140190 mmHg and
Target organ damage or
Diabetes or Chronic Kidney
Disease or BP? 1801110?
__,{f__, Diagnosis
of HTh
‘j,
No
Diagnosis
of HTN
ABPM or HBPM
Diagnosis
of HTN
Awake BP
135SBPor
 85 DBP
Or 24-hour
13OSBPor
 80 DBP
 35
SBPor
DBP85
Continue to
follow-up
Diagnosis
of HTN
Continue to
follow-up
Diagnosis
of HTh
<140190 fr

* 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

Machine generated alternative text: Home-monitored blood pressure
<1 35185mmHg
Perform ABPM
Mean awake BP
equals or over 135/85 mmHg
Office BP> 140190 mmHg
in low risk patients (with no target-organ disease)
I
I
Home-monitored blood pressure
equals or over 135/85mmHg
I I
Mean awake BP
Less than 135/85 mmHg
I
Follow-up with periodic home
BP measurement and or
repeated ABPM every 1-2yr.
Initiate antihypertensive therapy

* + - 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

|  |  |
| --- | --- |
| Machine generated alternative text: Masked HTN , (prevalence 10%) 140 Q CI) Q < w E V o w E o = C) = E E True hypertensive 135 True , Normotensive White Coat HTN (prevalence 10%) 135 140 Office SBP mmHg  Machine generated alternative text: Prevalence of both is approximately 10% of the adult population G) w-W o’ o. C.) ccl) V %- I_ CD (.) Noriiial BP White coat Hypertension Masked Hypertension Hypertension | 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   + Diastolic BP | <140  <90 |
| Diabetes   * + Systolic BP   + Diastolic BP | <130  <80 |

1. 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/m2
* 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  Normotensive | 11.4/5.5  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

Machine generated alternative text: loo
80
60
40
20
3 Drugs
2 Drugs
I drug
S % controlled
Canadian sites
Baseline 6 mo I , 3  5 ,, <140190 mm Hg

* + 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

Machine generated alternative text: .2 1.4
1.2 1.16
1.04
O.2
Thiazide 3-bIocker ACE-I CCB All
Combine • Double
1.01
0.89

* + 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  B  β-Blocker | **C**  Long-acting CCB  **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)

Machine generated alternative text: TARGET <140 mmHg
Lifestyle modification
therapy
*If blood pressure is still not
controlled, or there are adverse
effects, other classes of
antihypertensive drugs may be
combined (such as ACE
inhibitors, alpha blockers.
centrally acting agents, or
nondihydropyridine calcium
Long-acting
DHP CCB
Thiazide ARB
diuretic
I _ _
Dual therapy
T
J Triple therapy
CONSIDER
• Nonadherence
• Secondary HTN
• Interfering drugs or
lifestyle
• White coat effect
channel blocker).

* 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

|  |  |
| --- | --- |
| Machine generated alternative text: Threshold equal or over 130/80 mmHg and Target below 130/80 mmHg with *urinaw albumin to creatinine Nephropathy* ratio.? 2.0 mgirnmol in men or  2.8mglmmol in women* Diabetes without I Nephropathy** A combination of 2 first line drugs may I be considered as initial therapy if the . blood pressure is 20 mmHg systolic Systolic- or >10 mml-lg diastolic above target L., diastolic Hypertension Isolated Systolic Combinations of an ACEI with an ARB are specifically Hypertension not recommended in the absence of proteinuria * based on at least 2 of 3 measurements | Machine generated alternative text: 1. ACE Inhibitor or ARB or 2. DHP-CCB or Thiazide diuretic ?2-drug combinations Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria More than 3 drugs may be needed to reach target values for diabetic patients If Creatinine over 150 pmol/L or creatinine clearance below 30 mI/mm (0.5 mI/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired Threshold equal or over 130180 mmHg and TARGET below 130180 mmHg with Neph ropathy Diabetes — ____ ACE Inhibitor 0rARB ithout ‘ Nephropathy ‘ A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is .?20 mmHg systolic or>10 mmHg diastolic above target. Combining an ACEi and a DHP-CCB is recommended. |
| Machine generated alternative text: Threshold equal or over 130/80 mmHg and TARGET below 130/80 mmHg Diabetes i. ACE Inhibitor or ARB or without ____ ___ Combination of first line Nephropathy 2. Dihydropyridine CCB or agents Thiazide diuretic 1 DHP: dihydropyridiiie IF ACE Inhibitor and ARB and DHP-CCB and Thiazide are Addition of one or more of: contraindicated or not Cardioselective BB or tolerated, SUBSTITUTE Long-acting COB . Cardioselective BB or . Long-acting NON DHP-CCB Combinations of an ACE Inhibitor with an ARB are specifically not recommended in the absence of proteinuria fr Cardioselective BB: Acebutolol, Atenolol, Bisoprolol , Metoprolol More than 3 drugs may be needed to reach target values for diabetic patients | 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

### Glob**al 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

|  |  |
| --- | --- |
| Machine generated alternative text: Diagnosis of hypertension r— Follow-up at 3-6 month intervals With or without Pharmacological treatment Symptoms, Severe hypertension, Intolerance to anti-hypertensive treatment or Target Organ Damage L— I Non Pharmacological treatment Are BP readings below target during 2 consecutive visits? Visits every 1-2 Months . I I | 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/m2)
  + 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

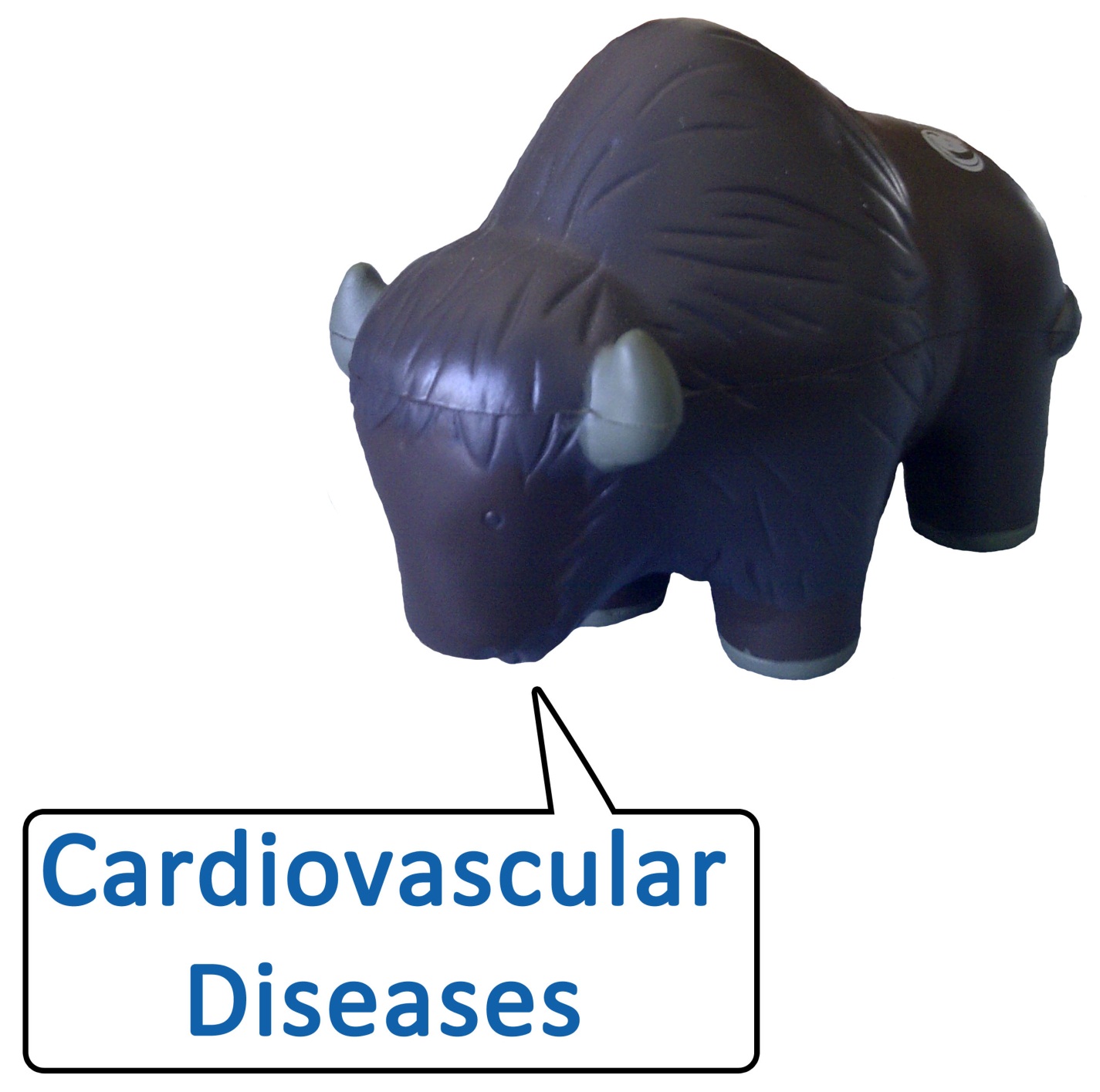
# Monitoring & Follow Up

## 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



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 O2) |
| 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= MVO2
* Balance between O2 deliver and MVO2
* 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 = ↑ MVO2
  + Afterload
    - Pressure which the heart has to pump against
    - ↑ afterload = ↑ work = ↑ MVO2

# Risk Factors

[To be filled in at a later date]

# Clinical Presentation & Complications

## Spectrum of Coronary Artery Disease

Machine generated alternative text: 00
u,!]’_
Acute
niyocardul
infarction
Endothellal Pogth.e Exeitional
dysfunction todefuig angina
‚ Death Ñom
culunery
inaammetor mat4cers disse
Clinicalêy sôent — Clinicaly apparenIir.
Incrarsaig Ostnadhq : Pbqw Iisiire œ
.tlirosclœattc .,oalon rei ulla n

* 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 MVO2 (demand for O2)
    - 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 Ca2+
    - 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

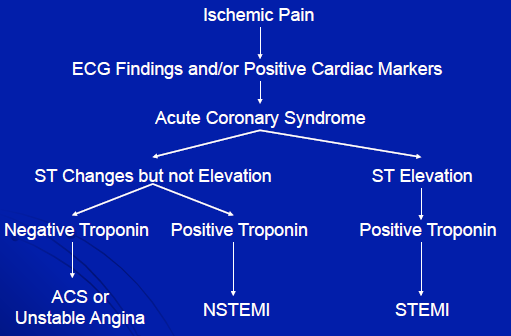
|  |  |  |  |
| --- | --- | --- | --- |
|  | STEMI | NSTEMI | UA |
| Death | 5% | 6% | 4% |
| Stroke | 1% | 1% | 1% |
| Hospitalized | 18% | 19% | 19% |

# 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 t1/2) |

* 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
* 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

## 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

* 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

## Heart Failure Pathophysiology

### Increasing afterload increases myocardial work

Machine generated alternative text: normal
_HF
Afterload (resistance)

* 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

Machine generated alternative text: Cardiac
Output
normal
HF
Preload (filling)

* + 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

Machine generated alternative text: renin
Ir
SNS = sympathetic nervous system, NE = norepinephriue
Aug I = angiotensin I; Ang 11= angiotensin II
________ ____ Jr
__THR1
f AFT rasoçonsfrjçtjon
aldo sterone
I
sodium & water
retention
SNS
JE
I
ACE
“

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

Machine generated alternative text: B Ventricular remodeling in diastolic and systolic heart failure
.
I
.
,
Hypertroph led heart
(diastolic heart failure)
Dilated heart
(systolic heart failure)
Normal heart

* + 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

|  |  |
| --- | --- |
| Machine generated alternative text: A A ‘ ALGORITHM FOR PREVENTION AND TREATMENT OF CLINICALLY STABLE HEART FAILURE To prevent HF: treat all cardiac RF’s, if low LVEF prescribe ACE -I +/-Beta -blocker [ If HF symptoms but LVEF> 40 %, treat Cause eg Hypertension, Ischemia, consider ACE -I/ARB, Beta-blocker For all symptomatic patients with systolic HF: • Tailored Diuretic HF • Education on: - HF syndrome - Warning S&S - Self monitoring - Drug therapy - Prognosis ; and tools If HF symptoms and LVEF< 40 % I ACEI I + BETA-BLOCKER + NYHA Class Il-lila “. NYHA Class IIIb-IV -] —0 Prescribe ARB ‘Prescribe ARB Consider nitrate/h ydralazine if intolerant to ACE! and ARB A A L In tolerance In tolerance J. IF LVEF<30%, CONSIDER lCD REFERRAL IF QRS> 120 MS, CONSIDER CRT REFERRAL Clinically Stable I — IF REFRACTORY, CONSIDER TRANSPLANT Continue Rx l- . Persistent SYmP __4....ip. for combine Diuretics See www.hfcc.ca for latest AddARB Digoxin / Nitrates I I Spironolactone Can J Cardiol 2006;22(1):23-45. - - | 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 |
| Machine generated alternative text: A ____ | Machine generated alternative text: |
| 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

#### CHADS2 Score

* Scoring

|  |  |  |
| --- | --- | --- |
| C | **C**ongestive Heart Failure | 1 |
| H | History of **H**ypertension | 1 |
| A | **A**ge > 75 | 1 |
| D | **D**iabetes | 1 |
| S2 | **S**troke/TIA | 2 |

* Risk of Stroke

|  |  |
| --- | --- |
| CHADS2 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

#### CHA2DS2-VASc

* Scoring

|  |  |  |
| --- | --- | --- |
| C | **C**HF/LV dysfunction | 1 |
| H | **H**ypertension | 1 |
| A2 | **A**ge ≥ 75 | 2 |
| D | **D**iabetes | 1 |
| S2 | **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

|  |  |
| --- | --- |
| CHA2DS2-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 CHADS2 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

Machine generated alternative text: Assess Thromboembolic
Risk
Detection and Treatment of
Underlying Causes
I Management of Arrhythmia I
Rate Control Rhythm Control
Relieve symptoms,
Improve functional capacity
and QOL
AF detected
.-
Antithrombotic
Therapy
Reduce AF-Associated Morbidity and Mortality

## Prevention of Thromboembolic Stroke

### Evaluating Benefits and Risks

1. Determine risk of stroke
   * CHADS2 Score
   * CHA2DS2VASc
2. Determine risk of bleed
   * HASBLED
3. Balance the risks with evidence
4. Select, implement, monitor

### Guidelines for Prevention of Stroke (CCS 2012)

|  |  |  |
| --- | --- | --- |
| CHADS2 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)

|  |  |  |
| --- | --- | --- |
| CHADS2 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** | **CHADS2 Score** | **Suggestions** |
| AF + Stent | 0-1 | 0-12 Months After BMS or DES  ASA + Clopidogrel > 12 months  > 12 Months  As per AF + Stable CAD |
| 2 | Initial Period: 1 Month After BMS or 3-6 Months After DES  Warfarin + ASA + Clopidogrel  After Initial Period until 12 months  Warfarin + single antiplatelet  > 12 Months  As per AF + stable CAD (warfarin) |
| AF + ACS without Stent | 0 | 0-12 Months After ACS  ASA + Clopidogrel  > 12 Months  As per AF + stable CAD |
| 1-2 | 0-12 Months  Warfarin + single antiplatelet  > 12 Months  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 + CHADS2 ≥ 1, PAD, or age = 55-74 years old  DM or CAD  Mean CHADS2 = 2, Mean Age = 70 | N = 7,554  AF with ≥ 2 episodes in last 6 months + CHADS2 ≥ 1, PAD, or CAD  Patients “unsuitable for warfarin” (50% due to physician judgement, 25% due to specific risk, 25% due to patient preference)  Mean CHADS2 = 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 CHADS2 score of ≥ 2 | N = 18,201  NVAF or Atrial flutter + ≥ 1 CHADS2 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 CHADS2 | 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 |
| 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 |
| III | 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

Machine generated alternative text: 1enous
rhrornbosis Varicose Veins
(eg.. DVrI

* 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

|  |  |
| --- | --- |
| Machine generated alternative text: CeVD CAD PAD | 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

Machine generated alternative text: j
Dependent rubor, shiny, Ischemic ulceration of the
hairless skin, dystrophic dorsum of the foot
nail changes in right foot

Machine generated alternative text: Wet gangrene
., 1
Ischemic Ulceration Wet Gangrene
1
I

* + 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

Machine generated alternative text: The Edinbwk CJaudcwwn Qiiesrio,j,alre
(1) Do you gel a pain oc dircomfort in your les(s) when ou walk’ Yes D
No D
I am unable to walic D
Does this pain eser begri tien you are standing still or siflirig? Yes D
Do you get it if you walk uphtll or htirr?
Do you get it when you walk at an ordinary paoc un the level? Yes fl
What liaptxns to t if ou stand still?
(Jiwilly continues mote thasi lO minutes
Usually disappears in lO minutes or less
16) Where do you get this pain or discomfort?
Mark (hz placctst with <‘ oct the diagram below.
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(2)
(4)
5)
If va. .,wer.4 “Yes” to quesdo. (1)—please aiw the following q.eatkiue. ßthrrwi you .red not ciouttesie.
Yes D
Nu D
No D
No U
o
o
Back
flellnådo. of posItive cIasså&.tI.. requires all of the following responses: “Yes” to (I). “No’ to (2). “Yes” to (3). and
‘usually disappears in 10 minutes or leus” lo (5); grade I — “No” to (4) and grade 2 “Yes” to (4). If these criteria are
fulfilled, a ddlnåte claudicant is one who indicates pain in the calf, rcgardlcss of whether pain is also marked in other sites;
a diagnosis of atypkai claudication is made il pain is indicated in the thigh or buttock. in the absence of any calf pain.
Subjects should not be considered to l’ave claudication if pain s indicated in the hamstnngs. feet. thins, joints or appears
to radiate, in the abscnce of inty pain n, 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
* 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

Machine generated alternative text: ,
Cos4Ivaic1w RI*
RclLlcton
- Smokrnç cessatcr
- Trt hypttenšion.
dysIEpdeme. debebs
- sntIpiaIee1 trerepy
CorI9ticuIir Riiš
RŒJctivn
- $mokiri cessation
- Treat hp.ršon
dysJpdmle. diabetes
• Antplatelet 1erepy
Cflca1 Lg lachemia (CU)
Car veacuiir Rak
Reouctien
• Srrokin cessaon
- Treat hpertershn,
dyalipdomie. dleb.tes
. A platelet therapy
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MecaI M roefren1 -
PentcxyllIie
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y
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Lnagem
- albon angbpIty
- Stenhing
. bypass Strgeiy
Treat CcmDIIcatIorn
- AntIbioIcs It uIceron or
ifec
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Claudication
Corflimed Lower xren1ty
Porpheral Arterial Dease
Asymptoniatic
Intermittent CIaucatiDn (IC)
cuIe Leg lachernia (ALl)
¿

## 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 (A1C < 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



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
  + β1 = cardioselective
  + β2 = vasoselective, bronchoselective
* Complete List

|  |  |  |
| --- | --- | --- |
| Organ | Receptor | Effect |
| Heart  Sinus Node  Atria  AV Node  His-Purkinje  Ventricle | β1, β2  β1, β2  β1, β2  β1 > β2  β1 > β2 | Heart rate increase  Increase in contractility and conduction velocity  increase in AV conduction velocity  Automaticity increases  Increase in contractility and conduction velocity |
| Vessels  Arterioles and veins  Coronary arteries | β1, β2  β2  β1 | Constriction  Relaxation  Relaxation |
| Lung | β2 | Bronchial muscle relaxation |

## Pharmacological Effect of β1-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 β2-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 t1/2   * 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  t1/2 = 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 | t1/2 = 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 | t1/2 = 35-48 hours | t1/2 = 3-7 hours | t1/2 = 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 |
| PDE5 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 (α1 or α2) or be non-selective

## Pharmacological Effects

### α1-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

### α2-Adrenergic Receptor Antagonists

* α2-adrenergic receptors are important in providing negative feedback to α1 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 |  |
| Distribution |  |
| Metabolism |  |
| Elimination |  |

# 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 Ca2+ 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 |  |
| Metabolism |  |
| Elimination |  |

# 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 HCO3- 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 |  |
| Elimination |  |

# 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 Ca2+ and M2+ 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 t1/2 = 1.5 hours  Active t1/2 = 3-24 hours  Urinary and bile excretion | t1/2 = 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 + H2RAs | 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 tmax   * Procan SR = 2.2 hours * Pronestyl SR = 3.8 hours * May be important in determining blood sampling times |
| Distribution | Extensively distributed   * Two-compartment distribution * Vdc = 0.1-0.9L/kg * Vdβ 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 Vdβ from weight   Large unbound fraction in plasma   * fu < 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 CSS   + 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 t1/2 = 3.5h   + Anephric t1/2 = 10 h * NAPA particularly is extensively renally excreted (80%)   + Normal t1/2 = 4-15 hours   + Anephric t1/2 > 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 t1/2 = 6 minutes   + β phase t1/2 = 3.5 hours → predominant phase   + γ phase t1/2 = 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, Ca2+ 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 * t1/2 > amiodarone * Same K+ and Na+ blocking activity * Less Ca2+ 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   * CLplasma = 8L/h * CLblood = 11.6L/h   Very long half-life   * t1/2 = 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

* 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 | fu > 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  t1/2 = 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

1. 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 | t1/2 = 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 | t1/2 = 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