Cardiovascular Disease

Manual for Health Professionals

Chronic Disease Network and Access Program (CDNAP)

2009

2009 These materials were developed by the Clinical Subcommittee of the Chronic Disease Network and Access Program of the Prince Albert Grand Council and its partners and funded by the Aboriginal Health Transition Fund.

It is recommended that prescribers evaluate their patients' individual conditions and circumstances before any diagnosis or treatment is made, or procedure is followed that may be based on suggestions by the authors of this resource. Prescribers should consult product monographs before prescribing any of the medications mentioned or discussed in this resource.

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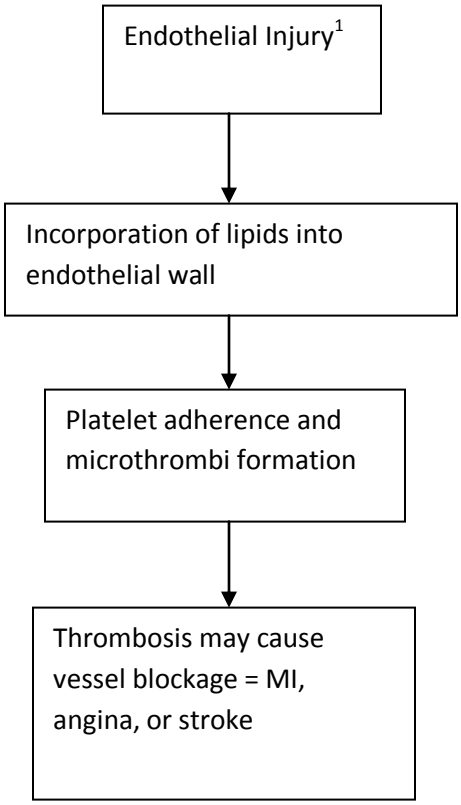
Cardiovascular Disease (CVD)

Definition: **diseases and injuries of the cardiovascular** system (ie the heart and blood vessels of the heart, the brain and throughout the body)

- CVD includes: ischemic heart disease (angina), stroke, myocardial infarction, heart failure, and peripheral vascular disease
- The term CVD (cardiovascular disease) is often used interchangeably with CAD (coronary artery disease) or CHD (coronary heart disease) however, CAD is specific to diseases of the heart and its blood vessels.

Mechanism of CVD



1. Endothelial injury is facilitated by hypertension, obesity, physical inactivity, smoking, diabetes, ↑LDL particles.

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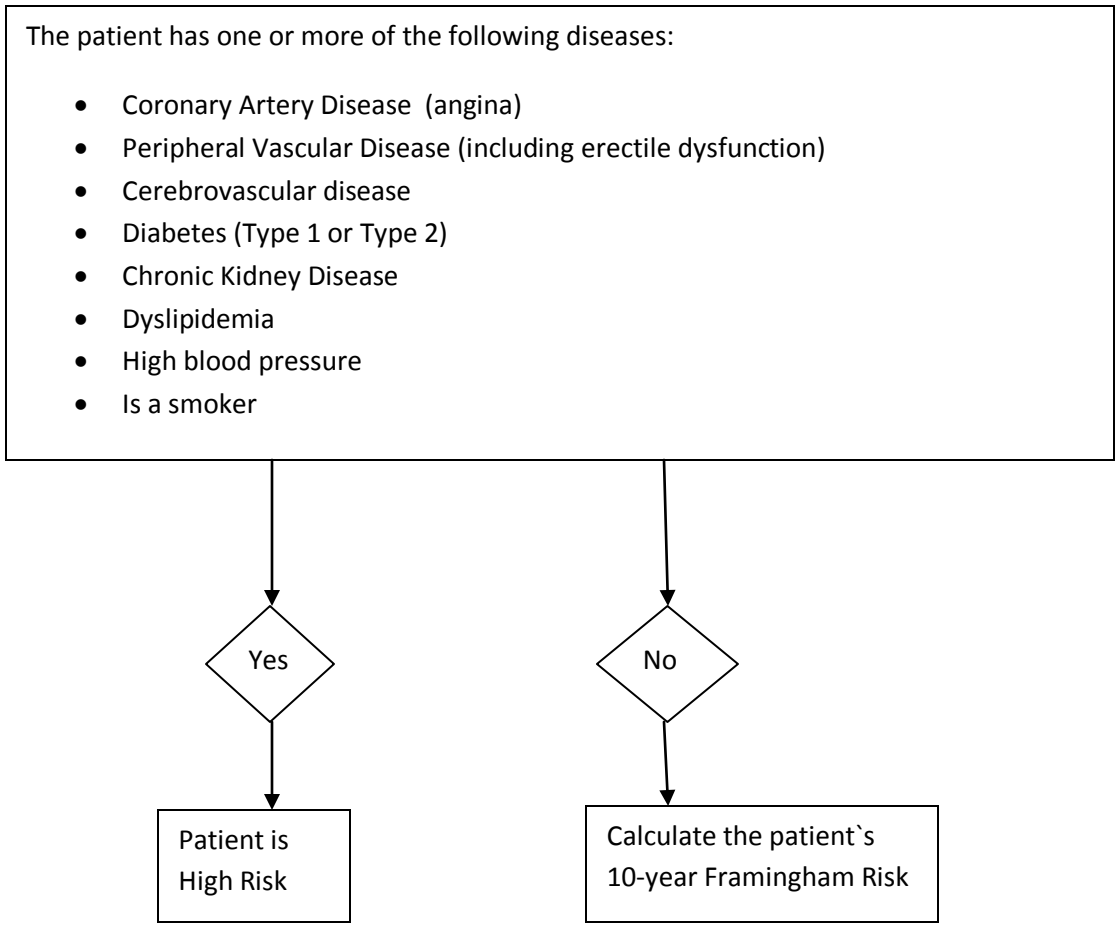
Risk Factors for CVD

Approximately 80% of Canadians have at least 1 risk factor for CAD and stroke.

- Obesity
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Excess alcohol intake
- Sedentary lifestyle

How to Identify Patients at Risk



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Risk Factors for CVD

Framingham Risk Assessment Tool

Model for estimating 10-year risk of CHD in a patient without diabetes or CVD using data from the Framingham Heart Study

Risk factor	MEN	Risk points
Age group, year		
20-34		-9
35-39		-4
40-44		0
45-49		3
50-54		6
55-59		8
60-64		10
65-69		11
70-74		12
75-79		13

	Age group, year				
Total cholesterol mmol/L	20-39	40-49	50-59	60-69	70-79
<4.14	0	0	0	0	0
4.15-5.19	4	3	2	1	0
5.20-6.19	7	5	3	1	0
6.20-7.20	9	6	4	2	1
≥7.21	11	8	5	3	1

Smoker		
No	0	0
Yes	8	5

HDL-C, mmol/L	
≥1.55	-1
1.30-1.54	0
1.04-1.29	1
<1.04	2

Systolic BP, mm HG	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Total risk points	10-year risk, %
<0	<1
0-4	1
5-6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

10 year risk _____ %

Risk factor	WOMEN	Risk points
Age group, year		
20-34		-7
35-39		-3
40-44		0
45-49		3
50-54		6
55-59		8
60-64		10
65-69		12
70-74		14
75-79		16

	Age group, year				
Total cholesterol mmol/L	20-39	40-49	50-59	60-69	70-79
<4.14	0	0	0	0	0
4.15-5.19	4	3	2	1	1
5.20-6.19	8	6	4	2	1
6.20-7.20	11	8	5	3	2
≥7.21	13	10	7	4	2

Smoker		
No	0	0
Yes	9	7	4	2	1

HDL-C, mmol/L	
≥1.55	-1
1.30-1.54	0
1.04-1.29	1
<1.04	2

Systolic BP, mm HG	Untreated	Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Total risk points	10-year risk, %
<9	<1
9-12	1
13-14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

10 year risk _____ %

If there is positive family history of CHD in a first degree relative, multiply 10-year risk by 1.7 to 2.

Risk category		Target level: LDL-C, mmol/L		TC:HDL ratio	
High	10-year risk ≥ 20% or history of diabetes or any atherosclerotic disease	< 2.5	and	<4.0	Immediate drug therapy +lifestyle changes
Moderate	10 year risk 11-19%	<3.5	and	<5.0	
Low	10-year risk ≤ 10%	<4.5	and	<6.0	
Very low	10-year risk < 5%	<5.0			

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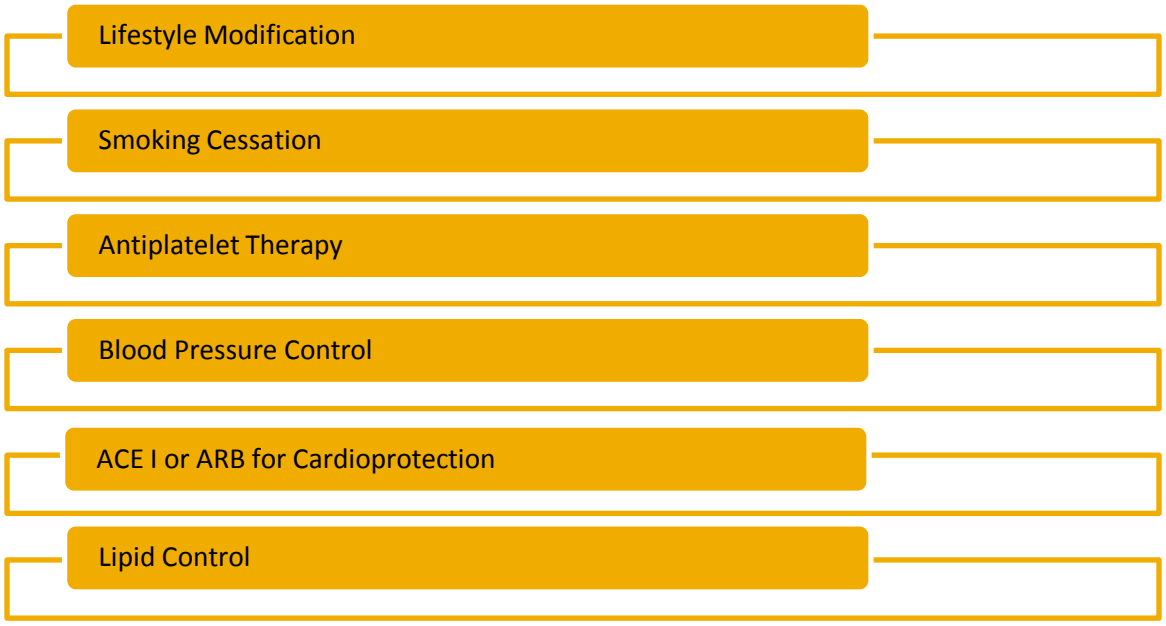
Management of Cardiovascular Disease



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Lifestyle Modification

Achieve and Maintain a Healthy Weight

- Complications of obesity: fatigue, depression, stroke, PVD, cataracts, respiratory disorders, heart disease, liver and gall bladder disease, pancreatitis, diabetes, gynaecologic disorders, certain cancers (including breast, colorectal, esophageal, kidney), osteoarthritis, GI reflux, phlebitis, gout, sleep apnea.

Classification of Overweight and Obesity by BMI and Associated Disease Risk

Classification	BMI category[1]	Disease Risk[2] Men WC ≤102cm Women WC ≤88cm	Disease Risk[2] Men WC >102cm Women WC >88cm
Underweight	<18.5		
Normal weight	18.5-24.9		
Overweight	25.0-29.9	Increased	High
Obese:			
Mild	30.0-34.9	High	Very High
Moderate	35.0-39.9	Very High	Very High
Severe	≥40.0	Extremely High	Extremely High

1. BMI = Body Mass Index = kg/m^2
2. IE risk for Type 2 Diabetes, hypertension, and CVD

Management of Obesity

1. Healthy Diet

- Consultation with a Dietician will help ensure the weight management strategies are individualised and sustainable over time.
- Weight loss is a significant challenge and is not usually achieved with diet intervention alone.
- A calorie deficit (IE 500 fewer calories consumed than expended) of 500 kcal will promote a gradual weight loss of about 1-2kg per month.
- A healthy diet is low in fat; high in fibre; <2300mg salt/day; no more than 2 standard drinks of alcohol/day.

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Management of Obesity cont'

2. Physical Activity

- An exercise program should be individualised (according to the patient's interests and physical abilities) and sustainable.
- An overall weight-loss program should include 30 minutes of moderate physical activity per day, increasing when appropriate to 60 minutes per day.
- **Canada's Physical Activity Guide** recommends:
  Endurance (aerobic) Activities 4-7 days per week (ex walking, golfing, yard work, cycling, skating, dancing, swimming, etc);
  Flexibility Activities 4-7 days per week (ex gardening, yard work, vacuuming, stretching exercises, bowling, yoga, curling, dancing, etc); and
  Strength Activities 2-4 days per week (ex lifting and carrying groceries, climbing stairs, strength training exercises, push-ups, abdominal curls, etc).

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3. Anti-obesity Agents

Agents Indicated for Weight Loss[1]

Drug	Trade Name	Dosing
	GI Lipase Inhibitor[2]	
Orlistat[3]	Xenical	120mg CC (max TID)[4]

1. Agents that are officially indicated for weight loss: BMI ≥30 or BMI ≥27 with risk factors (hypertension, diabetes, dyslipidemia, excess visceral fat)
2. Decreases fat breakdown and absorption. Not studied in children <12 years old. Seems safe in children 12-16 years old.
3. Side Effects: Common: diarrhea, oily stools, ↑bowel movements, flatulence, abdominal pain, bloating, nausea, vomiting, dry skin, pedal edema; Serious: anaphylaxis, angioedema, urticaria
   Drug Interactions: warfarin (↑INR); cyclosporine
   Contraindications: chronic malabsorption syndromes; cholestasis
4. Start on a weekend (ie while at home) OD and slowly titrate up to TID. Give during or within 1 hour of a meal. Omit dose if meal is skipped or contains no fat. Recommend a multivitamin to prevent deficiency in fat-soluble vitamins.

Agents Not Officially Indicated for Weight Loss

Drug	Trade Name	Dose[4]
	Antidepressants	
Bupropion[1] SR,XL	Wellbutrin	150mg-200mg BID 300mg XL OD
Fluoxetine[2]	Prozac	60mg OD
	Mood Stabilizer	
Topiramate[3]	Topamax	50-100mg BID

1. Not enough evidence to recommend for weight loss. May ↑seizure risk at >300mg/day. Consider if bupropion would be of other benefit to the patient besides weight loss.
2. Weight loss appears to be dose dependant and may lose effectiveness over time. May result in modest ↓A1C in type 2 diabetes. Consider if patient suffers depression +/- anxiety.
3. Weight loss may be dose related. May minimize weight gain by other psychotropics. May be beneficial in obese type 2 diabetes along with metformin and exercise, but side effects may limit its use.
4. ↓ dose in renal impairment

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4. Herbal/Natural Products for Weight Loss

- Overall evidence of efficacy is weak.
- Herbal/Natural products for weight loss are often expensive and not covered by NIHB, provincial drug plans, or private health plans.
- Some have the potential for serious complications.
- **Avoid their use in CVD and hypertension**. Many contain caffeine , ephedrine, or other stimulants that may ↑BP, ↑HR, cause tremors and CNS stimulation (irritability, insomnia), and have a diuretic effect.
- **Avoid their use in patients taking medications with possible drug interactions** (ex warfarin, digoxin, statins).
- **Avoid their use in pregnancy and breast feeding.**
- Because of the lack of evidence of efficacy and possible safety concerns, generally advise against their use. If the patient insists on trying a herbal/natural product, however, encourage choosing a product with a NHP (Natural Health Product) number (ie regulated by Health Canada for quality) that is purchased at a pharmacy (so the pharmacist can be consulted for information).
- Common mechanisms of action:
  - Stimulant (↓appetite, ↑metabolism): caffeine, ephedra (Ma Huang), green tea products, guarana, yerba mate, kola, bitter orange, pinellia. Note safety concerns above.
  - Laxative (ie bowel cleansers): cascara sagrada, rhubarb, golden seal, fennel, ginger, marshmallow, slippery elm, probiotics, flax, psyllium. Concern with electrolyte imbalance.
  - Bulking agent (↓appetite): PGX, psyllium, flax, xanthan gum. May ↓absorption of oral medications
- **Health Canada Warnings:** (This is not a complete list. Many herbal/natural products are taken off the market because of safety concerns.)
  - Hydroxycut: nausea, tremor, dizziness, palpitations, chest pain, SOB, vomiting, insomnia, syncope, fatal MI.
  - Zantrex-3: headache, nervousness, tachycardia, nausea, diarrhea, tremor, sweating
  - Xenadrine EFX: tachycardia, abdominal cramps, nausea, vertigo, tremor, chest pain, SOB, ↑amylase
  - Ephedra (Ma Huang): banned because of MI and death
  - Ezee Slimming Patch: leucopenia, thrombocytopenia, neutropenia, ↓hemoglobin, menstrual irregularity, agitation, possible fatal jaundice, hepatitis, and clotting disorder
- Other common products:
  - Hoodia (non-stimulating appetite suppressant; evidence is weak)
  - Green Tea (conflicting evidence; contains caffeine)
  - Pyruvate (↑exercise capacity; evidence is weak)
  - Iodine (no evidence and may cause thyroid disorders)

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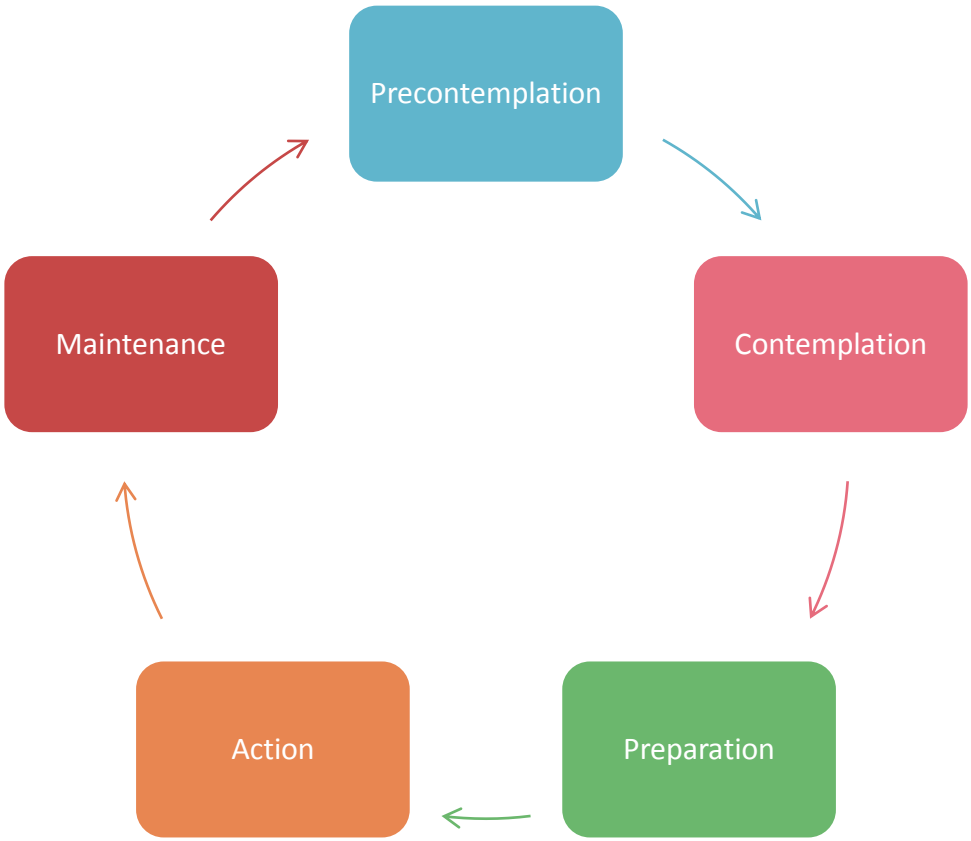
Smoking Cessation

- **A combination of counselling (individual or group) and pharmacologic agents increases success**
- **Assess Stage of Change (ie readiness to quit) and offer support to help patient progress through each level (including possible relapse) to maintenance stage.**



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Smoking Cessation – Pharmacologic Agents

Medication	Dose	Use	Duration
Nicotine Gum[1]			
Nicorette	2mg[2] Maximum 24pieces/day	1 piece/hour or prn	Up to 12 weeks[3]
Nicorette Plus	4mg[4] Maximum 24pieces/day	1piece/hour or prn	Up to 12 weeks[3]
Thrive[2,3,4]	As per Nicorette Gum		
Nicotine Lozenge[5]			
Thrive	1, 2mg[6] Maximum 30mg/day	1 lozenge q1-2h 1 lozenge q2-4h 1 lozenge q4-8h	6 weeks 3 weeks 3 weeks
Nicorette			
Nicotine Patch[7]			
Nicoderm	21mg/24h[8] 14mg/24h *7mg/24h*	1 patch/24 hours[9] 1 patch/24 hours[9] 1 patch/24hours[9]	4 weeks 2 weeks 2weeks
Nicotine Inhaler[10]	10mg/cartridge 6-12 cartridges/day	Puff on cartridge x 20min or prn	Use for up to 12 weeks initially, then taper over 6-12 weeks
Bupropion[11]			
Zyban	150mg AM x 3days then 150mg BID[12]	Stop smoking between day 8 and 14	7 to 12 weeks[13]
Varenicline[14]			
Champix	0.5mg AM x 3days then 0.5mg BID x 4 days,then 1mg BID[15]	Stop smoking after 7 days	12 weeks[16]

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Smoking Cessation – Pharmacologic Agents cont'

1. Do not chew as per non-medicated gum; chew 2 or 3 times, then park gum between gingival and cheek for 30-60 seconds. Repeat for 30 minutes. Do not eat or drink 15 minutes before or after using gum.
   Side Effects: burning, jaw pain, hiccups
   Contraindications: recent MI; unstable angina; severe cardiac arrhythmia; recent stroke; pregnancy and breastfeeding (? Yet many experts believe use of NRT is safer than smoking in pregnancy); <18 years of age; dental problems; TMJ; ***be aware of potential harm to children and pets if not properly disposed of**
   Drug Interactions: coffee, acidic beverages ↓absorption (separate use by ≥15 minutes)
2. If <25 cigarettes (1pack) is smoked per day
3. Or longer if required. Taper by at least 1 piece every 4 to 7 days.
4. If ≥25 cigarettes (1pack) is smoked per day.
5. Suck lozenge until strong taste, then park in cheek. Repeat as long as required or until lozenge is gone (about 30 minutes).
   Side Effects: sore gums, teeth, or throat; hiccups; heartburn
   Contraindications: As per nicotine gum. ***be aware of potential harm to children and pets if not properly disposed of***
   Drug Interactions: As per nicotine gum.
6. Strength to use depends on interval to first craving upon awakening: <30minutes, use 4mg; > 30minutes, use 2mg.
7. Place patch on relatively hairless area between neck and waist. Apply patch to different place each day. See package insert for tips to maximize adhesion.
   Side Effects: Local skin irritation; vivid dreams
   Contraindications: *not* contraindicated in CVD; with caution post MI or stroke (though safer than smoking?); pregnancy and breastfeeding; <18 years of age ***ensure proper disposal of used patches***
   Drug Interactions: smoking ↑ side effects
8. Heavy smokers may need 2 patches to start. Start with lower dose if < 10 cigarettes/day. Tapering and duration should be individualized.
9. May remove patch at night if vivid dreams are troublesome, however craving for nicotine in the morning may be quite strong. Using nicotine inhaler, lozenge, or gum first thing in the morning may be helpful
10. Ten puffs = 1 puff from cigarette. Do not eat or drink 15 minutes before or after using inhaler.
    Side Effects: throat irritation; cough; rhinitis; dyspepsia
    Contraindications: as per nicotine gum
11. Can be used with NRT, but monitor BP. Decreases weight gain.
    Side Effects: insomnia, dry mouth, tremors, skin rashes, serious allergic reaction
    Contraindications: current seizure disorder; current/past diagnosis of bulimia or anorexia nervosa; concurrent use of other agents containing buproprion; recent/current withdrawal from alcohol, benzodiazepines or other sedatives; current/use within 14 days of MAOI; use with caution in situations that may reduce seizure threshold (history of head trauma, prior seizure disorder, CNS tumor, excessive alcohol use, stimulant/opioid addiction, diabetes)
    Drug Interactions:
12. ↓ dose in renal or hepatic impairment (not recommended)
    Ensure at least 8 hours between doses. Do not give second dose close to bedtime to avoid insomnia. If insomnia persists, reduce dose to 150mg AM
13. Consider longer treatment for smokers who suffer significant mood swings or who continue to experience strong cravings after discontinuing bupropion.
14. Safety in children <18 unknown.
    Side Effects: nausea, abnormal dreams, constipation, vomiting, flatulence, dry mouth
    Contraindications: severe renal impairment; pregnancy and breastfeeding;
    Drug Interactions: cimetidine; possible ↑adverse effects with NRT; ? safety with bupropion
15. 0.5mg BID if CrCl < 30mL/min. Use ↓dose in elderly or those suffering intolerable side effects.
16. Those who are still not smoking after 12 weeks of varenicline use may continue for another 12 weeks.

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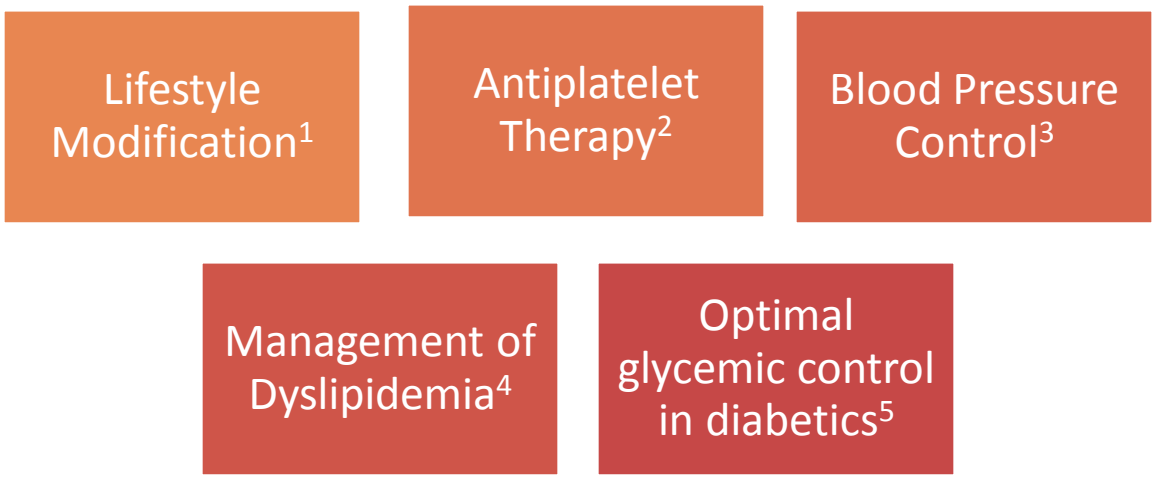
Vascular Protection



1. Lifestyle Modification includes: healthy diet (low fat, high fibre, low salt); regular physical activity; smoking cessation; limitation of alcohol intake.
2. Unless contra-indicated. See section of the same title.
3. **Targets for Blood Pressure Control** according to patient circumstances:

Condition	Target (SBP/DBP mmHg)
Diastolic +/- Systolic HTN without compelling indication	<140/90
Home BP reading	<135/85
Isolated systolic HTN without compelling indication	<140
Diabetes	<130/80
Chronic kidney disease	<130/80

*Note that it is recommended that normotensive patients with established CVD be treated with an ACEI or ARB. Normotensive patients who have had a stroke or TIA should be treated with an ACEI and a diuretic. Please refer to CDNAP's Management of Hypertension Guide.

4. See section of the same title.
5. Target A1C for most patients with diabetes (type 1 or 2) is <7.0%. Please refer to Diabetes Management Guide for more information.

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Vascular Protection cont' - Antiplatelet/Anticoagulation Therapy

Condition	Sub-set	Recommendation
Primary Prevention	Moderate risk[1] Non-ischemic CHF High risk[3] Moderate-high risk with ASA intolerance Women<65 years at risk of ischemic stroke[5] Women>65years at risk of ischemic stroke or MI[5]	ASA 81mg[2]/d No ASA or warfarin Low dose warfarin[4] Clopidrogel 75mg/d ASA 81mg/d[2] ASA 8mg/d[2]
Secondary Prevention[12]	Post MI Post MI-high risk[7] Symptomatic CAD	Warfarin[6] + ASA 81mg/d[2] Warfarin[6] + ASA 81mg/d[2] ASA 81mg/d[2] + clopidrogel 75mg/d
Acute MI (STEMI)[12]	all	ASA indefinitely[8] + clopidrogel[9]
Stent Implantation[12]	Bare-metal stent (BMS) Drug-eluding stent (DES) Strong indication for concomitant warfarin[11]	ASA 81mg/d[2] + clopidrogel 75mg/d *or* prasugrel 10mg OD *or* ticagrelor 90mg BID ASA 81mg/d[2] + clopidrogel 75mg/d for at least 1 year[9] *or* prasugrel/ticagrelor BMS: ASA + warfarin[6] indefinately + clopidrogel 75mg/d for 4 weeks DES: ASA + warfarin[6] indefinately + clopidrogel 75mg/d for 1 year
Coronary Artery Bypass Graft[12]	Saphenous Vein Graft (SVG)[10] SVG – ASA intolerant SVG – Acute non-STEMI MI SVG-indication for warfarin[11] Internal Mammary Artery Graft	ASA 81mg/d[2] indefinately Clopidrogel 75mg/d *or* prasugrel *or* ticagrelor ASA 81mg/d[2] + clopidrogel 75mg/d for 9-12 months following procedure *or* prasugrel *or* ticagrelor ASA 81mg/d + warfarin ASA 81mg/d[2] indefinately

1. IE based on age and FRA >10%.
2. Note that dose range is 75-100mg/d, but ASA is available commercially as 81mg. It should be used indefinitely unless otherwise contra-indicated. Note that the maximum dose to be used with ticagrelor is 150mg
3. IE FRA ≥20%.
4. Target INR 1.5 and only if regular INR monitoring is possible.
5. With low risk of major bleed.
6. Target INR 2.0-3.0 and with meticulous INR monitoring. Note that because of the increased risk of bleeding and demands of intense monitoring if INR, warfarin is not routinely used in the secondary prevention of MI except in select patients with risk of thrombolic event (see next section).
7. IE large anterior MI, significant HF, intracardiac thrombus, AF, history of thromboembolic event.
8. ASA 160-325mg then 75-162mg/d indefinitely.
9. Clopidrogel dose: ≤75 years – 300mg bolus then 75mg/d; >75year - 75mg/d.
10. No dipyridamole with ASA.
11. Ex heart valve.
12. Prasugrel or ticagrelor can be used in patients who suffer MI while on clopidogrel.

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Vascular Protection cont'

Antiplatelet Agents

Drug	Trade Name	Dose
Acetylsalicylic Acid[1,2,4]	ASA, Aspirin, Novasen	81-325mg/day
Clopidrogel[1,3,4]	Plavix	75mg OD
Prasugrel[1,5]	Effient	10mg OD
Ticagrelor[1,6]	Brilinta	90mg BID

1. Side Effects: GI upset, hypersensitivity, GI bleed, major bleed, hemorrhagic stroke.
2. Drug Interactions with ASA: agents that cause GI irritation (NSAIDs, alcohol); agents that cause bleeding (warfarin).
3. Drug Interactions with Plavix: same as with ASA; also certain proton pump inhibitors ↓efficacy of Plavix (omeprazole (Losec), esoeprazole (Nexium), lansoprazole (Prevacid), rabeprazole (Pariet) – assess whether PPI treatment is necessary and change acid suppression medication accordingly (ex to H_2 antagonist such as ranitidine)
   *Compliance with Plavix is important: if stopped within the first month after DES placement, there is ↑↑risk of stent thrombosis. If ≥3 doses are missed, consider another loading dose.
4. Contraindications: recent bleed; active bleed; major GI intolerance; history of allergy to agent; ASA – persons <21 years of age
5. Side Effects: as per ASA
   Drug Interactions: as per ASA; efficacy not affected by PPI's though may be decreased by ranitidine, rifampin, carbamazepine, phenytoin, phenobarb
   Contraindications: as per ASA, also ≥75years or <60kg (↑risk of bleed); not to be given to patients with prior stroke or TIA
   *Only for use after angioplasty; not for MI, stroke or PAD
6. Side Effects: as per ASA; also possible shortness of breath during the first week; also headache, diarrhea, constipation
   Drug Interactions: as per ASA; also ↑ toxicity with ketoconazole, clarithromycin, certain HIV drugs;↑effect of carvedilol, digoxin, simvastatin, lovastatin
   Contraindications: as per ASA

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ASA Combinations:

ASA + dipyridamole – recurrent stroke

ASA + clopidorgel - ≥1 year post coronary stent (drug-eluding; CABG for NSTEMI indefinitely)

ASA + prasugrel - 1 year post coronary stent (consider 15months or longer for DES)

ASA + ticagrelor – 1 year post coronary stent (safety beyond 1 year has not been established)

ASA (81mg) + warfarin(INR 2-3) – recurrent systemic embolism in mitral valve stenosis or regurgitation; mechanical valve; atrial fibrillation; post MI x 3 months in high risk persons

Anticoagulation Agents

Drug	Trade Name	Dose
Warfarin[1]	Coumadin	Adjusted to maintain INR 2-3 (usually 0.5-10mg/day)

1. Side Effects: bleeding; hair loss; blue fingers and toes; skin necrosis.
   Drug Interactions: many potential. Monitor INR carefully when inducing drug is started, discontinued, or dose changed and adjust dose of warfarin accordingly. Ensure patients are educated about potential for drug interactions with warfarin (including herbal products) and to seek advice before self-medicating.
   IV warfarin is an alternative in patients who cannot take it orally. Do not administer warfarin IM.

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Vascular Protection
Dyslipidemia

Screening (Fasting Lipid Profile)

- Men ≥40years of age
- Women ≥50 years of age or postmenopausal
- Adults of any age with the following risk factors:
  diabetes;
  cigarette smoking;
  hypertension; obesity (BMI > 27kg/m^2;
  family history of premature CAD;
  evidence of atherosclerosis;
  rheumatoid arthritis, lupus, psoriasis;
  HIV on antiretroviral therapy;
  GFR < 60mL/min;
  erectile dysfunction
- Children with a family history of hypercholesterolemia or chylomicroenimia

Targets of Lipid-lowering Therapy

Risk Level	Primary Target[4]
High[1]	LDL <2mmol/L *or* ≥50% ↓LDL, apoB <0.80g/L
Moderate[2]	LDL <2mmol/L *or* ≥50% ↓ LDL, apoB <0.80g/L
Low[3]	≥50% ↓ LDL

1. High risk: FRS ≥20%; CAD; PVD; atherosclerosis; most patients with diabetes
2. Moderate risk: FRS 10-19%; LDL >3.5mmol/L; TC/HDL >5; hs-CRP >2mg/L in men >50years and women >60 years
3. Low risk: FRS < 10%
4. Secondary Targets (once target LDL is reached):
   TC/HDL ratio <4.0;
   TG <1.7mmol/L;
   apoB/apoAI ratio < 0.80;
   hs-CRP < 2mg/L

Treatment

Low-risk: lifestyle modifications

Moderate-risk: lifestyle modifications, *then* medication if target is not reached

High-risk: lifestyle modifications *and* medication

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Pharmacologic Management of Dyslipidemia

Statins = HMG Co-A Reductace Inhibitor
= ↓LDL, ↓TG, ↑HDL

Drug	Trade Name	Dose Range	Usual Dose
	Statin[1,2,4]		
Atorvastatin[3]	Lipitor	10-80mg OD	10-40mg OD
Fluvastatin[5]	Lescol	20-80mg/d OD or BID	20-40mg/d
Lovastatin[5]	Mevacor	20-80mg/d OD[7] or BID	20-40mg OD[7]
Pravastatin[3,6]	Pravachol	20-80mg HS	-
Rosuvastatin[3,6]	Crestor	5-40mg OD	-
Simvastatin[8]	Zocor	10-80mg OD[7]	20-40mg OD[7]

Source: Therapeutic Choices, RxFiles

1. Side Effects of Statins: common: upper GI effects, headache, muscle pain, rash, sleep disturbances; rare: peripheral neuropathy, lupus-like symptoms, impotence, pancreatitis; ↑LFT (dose dependant); myopathy (concern if weakness accompanies muscle pain – check CK); rhabdomyolysis (increased risk with combinations of lipid-lowering agents or drug interactions that increase level of statin ex amiodarone, verapamil, amlodipine, diltiazem)
2. Drug Interactions: many potential including: ↑effect of digoxin and warfarin; increased toxicity of statin with amiodarone, clarithromycin, erythromycin, gemfibrozil, grapefruit juice, -conazole antifungals, certain HIV meds, verapamil, also transplant meds, diltiazem, ethynyl estradiol, fenofibrate, fluoxetine, niacin; decreased effect of statin with: cholestyramine (separate by 2 hours), phenytoin, phenobarb, carbamazepine, rifampin, St John's Wort, certain HIV meds. **Avoid with macrolides, gemfibrozil, grapefruit juice, azoles, amiodarone, non-DHP CCB, cyclosporine, protease inhibitors.**
3. Few Drug Interactions with pravastatin and rosuvastatin – some transplant meds and gemfibrozil.
4. Contraindications: acute liver disease, pregnancy, excessive alcohol use
5. Use lower dose in hepatic dysfunction.
6. Use lower dose in renal dysfunction.
7. Take at evening meal.
8. Avoid 80mg to prevent myopathy. If 40mg is not effective, switch to atorvastatiin 40mg or rosuvastatin 20mg. Give simvastatin 10mg with amiodarone, verapamil, diltiazem; give 20mg with amlodipine.

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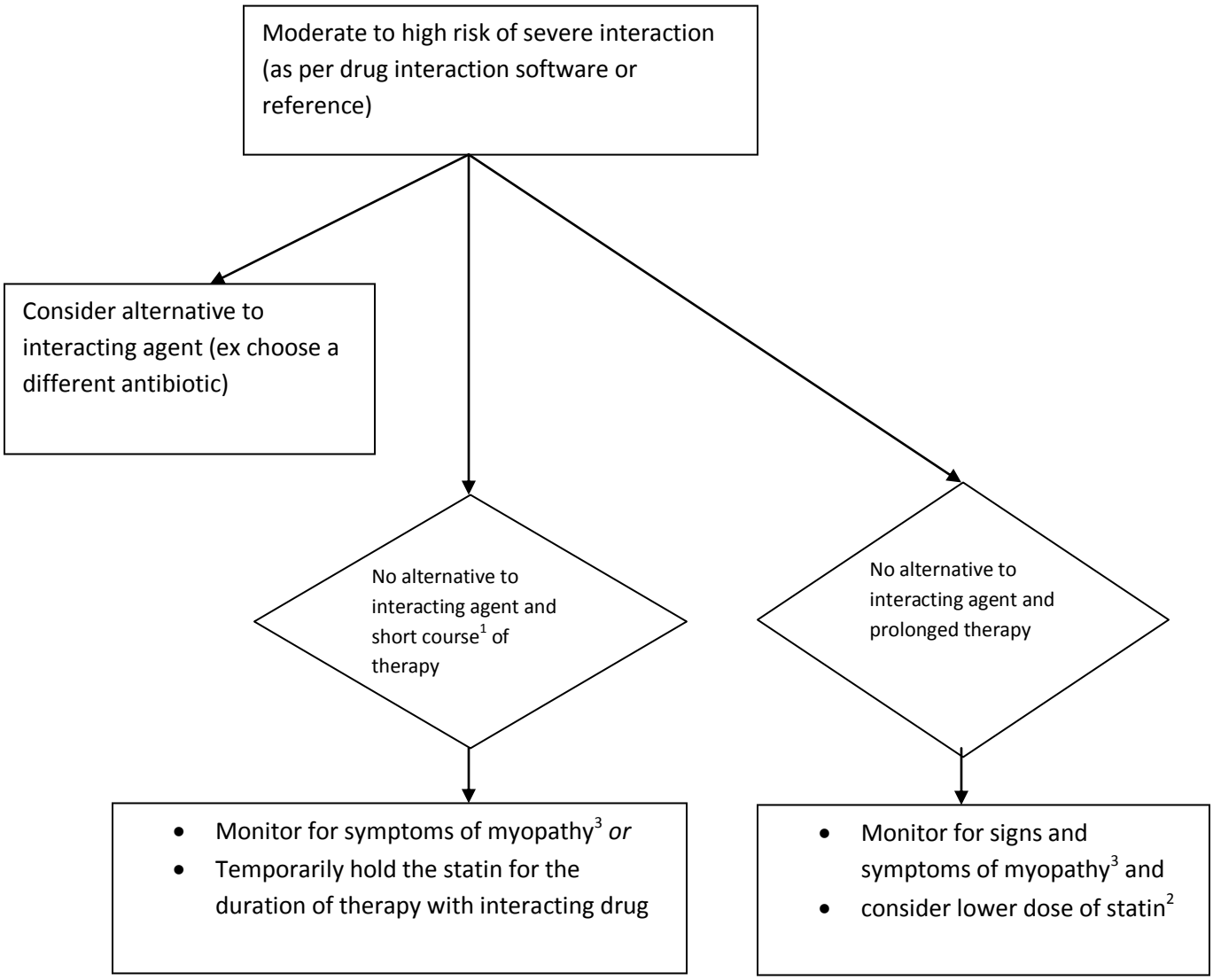
Pharmacologic Management of Dyslipidemia cont'

Drug Interactions with Statins



1. IE < 10 days.
2. May also consider using a different statin or alternative lipid-lowering agent.
3. Signs and symptoms of myopathy: muscle pain, cramps, or weakness; ↑CK.

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Pharmacologic Management of Dyslipidemia cont'

Other Lipid-Lowering Agents

Drug	Trade Name	Dosing	Effect on Lipids
	↓cholesterol absorption		
Ezetimibe[1]	Ezetrol	10mg OD[2]	↓LDL,↑HDL,↓TG
	Nitcotinic acid		
Niacin[3]	-	50-100mg B-TID CC, ↑ by 100mg/week to 500mg TID	↑HDL, ↓TG[4]
	Niaspan	500-750mg HS	
	Fibrate[5]		
Benzafibrate	Benzalip	200mg B-TID CC 400mg SR OD	↑HDL,↓TG[6]
Fenofibrate	*Lipidil Micro*	200mg OD CC	
	Lipidil Supra	160mg OD CC	
	Lipidil EZ	144mg OD	
Gemfibrozil[10]	*Lopid*	300-600mg BID AC	
	Resins[7]		
Cholestyramine	Quenstran	4-8g BID AC[8]	↓LDL, ↑HDL[9]

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Pharmacologic Management of Dyslipidemia cont'

Other Lipid-Lowering Agents cont'

1. Side Effects of Ezetrol: generally well tolerated, but monitor LFT
   Drug Interactions: ↑levels with cyclosporine, fibrates
   Contraindications: hepatic dysfunction
2. When added to statin, may allow ↓dose of statin.
3. Side Effects of niacin: flushing (pre-treat with ASA or ibuprofen 30minutes prior; abates with time); dry eyes, itching; headache; GI upset; ↑LFT; torsades de pointes; ↑uric acid; ↑glucose. Monitor LFT, glucose, uric acid at 3 months, 6 months, 12 months, then yearly.
   Drug Interactions: ↑myopathy with lovastatin, ASA may ↑niacin level
   Contraindications: chronic liver disease, overt diabetes, sever gout, peptic ulcer disease
   Note: do not use No-flush Niacin b/c less effective and ↑hepatic side effects
4. Only higher doses of niacin affect LDL (ie >2g/day)
5. Side Effects of fibrates: common: GI upset, rash, abdominal pain; less common: headache, itching, ↓libido, dizziness, drowsiness, arthralgia, ↑glucose, sleep/vision changes; rare: ↓renal function, anemia, myopathy, ↑LFT, pancreatitis, gallstones
   Drug Interactions: ↑toxicity with furosemide, statins, cyclosporin, MAOIs, probenacid; ↓effect with cholestyramine; ↑levels of glitazones, sulfonylureas, warfarin (monitor INR); chlorpropamide, furosemide; monitor for rhabdomyolysis if given with statin
   Contraindications: severe hepatic disease; smoking (gemfibrozil)
   Use lower dose in renal impairment.
6. Variable effect on HDL. Benefits in persons with diabetes and hyperinsulinemia.
7. Side effects of resins: common: constipation (↑fluid and bulk in diet or Metamucil), nausea, bloating; rare: hyperchloremic acidosis in kids or ↓renal function; monitor LFT, TG
   Drug Interactions: separate administration of other medications by 2 hours (↓ absorption otherwise)
   Contraindications: biliary obstruction; TG >4.6mmol/l; dysbetalipoproteinemia
8. Can mix with Metamucil+orange juice/lemonade the night before; refrigerate and give the next day – ½ before breakfast and ½ before supper (shake well)
9. Possible ↑TG (monitor)
10. Contraindicated with simvastatin

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Pharmacologic Management of Dyslipidemia cont'

Non-prescription Lipid-lowering Agents

Agent	Dose	Comments
Fish Oils and Omega-3 supplements[1]	1-4g/d salmon oil; 4-6g/d Omega-3 supplements	Salmon Oil provides most concentrated amount of DHA and EPA; other sources less-well studied; less effective than gemfibrozil 1200mg/d
Garlic[2]	600-900mg/d	Only modest benefit if any; no benefit >6months
Flaxseed[3]	30-50g/d	Studies used dietary flaxseed; flaxseed oil not studied
Guggulipids[4]	50mg BID	Conflicting evidence
Lecithin[5]	0.5-2g/d	Conflicting evidence
Grape Seed[6]	50-300mg/d	Few studies

1. Source of omega-3 fatty acids (DHA and EPA) which have several proposed mechanisms of action including: ↓thromboxane, blood viscosity, blood pressure, TG; and ↑prostacycline, fibrinolysis. This may stabilize arterial endothelium and exert antihypertensive and antiatherosclerotic actions. There is interest in combining a statin with omega-3 supplements instead of with a fibrate. Note that 3 tablespoonfuls of ground flax = 4.5g omega-3 and 90g salmon = 1g omega-3.
2. Inhibits cholesterol synthesis in the liver.
3. Source of fibre and α-linoleic acid which is converted into DHA and EPA.
4. Inhibits cholesterol synthesis in the liver; antioxidant.
5. May inhibit absorption of cholesterol.
6. Source of α-linoleic acid and antioxidants. May also ↓PVD and atherosclerosis.

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Pharmacologic Management of Dyslipidemia cont'

Monitoring (Prior to and After Initiation of Lipid-lowering Agent)

Parameter	Circumstance	Action
CK-baseline	2-5x reference range	Start with low dose of lipid-lowering agent[1];
	>5x reference range	Investigate cause of ↑CK; consider risks vs benefits when choosing therapy[1]
CK- after agent initiated	No risk of myopathy	No routine CK monitoring required
	Risk of myopathy[2]	CK q3-12 months[3]
	Mild symptoms of myopathy	Check CK; Consider lower dose or switching agent[4]
	Severe symptoms of myopathy	Check CK; d/c agent[5]
ALT-baseline	3x reference range	Start with low dose[6]
	>3x ULN reference range	Investigate cause; consider risks vs benefits when choosing therapy[7]
ALT-after agent initiated[8]	3x ULN reference range	Repeat ALT in 3-6 weeks, consider d/c agent if ALT remains ↑
	>3x ULN	Repeat ALT in 3-6 weeks; investigate cause if ALT remains ↑and consider d/c agent

1. Repeat CK at appropriate time intervals (ex every 8 to 12 weeks)
2. Risks of myopathy: drug interaction with statin, advanced age, underlying muscle disease, females, renal insufficiency, liver dysfunction, alcohol abuse, untreated hypothyroidism.
3. CK normal: continue agent; CK ↑ <10x reference range: continue monitoring CK; CK >10x ULN: ↓dose or d/c agent.
4. CK <10x ULN: consider lower dose or different agent; CK >10xULN: d/c agent and monitor resolution of CK.
5. Symptoms should improve or resolve within 1-6 weeks.
6. Repeat ALT in 3-4 weeks. If ALT ↑ or remains elevated, investigate cause and consider risks vs benefits of lipid-lowering therapy.
7. Repeat ALT at appropriate intervals (ex every 8 to 1 weeks).
8. Repeat ALT at 18-12 weeks. If at any time symptoms of liver failure develop (jaundice, fever, lethargy, dark-colored urine, abdominal pain), discontinue lipid-lowering agent and investigate for liver injury (direct bilirubin).

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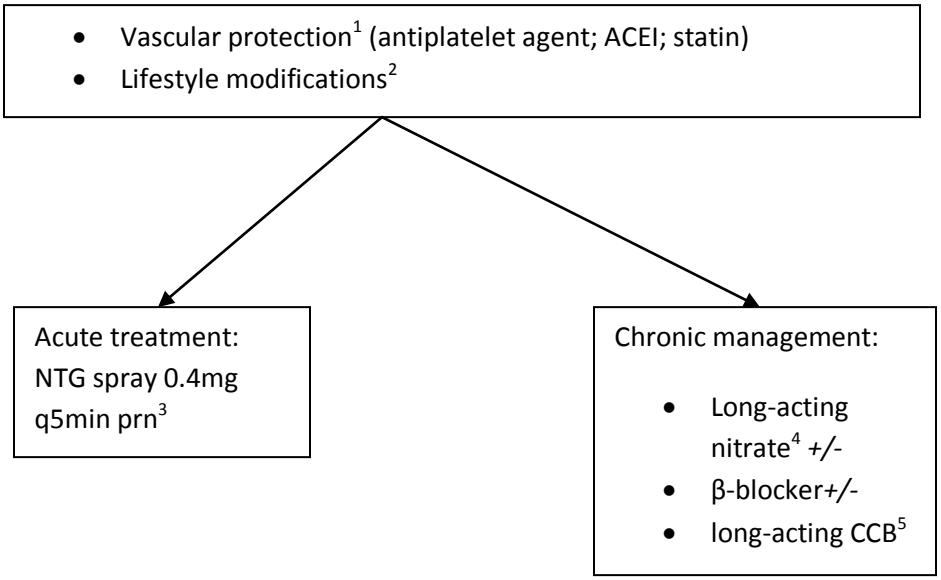
Stable Angina

Goals of Therapy:

- ↓risk of non-fatal MI and cardiovascular death
- ↓ or prevent angina
- ↑exercise tolerance

Management of Stable Angina



1. Unless contra-indicated. Please refer to the section of the same name
2. Including healthy diet (consultation with a dietician is recommended) and regular exercise (ideally via participation in a rehabilitation program with trained personnel). If a rehab program is not available, recommend aerobic exercise (walking, cycling, swimming) *not* strength training. The exercise program should increase gradually over 6-8 weeks with a goal of 20-45minutes 3-6 times per week.
3. May repeat twice in 5 minute intervals. If the first dose is not effective after 5 minutes, seek medical attention.
4. Oral or transdermal. Allow 12 hour nitrate-free period to prevent tolerance.
5. Avoid short-acting nifedipine.

Stable Angina cont'

Pharmacologic Management of Stable Angina

Drug	Trade Name	Initial Dose	Maximum Dose
Nitrates[1]			
Nitroglycerin tablet[2]	Nitrostat	0.3-0.6mg SL q5min prn	3 doses
Nitroglycerin spray[3]	Nitrospray	0.4mg SL q5min prn	3 doses
Nitroglycerin patch[4,5]	Nitropatch; Transderm Nitro; Trinipatch	0.2mg/h applied daily	0.8mg/h patch
Isosorbide dinitrate[5]	ISDN	IR: 10-30mg tid; CR 20-40mg BID	
Isosorbide mononitrate[5]	Imdur	30-60mg OD	240mg OD
Antiplatelet Agents[6]			
ASA[7]		80-325mg OD	
Clopidrogel	Plavix	75mg OD	
Ticlopidine[8]	Ticlid	250mg BID	
Prasugrel[19]	Effient	10MG OD	
Ticagrelor	Brilinta	90mg BID	
B-Blockers[9]			
Nadolol[10,18]		20mg OD	320mg/d
Propranolol[10,11]		40-60mg QID	80-320mg/d B-QID
Timolol[10]		10mg BID	30mg BID
Atenolol[12,18]	Tenormin	25mg/d OD or BID	200mg/d OD or BIDBID
Bisoprolol[12,18]	Monocor	2.5mg OD	20mg OD
Metoprolol[12]	Lopressor, Betaloc	50mg/d (regular BID; SR give OD)	400mg/d(regular give BID; SR give OD)
Pindolol[13]	Viskin	5mg TID	15mg QID
Acebutolol[14,18]	Sectral	200mg BID	400mg BID
Labetolol[15]	Trandate	100mg BID	1200mg BID
DHP-CCB[16]			
Amlodipine	Norvasc	2.5mg/d	10mg/d
Nifedipine	Adalat XL	30mg OD	120mg OD
Non-DHP CCB[17]			
Diltiazem	Cardizem CD; Tiazac; Tiazac XC	120mg/d (give CD and XC formulations OD)	360mg/d
Verapamil[18]	Isoptin; Isoptin SR; Covera HS	Regular - 80mg; SR – 180mg OD	Regular-160mg TID; SR – 480mg OD

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Stable Angina cont'

Pharmacologic Management of Stable Angina cont'

1. Side Effects: headache (usually resolves with time); ↑HR; ↓BP; syncope; dizziness; flushing; edema.
   Drug Interactions: potentiates hypotensive effect of vasodilators
   Contra-indications: concomitant administration with PDE5 inhibitors (Viagra, Cialis, Levitra)
   *Should not be used alone for angina or heart failure
2. Expire 3 months after opening. Must be stored in glass container.
3. Do not shake container. Spray under or onto tongue.
4. May also cause skin irritation. Ensure safe disposal of used patch (IE to prevent poisoning of children or pets).
5. Allow 10-12 hour nitrate-free period to prevent tolerance. IE apply patch in the morning and remove 12 hours later. ISDN 7am, 12pm, 5pm or 7am, 12pm
6. Side Effects: Bleeding, diarrhea, rash.
7. May also cause nausea, vomiting, or gastritis. Serious GI bleed less common with lower doses (80-160mg/d). ↑ risk of bleeding when combined with other antiplatelets or anticoagulants.
8. May also cause purpura or neutropenia. Monitor neutorphils q2w for the first 3 months of therapy. Consider only if patient cannot tolerate ASA but cannot afford clopidrogel.
9. Side Effects: fatigue; hypotension; ↓HR; impotence; sleep disorders; hyperglycemia; depression; heart failure; heart block.
   Drug Interactions: ↓HR with digoxin and non-DHP CCB; cardiodepressant effects with non-DHP CCB and amiodarone
   Contraindications: asthma; 2nd or 3rd degree heart block in the absence of a pacemaker.
   Other concerns: taper dose before discontinuation (abrupt withdrawal may cause ischemia); avoid in severe PAD.
10. Non-selective beta-blocker
11. Initiate therapy with immediate release formulation (dosed B-QID). Propranolol ↑level of rizatriptan. Propranolol is more likely to cause CNS side effects (insomnia, depression, vivid dreams)
12. Cardioselective beta-blocker.
13. Non-selective beta blocker with ISA (intrinsic sympathomimetic activity); has less effect on resting HR.
14. Cardioselective beta-blocker with ISA (less effect on resting HR).
15. Beta-blocker with α_1-blocking activity. May also cause edema, dizziness, nasal congestion, postural hypotension. Labetolol is considered safe in pregnancy.
16. Side Effects: ankle edema; flushing; headache; hypotension; ↑HR.
    Drug Interactions: Many potential including azole antifungles; macrolides; quinidine; grapefruit juice; certain HIV drugs.
17. Side Effects: headache; dizziness; ↓HR; heart block; new onset or worsening heart failure; verapamil may cause constipation.
    Drug Interactions: many potential including azole antifungles; macrolides; quinidine; grapefruit juice; certain HIV drugs; ↑toxicity of carbamazepine, cyclosporine, lovastatin, simvastatin; ↓level with rifampin; ↑negative inotropic effects with amiodarone, beta-blockers and digoxin. Verapamil ↑level of digoxin (monitorlevels).
    Other concerns: use with caution in heart failure or 2nd or 3rd degree heartblock without a pacemaker.
18. Adjust dose in renal failure
19. Do not give to persons ≥75years or < 60 kg.

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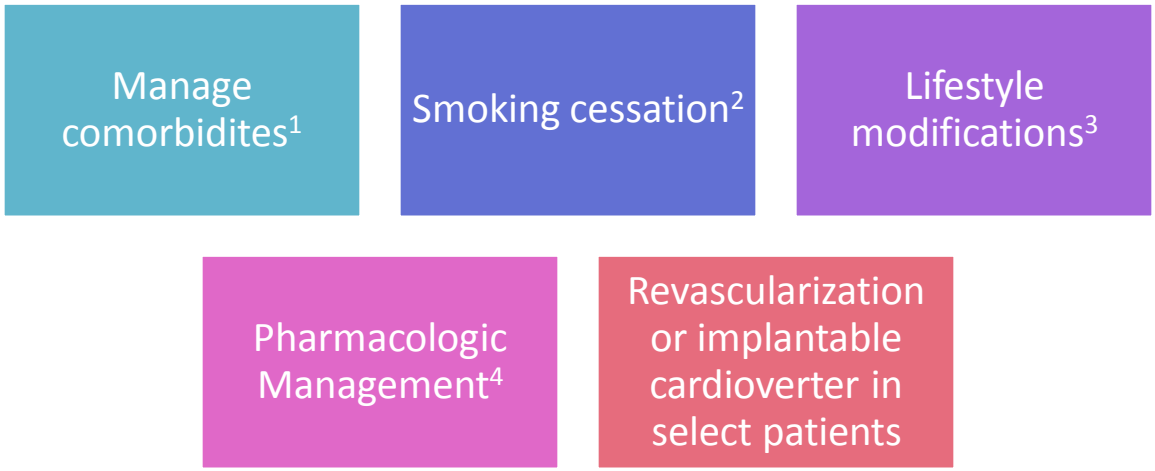
Post-Myocardial Infarction Care



1. Treat hypertension, dyslipidemia, and diabetes.
2. Encourage the use of pharmacologic agents where appropriate (see section of the same title).
3. Weight loss is indicated if BMI >25 or WC >100cm in men or >90cm in women. Nutritional counselling is beneficial to help achieve and maintain a 5-10% ↓ in body weight. An individualized exercise program is beneficial with a goal or 30-45 minutes of moderate aerobic activity 3-4 times per week. Please refer to the section titled "Elements of a Cardiac Rehab Program"
4. Unless contraindicated, the following medications are recommended: antiplatelet agents; beta-blockers; ACEI or ARB; statin. Please refer to the following section.

Other factors in post-MI care:

- Give all patients nitroglycerin spray or tablets for chest pain with education about what to do in the event of recurrent chest pain.
- Some NSAIDs or cox-2 inhibitors may reduce the protective effects of ASA. Avoid concomitant use if possible, or separate doses by several hours.
- Monitor for depression using the PHQ-9 or other screening tool and treat accordingly. Avoid using TCA.

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Post-Myocardial Infarction Care cont'

Elements of a Cardiac Rehab Program

Evaluation	• medical history • assessment of risk factors • exercise stress test • vocational counselling
Prescribed exercise	• aerobic training • resistance training • on-site or at-home
Modification of risk factors	• education • nutritional couselling • regular exercise • medication compliance

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Post-Myocardial Infarction Care cont'

Post-MI Medications

Drug	Trade Name	Initial Dose	Usual Dose
Antiplatelet Agents[1]	*See page 19*		
Beta-Blockers[2]	*See page 27*		
Nadolol[8]		40-80mg/d	120mg/d
Propranolol	Inderal	40mg B-TID	40mg QID
Timolol		5-10mg BID	10mg BID
Atenolol[8]	Tenormin	50mg/d	100mg/d
Bisoprolol[8]	Monocor	2.5mg/d	10mg/d
Metoprolol	Lopressor, Betaloc	100mg/d (give IR BID; give SR OD)	200mg/d
Acebutolol[8]	Sectral	100-200mg BID	400mg BID
Carvedilol[3]	Coreg	3.125mg BID	25mg BID
ACEI[4]			
Captopril[8]	Capoten	6.25mg TID	50mg TID[7]
Enalapril[8]	Vasotec	2.5mg BID	10mg BID[5]
Lisinopril[8]	Zestril, Prinivil	2.5mg/d	20-35mg OD[6]
Perindopril[8]	Coversyl	2mg/d	8mg/d[7]
Ramipril[8]	Altace	2.5mg/d	5mg BID or 10mg OD[7]
Trandolapril[8]	Mavik	1mg/d	4mg/d[7]
ARB[9]			
Candesartan[8]	Atacand	4-8mg/d	32mg OD[5]
Valsartan[8]	Diovan	20mg BID	160mg BID[7]
Statins	*See page 19*		

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Post-Myocardial Infarction Care cont'

1. ASA is the agent of choice for all CAD patients, including post-MI (unless contraindicated). 80-325mg is usually well-tolerated.
   Clopidrogel is recommended when ASA is not tolerated or contraindicated. Clopidrogel is essential when stents are implanted. ASA + clopidrogel is used in unstable angina, STEMI treated with thrombolytics, and after stent placement.
2. Beta-blockers are recommended for all post-MI patients (including non-STEMI and those receiving thrombolytics or undergoing angioplasty (unless contraindicated). They should be avoided in hypotension, bradycardia, and heart failure. The benefits of beta-blocker use post-MI outweighs the risk in diabetes, COPD, severe PVD. Low doses may be safely given to some patients with asthma.
3. Beta-blocker with α_1-blocking activity. In addition to the side effects listed on page 24, it may cause nasal congestion, edema, dizziness, postural hypotension.
4. Side Effects of ACEI: Dry cough; Hyperkalemia (especially with renal insufficiency, K^+ sparing diuretics, K^+ supplements, NSAIDs); angioedema, hypotension (especially if volume depleted or with diuretics); acute renal failure with bilateral renal stenosis; headache; dizziness; fatigue; rash; loss of taste; hepatotoxicity; dysguesia; pancreatitis; blood dyscrasias
   Drug Interactions: K^+ supplements; K^+ sparing diuretics (assess K^+ and SCr regularily); NSAIDs; Lithium (possible toxicity)
   Contraindications: pregnancy, history of angioedema, renal artery stenosis (solitary kidney or bilateral)
   Use lower dose in renal impairment.
   Renal function and K^+ must be monitored. Check BUN, CrCl, electrolytes before starting, after 7 days, then regularly thereafter, including when dose ↑ or when a diuretic is added or ↑.
5. Target dose in heart failure.
6. Target dose in CAD.
7. Target dose post-MI.
8. Lower dose in renal failure.
9. Side effects of ARBS: same as ACEI but no cough and less dizziness and headache.
   Drug Interactions: same as ACEI.
   Contraindications and warnings: same as ACEI.

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Secondary Prevention of Ischemic Stroke

Goals:

- Prevent stroke and recurrent TIA
- Prevent cerebrovascular and cardiovascular mortality

Non-pharmacologic Management

- Smoking cessation
- Lifestyle modifications (achieve and maintain healthy weight; reduce alcohol, salt, and fat intake)
- Rehab therapy (physiotherapy, occupational therapy, speech therapy) as indicated

Pharmacologic Management

- **Antiplatelet and Anticoagulant Agents**
  -are drugs of choice for long-term prevention of stroke
  -ASA 80-325mg/day is well-tolerated and effective
  -ASA 100mg/d+warfarin in patients with heart valves, however ↑risk of bleeding
  -use clopidrogel 75mg/d if ASA intolerant
  -ASA+clopidrogel ↑ risk of bleeding; also ↑ risk of intracranial hemorrhage in persons with previous history of stroke thus the combination is not recommended for the long-term secondary prevention of stroke
  -ticlopidine 250mg BID is not recommended for the long-term prevention of stroke because of the risk of neutropenia and other side effects
  -warfarin is used to prevent stroke from emboli of cardiac origin (acute MI, AF, heart valves)
  -dipyridamole/ASA (Aggrenox) BID is an alternative for prevention of non-cardiogenic stroke
  -Aggrenox + ASA 81mg/d is reasonable in patients with concomitant CAD

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Heart Failure

- Systolic HF: LVEF ≤40%
- HF with preserved systolic function: signs and symptoms of HF with LVEF >40%

Signs and Symptoms

- Classic: dyspnea, edema, fatigue
- Common: orthopnea, exercise intolerance, cough, weight gain, abdominal distention, nocturia, cool extremeties
- Warning signs: ↑SOB with mild exercise; waking up at night with sudden SOB or chest discomfort; ↑fatigue or weakness; swelling in feet/ankles; rapid weight gain (2lbs in 2 days or 5 lbs in 1 week)
- If HR>SBP and patient is post-op or poor nutrition, consider thiamine deficiency (correct with vitamin B1 100mg OD)

Factors that Exacerbate Heart Failure

- Patient-specific:
  -non-compliance with medication or diet;
  -anemia; arrhythmias;
  -myocardial ischemia;
  -pulmonary embolism;
  -renal dysfunction;
  -thyroid dysfunction;
  -uncontrolled hypertension;
  -valvular heart disease;
  -infections
  -post-op or poor nutrition
- Medications:
  - drugs that cause sodium and fluid retention (NSAIDs; corticosteroids, minoxidil, androgens),
  -glitazones,
  - drugs with high sodium content (ex Eno);
  - products containing licorice
  -negative inotropes (antiarrythmics except amiodarone and dofetilide, beta-blockers, CCB except amlodipine and felodipine; itraconazole
  -cardiotoxic drugs (alcohol, certain cancer drugs, cocaine, others)

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Heart Failure cont'

Classification (New York Heart Association Functional Classification)

Class I – no symptoms

Class II – symptoms occur with ordinary activity

Class III – symptoms occur with less than ordinary activity

Class IV - symptoms occur with minimal activity or at rest

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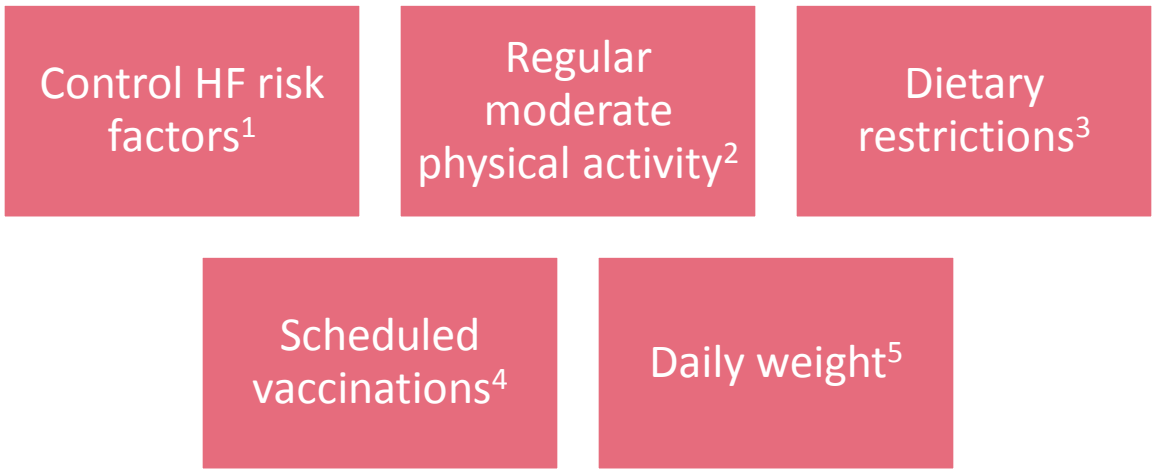
Heart Failure cont'

Non-pharmacologic Management



1. Heart failure risk factors: hypertension, obesity, diabetes, supraventricular arrhythmias, dyslipidemia, CAD, and other vascular diseases.
2. In stable patients; 30-45minute session 3-5 times/week.
3. Limit alcohol intake to no more than 1 standard drink/day; restrict sodium intake to <2-3g/day (<1-2g/day in severe HF); restrict fluid intake to <1.5-2.0L/day in patients with hyponatremia or fluid retention not controlled with diuretics; not more fluid than what is required to prevent thirst.
4. Annual influenza and H1N1 vaccination. Pneumonia vaccination every 5 years. Ensure all other vaccinations are up to date.
5. Patients should weigh themselves in the morning. Patients who gain >0.5kg/day on several consecutive days or 2kg in 3 days should seek medical attention.

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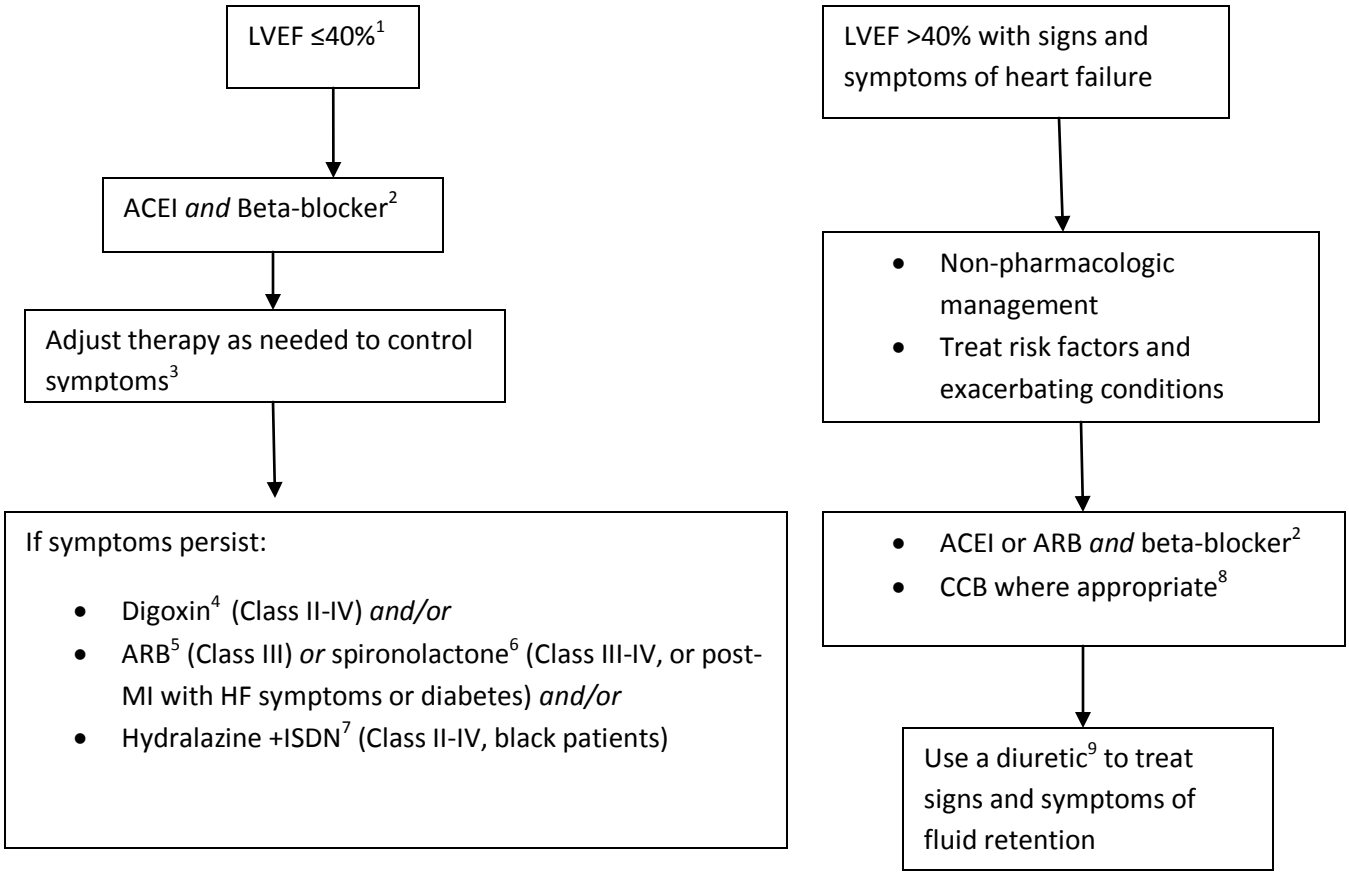
Heart Failure cont'

Pharmacologic Management



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Heart Failure cont'

Pharmacologic Management

1. With or without symptoms of HF (dyspnea, fluid retention, fatigue).
2. Unless contraindicated (see next section). Titrate to target doses: double beta-blocker dose q2weeks, double ACEI dose q1week. An ARB may be used if ACEI is not tolerated. May have to ↓dose of other antihypertensives in order to achieve target dose of ACEI and beta-blocker. Systolic BP <100mmHg is OK if no symptoms of hypotension.
3. Use diuretics to control fluid retention. A combination of diuretics may be needed with severe symptoms. Thiazide diuretics can be used with minimal fluid retention, but furosemide is needed for most patients. SCr and electrolytes should be measured before and 3-7 dyas after starting a diuretic, then when necessary after dose increases (until K^+ and renal function are stable). K^+ should be maintained at ≥4mmol/L to avoid ventricular arrhythmias and digoxin toxicity. Amiloride and Triamterene are used only to prevent ↓K^+ and ↓Mg in patients treated with thiazides or furosemide. The role of spironolactone is described below.
4. Digoxin improves symptoms but does not reduce mortality in HF patients. It may be considered for atrial fibrillation where beta-blockers are not effective or are not tolerated. It has a narrow therapeutic window (0.6-1.0nmol/L), so levels should be monitored when renal function declines, an interacting drug is added or discontinued, or when digoxin toxicity is suspected.
5. ARB may be given with an ACEI if symptoms persist despite optimal dose of ACEI and beta-blocker. ARB + ACEI may also be considered if patient cannot tolerate beta-blocker. Vital signs, K^+, and SCr must be closely monitored. Some recent information recommends not using ACEI and ARB together. Using spironolactone with ARB+ACEI is not recommended.
6. Spironolactone should not be used in patients with baseline K^+ > 5.0mmol/L, SCr >221µmol/L, or CrCl <30mL/min. In patients with CrCl 30-50mL/min, start with 12.5mg OD or every other day. Vital signs, SCr, and K^+ should be monitored 3-7 days after starting or ↑ dose of spironolactone, then when necessary until K^+ and renal function are stable. Thereafter, monitor q30d for 3 months, then q3months.
7. This combination is also beneficial in blacks with Class II HF and patients who cannot tolerate ACEI or ARB. ISDN does not reduce mortality when used without hydralazine. Nitrate monotherapy may be useful for exercise-induced angina or dyspnea, paroxysmal nocturnal dyspnea, and orthopnea.
8. CCB improve symptoms by ↓HR and ↑ diastolic filling time. (Unless contraindicated – see page 26). Amlodipine and felodipine are used in HF. Diltiazem and verapamil should be avoided because of their negative inotropic effects. Evidence for nifidipine use is lacking.
9. Use diuretics with caution in this situation because excessive dieresis may ↓cardiac output and compromise renal function.

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Heart Failure cont'

Pharmacologic Agents

Drug	Trade Name	Initial Dose	Target Dose
ACEI[1]			
Captopril[2]	Capoten	6.25mg-12.5mg TID	25-50mg TID
Enalapril[2]	Vasotec	1.25-2.5mg BID	10mg BID
Lisinopril[2]	Zestril, Prinivil	2.5-5mg OD	20-35mg OD
Ramipril[2]	Altace	1.25-2.5mg BID	5mg BID
Trandolapril[2]	Mavik	1mg OD	4mg OD
ARB[1]			
Candesartan	Atacand	4mg OD	32mg OD
Valsartan	Diovan	40mg BID	160mg BID
Beta-blockers[1]			
Bisoprolol	Monocor	1.25mg OD	10mg OD
Carvedilol	Coreg	3.125mg BID	25mg BID
Diuretics			
Chlorthalidone[2,3]		50-100mg OD	Max 200mg OD[4]
Hydrochlorothiazide[2,3]		25-100mg/day OD or BID	Max 200mg/day[4]
Metolazone[3]	Zaroxolyn	2.5-10mg OD[4]	
Furosemide[5]	Lasix	20-500mg/day OD or BID[6]	
Ethacrynic acid[2,5,7]	Edacrin	50-200mg/day OD or BID	
Spirololactone[2,8]	Aldactone	12.5mg OD	25-50mg OD
Vasodilators			
Hydralazine[9]		37.5mg TID	75mg TID
Isosorbide dinitrate[10]		20mg TID	40mg TID
CCB[1]			
Amlodipine	Norvasc	2.5-10mg OD	
Felodipine	Plendil, Renedil	2.5-10mg OD	
Inotropics			
Digoxin[2,11]	Lanoxin	0.0625-0.25mg OD	

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Heart Failure cont'

Pharmacologic Agents cont'

1. See page 30 for Side Effects, Drug Interactions, and Contraindications.
2. ↓dose in renal impairment.
3. Thiazide diuretic. Use in patients with mild HF or with a loop diuretic. See previous section for other comments on their use in HF. Dose 30 minutes before furosemide.
   Side Effects: lower doses are well-tolerated; rash; allergic reaction; photosensitivity; ↑calcium; ↑uric acid; ↑cholesterol; ↑glucose; ↓sodium; ↓potassium; ↓magnesium;↓zinc; pancreatitis; sexual dysfunction.
   Drug Interactions: Digoxin (toxicity if K^+ is low); ↑lithium; NSAIDs (loss of BP control), corticosteroids (↓K^+)
   Contraindications: symptomatic hyperuricemia (gout); sulfa allergy; anuria; hyponatremia
4. Use lower dose when combined with a loop diuretic and monitor carefully.
5. Loop diuretics. See previous section for comments on their use in HF.
   Side Effects: dehydration; ↓(K^+, magnesium, calcium); ↑(glucose, uric acid, glucose, lipids); azotemia; nausea; anorexia; weakness; fatigue; rash; ototoxicity at high doses
   Drug Interactions: Digoxin (toxicity if K^+ is low); ↑lithium; NSAIDs (loss of BP control), corticosteroids (↓K^+)
   Contraindications: symptomatic hyperuricemia (gout); sulfa allergy; anuria; hyponatremia
6. May be given BID or TID in decompensated HF.
7. An alternative in the case of allergy to furosemide. ↑ototoxicity than furosemide.
8. Aldosterone antagonist; potassium-sparing diuretic.
   Side Effects: ↑K^+ (especially in renal failure, diabetes; avoid if K^+ >5mmol/L); ↓Na; dehydration; rash; gynecomastia; abnormal menstruation; GI ulcers
   Drug Interactions: ↑K^+ with ACEI, ARB, potassium supplements; ↓diuretic effect, worsening renal function with NSAIDs
9. Used in combination with ISDN for HF.
   Side Effects: reflex tachycardia; headache; edema; Lupus syndrome (at high doses); aggravate angina; dizziness; hepatitis
   Contraindications: left ventricular hypertrophy, dissecting aortic aneurism, rheumatic heart disease
10. Use in combination with hydralazine for HF. Allow 10-12 hour nitrate-free period to prevent tolerance.
    Side Effects: headache (usually resolves with time); ↑HR; ↓BP; syncope; dizziness; flushing; edema.
    Drug Interactions: potentiates hypotensive effect of vasodilators
    Contra-indications: concomitant administration with PDE5 inhibitors (Viagra, Cialis, Levitra)
11. See previous section for comments about its use in HF.
    Side Effects: anorexia, nausea, vomiting, visual disturbances, fatigue, dizziness, confusion, delirium, cardiac arrhythmia
    Drug Interactions: many potential including ↑levels with amiodarone, quinidine, verapamil, propafenone, macrolides, tetracycline, itraconazole, cyclosporine, certain HIV meds; ↓levels with antacids, cholestyramine, sulfasalazine, neomycin, rifampin, St. John's Wort; ↑risk of bradycardia with beta-blockers, amiodarone, verapamil, diltiazem
    Contraindications: ventricular fibrillation, with caution in acute MI, AV block, bradycardia, thyroid disease, chronic constrictive pericarditis

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Peripheral Vascular Disease

Intermittent Claudication

- Symptom of severe atherosclerotic disease of the peripheral vasculature; leads to arterial insufficiency
- Symptoms occur intermittently and disappear after a period of rest
- Signs/symptoms: cyanosis, hair loss and shiny skin of affected limb; ↓temperature and↓ pulse of affected limb; pain; paralysis and paresthesia
- Defined by the distance (in blocks) the patient can walk before pain occurs. Doppler ankle/arm systolic pressure index is used to classify obstruction (<0.5 – severe obstruction; 0.5-0.9 – mild to moderate obstruction; >0.95 - normal)
- Patients with intermittent claudication are at risk for other cardiovascular complications and should be treated accordingly.

Non-pharmacologic Management:

- Smoking cessation
- Optimise treatment of associated diseases (hypertension, dyslipidemia, diabetes) and risk factors (TIA/stroke, angina/MI)
- Achieve and maintain healthy body weight
- Regular dynamic leg exercise. Start with 5 times per week for 8 weeks. Continued exercise for 6 to 12 months after onset of claudication allows collateral circulation to develop. Exercise ≥3 times per week for 2 to 3 years slows functional decline.

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Peripheral Vascular Disease

Intermittent Claudication cont'

Pharmacologic Management:

- The role of drug therapy for intermittent claudication is mostly to minimize cardiovascular risk factors. Medications to improve mobility and restore circulation are limited.
- **Anti-platelet agents:** Clopidrogel may be more effective than ASA in PVD but tends to be used only when ASA is not tolerated or in combination with ASA when ASA alone fails to prevent CV events. Routine use of ASA+clopidrogel is not recommended because of ↑ risk of bleeding.
- **ACEI:** ↓risk of ischemic events beyond what would be expected from lowering BP in patients with PVD
- **Beta-blockers:** these agents have previously not been used in patients with PVD because they were thought to worsen the condition. However, since they do not seem to affect walking capacity in patients with PVD, they may be used to treat hypertension in this population. Beta-blockers should be used cautiously in severe PVD and are not recommended in persons >60 years without compelling indications (angina or recent MI).
- **Lipid-lowering agents:** ↓risk of CV event and may improve symptoms of intermittent claudication
- **Pentoxiphylline:** ↓ blood viscosity, platelet reactivity, and plasma hypercoagulability
  Mild claudication: not indicated
  Moderate claudication: smoking cessation and dynamic leg exercises are more effective than pentoxiphylline
  Severe claudication: 400mg TID; start with 8 week trial; if symptoms improve (ie 50% improvement in walking distance), continue for a total of 24 weeks , then allow 8 week drug-free period; consider as adjuvant for trophic ulcers
  Side Effects: nausea, vomiting, dyspepsia, bloating, flatulence, dizziness, nervousness, agitation, flushing, palpitations
  Drug Interactions: ↓effect of adenosine; ↑effect of theophylline, wafarin, sympathomimetics, antihypertensives, hypoglycemics
  Contraindications: acute MI; hemorrhage; peptic ulcer disease; xanthine intolerance (ex theophylline). Not recommended in hepatic or renal dysfunction.
- **Other therapies:** warfarin, heparin, vitamin E, and chelation therapy are not effective for PVD. Bypass surgery or angioplast are considered for severe disease to prevent need for amputation. Paresthesia and paralysis require immediate surgical intervention.

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Peripheral Vascular Disease

Venous Thromboembolism (Pulmonary Embolism and Deep Vein Thrombosis)

Signs and Symptoms

- VTE: leg pain; edema; erythema; warmth of affected limb; may be distension of collateral veins
  Differential diagnosis: muscle or tendon tear; muscle strain; knee injury; edema from inactivity; lymphatic disorders; venous reflux; cellulitis; Baker's cyst
- PE: dyspnea; pleuritic chest pain; cough; leg edema; leg pain; hemoptysis; palpitations; tachypnea; rales; diaphoresis; 4^{th} heart sound; accentuation of 2^{nd} heart sound
  Differential diagnosis: aortic dissection; angina; CHF; pericardial disease; asthma; acute exacerbation of COPD; pneumonia; pneumothorax; musculoskeletal conditions; esophageal spasm; malignancy; anxiety
- Note that 50% of patients with DVT have asymptomatic PE at the time of diagnosis.

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Peripheral Vascular Disease

Venous Thromboembolism (Pulmonary Embolism and Deep Vein Thrombosis)

Risk Categories and Prophylaxis

Risk Group	Clinical Features	Prophylactic Measures[1]
Low	Minor surgery (<30minutes); no risk factors[2] besides age Major surgery (>30minutes); <40years and no other risk factors Minor trauma or medical illness	• Mobilize • Graduated compression stockings
Moderate	Major surgery[3]; ≥40years or other risk factor Major illness[4] Major trauma or burns Minor surgery, trauma, or illness in patients with previous DVT, PE, or thrombophilia	• Low molecular weight heparin • Graduated compression stockings • External pneumatic compression
High	Fracture or major orthopaedic surgery of the hip, pelvis, or lower limb Major pelvic or abdominal surgery for cancer Major surgery, trauma, or illness in patients with previous DVT, PE, or thrombophilia Lower limb paralysis (hemorrhagic stroke, paraplegia) Major lower limb amputation	• Fondaparinux[5] • Low molecular weight heparin • External pneumatic compression

1. Continue combination of listed factors as indicated for a minimum of 5-7 days until the patient is ambulant.
2. Risk factors for VTE: ↑age; obesity; smoking; previous VTE; cancer therapy; pregnancy; estrogen-containing contraceptives or hormone therapy; selective estrogen receptor modulators (raloxiphene); heart or respiratory failure; inflammatory bowel disease; nephritic syndrome; myeoprolipherative disorders;
3. IE major general, urologic, gynaecologic, cardiothoracic, vascular, or neurologic surgery.
4. IE heart or lung disease, cancer, inflammatory bowel disease
5. Orthopaedic surgery only.

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Peripheral Vascular Disease cont'

Venous Thromboembolism (Pulmonary Embolism and Deep Vein Thrombosis)

Management:

- **Graduated compression stockings** and **pneumatic compression** ↓risk of VTE and are useful in clinical settings where the risk of bleeding is high (ex after neurosurgery)
- **Low molecular weight heparin** are approved for the prophylaxis and treatment of VTE. Their kinetics are more predictable and their half-life longer than unfractionated heparin.
- **Unfractionated heparin** is used to treat VTE. The dose is adjusted according to the aPTT.
- **Warfarin** is dosed to maintain INR 2-3. INR is measured daily or every other day for the first few days, then every 3 days for a week, then once or twice a week, then every 2 to 4 weeks once stable. Warfarin therapy is initiated concomitantly with LMWH in the treatment of DVT. LMWH is continued for about 5 days or until INR 2-3 is maintained for 2 consecutive days.
- **Anticoagulation in pregnancy and breastfeeding:** use UFH or LMWH during pregnancy but stop at first signs of labor. Warfarin or UFH can be used for about 6 weeks postpartum for secondary prevention of VTE. Warfarin is safe while breastfeeding.

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Peripheral Vascular Disease cont'

Pharmacologic Management of VTE

Drug	Trade Name	Dose (Treatment)	Dose (Prophylaxis)
Low molecular weight heparins[1]			
Dalteparin	Fragmin	200 IU/kg sc q24h (max 18000 IU/day)	General surgery:2500 IU sc daily Orthopedics: 5000 IU sc daily
Enoxaparin	Lovenox	100 IU/kg sc BID or 150 IU sc Q24h (max 18000 IU/day)	General surgery: 4000 IU sc daily Orthopedics: 3000 IU sc q12h
Nadroparin	Fraxiparin	171 IU/kg sc q24h or 86 IU/kg BID (max 17100 IU/day)	General surgery: 2850 IU sc daily Orthopedics: 38 IU/kg sc q12h x 2 then q24h to postop day 3 then 57 IU/kg daily
Tinzaparin	Innohep	175 IU/kg sc q24h (max 18000 IU/day)	General surgery: 3500 IU sc q24h Orthopedics: 50-75 IU/kg sc q24h
Specific Factor Xa Inhibitors			
Fondaparinux[2]	Arixtra	<50kg: 5mg sc daily 50-100kg: 7.5mg sc daily >100kg: 10mg sc daily	<50kg not recommended ≥50kg 2.5mg daily after high-risk orthopedic surgery
Rivaroxaban[3]	Xarelto	Not used to treat VTE	Orthopedics: 10mg po OD
Unfractionated heparin[4]			
Heparin	Hepalean	IV infusion most common; dose to achieve therapeutic aPTT[5] *Or* 5000-10000 IU iv bolus followed by 15000-20000 IU sc q12h adjusted to maintain therapeutic aPTT	General surgery: 5000 IU sc q12h or q8h
Oral anticoagulants[6]			
Warfarin	Coumadin	Adjusted to maintain INR 2.0-3.0; usually 0.5-5mg orally OD IV dose[7]: same as oral given as a slow bolus over 1-2 minutes	

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Peripheral Vascular Disease

Pharmacologic Management of VTE cont'

2. Adjust dose in renal impairment.
   Side Effects: bleeding; heparin-induced thrombocyctopenia; osteoporosis
   Contraindications: history of heparin-induced thrombocytopenia; active bleed; severe hypertension; hemorrhagic stroke; allergy to pork or heparin.
   Duration of prophylactic therapy is 7 to 10 days. When used to treat VTE, warfarin is started concomitantly and LMWH is continued until INR of 2-3 is reached (usually 5 days).
3. Side effects: bleeding; allergic reaction
   Adjust dose in renal impairment (not recommended in renal dysfunction)
4. Side effects: bleeding; nausea; anemia; ↑liver enzymes
   Drug Interactions: ↑bleeding with azole-antifungals and certain HIV meds
   Contraindications: active bleed; hepatic disease; bleeding disorder; stroke/TIA within last 6 months; pregnancy; breastfeeding; not recommended in renal failure
   Drug is initiated within 6 to 10 hours of surgery. The duration depends on the type of surgery: hip replacement – 35 days; knee replacement – 14 days.
5. Side Effects: bleeding; heparin-induced thrombocytopenia (monitor platelets during first week of therapy); osteoporosis
   Contraindications: history of heparin-induced thrombocytopenia
   Duration of therapy for prophylaxis is 5 to 7 days or until patient is ambulatory (whichever is longer). When used to treat VTE, warfarin is started concomitanty and UFH is continued for at least 5 days – until INR of 2 to 3 is achieved for 2 consecutive days.
6. Therapeutic range is determined by the facility's lab. IV infusion should be adjusted to give aPTT 1.5 to 2.5 times control.
7. Side Effects: bleeding; hair loss; blue fingers and toes; skin necrosis.
   Drug Interactions: many potential. Monitor INR carefully when inducing drug is started, discontinued, or dose changed and adjust dose of warfarin accordingly**. Ensure patients are educated about potential for drug interactions with warfarin (including herbal products) and to seek advice before self-medicating.**
8. IV warfarin is an alternative in patients who cannot take it orally. Do not administer warfarin IM.

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Abbreviations

A1C – glycated haemoglobin

ACEI – angiotensin converting enzyme inhibitor

AF – atrial fibrillation

ALT – alanine transaminase

aPTT – activated partial thrombin time

ARB – angiotensin receptor blocker

ASA – acetylsalicylic acid

AV – atrioventricular

BMI – body mass index

BMS – bare metal stent

BP – blood pressure

BUN – blood urea nitrogen

CAD – coronary artery disease

CCB – calcium channel blocker

CHD – coronary heart disease

CHF – congestive heart failure

CK – creatinine kinase

CNS – central nervous system

CrCl – creatinine clearance

CVD – cardiovascular disease

DES – drug eluding stent

DHA – docosahexanoic acid

DHP – dihydropyridine

EPA – eicosapentanoic acid

FRA-Framingham risk assessment

GFR – glomerular filtration rate

GI – gastrointestinal

HDL – high density lipoprotein

HIV – human immunodeficiency virus

HR – heart rate

HTN – hypertension

INR – international normalized ratio

ISDN – isosorbide dinitrate

K^+ - potassium

LDL – low density lipoprotein

LFT – liver function test

LMWH – low molecular weight heparin

LVEF – left ventricular ejection fraction

MAOI – monoamine oxidase inhibitor

Mg – magnesium

MI – myocardial infarction

Na – sodium

NRT-nicotine replacement therapy

NSAID – nonsteroidal anti-inflammatory drug

NTG – nitroglycerine

PE – pulmonary embolism

PHQ – patient health questionnaire

PVD – peripheral vascular disease

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Abbreviations cont'

SCr – serum creatinine

SOB – shortness of breath

STEMI – ST segment elevation MI

SVG – saphenous vein graft

TC – total cholesterol

TIA – transient ischemic attack

UFH – unfractionated heparin

ULN – upper limits if normal

VTE – venous thromboembolism

WC – waist circumference

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