

# Cardiovascular disease....

What is new, what is different?

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# Introduction

# What is cardiovascular disease?

- Cardiovascular disease is any disease of the heart or the blood vessels.
- Cardiovascular diseases include;
  - arteriosclerosis,
  - coronary artery disease,
  - heart valve disease,
  - arrhythmia,
  - heart failure,
  - hypertension,
  - orthostatic hypotension,
  - shock,
  - endocarditis,
  - diseases of the aorta and its branches,
  - disorders of the peripheral vascular system,
  - congenital heart disease.

# Epidemiology

- Cardiovascular diseases (CVD) are the leading cause of death globally.
- According to the WHO, CVD resulted in 17.9 million deaths (32.1%) in 2015, (12.3 million (25.8%) in 1990).
- Coronary artery disease and stroke account for 80% of CVD deaths in males and 75% of CVD deaths in females.
- Most cardiovascular disease affects older adults.
- In the United States 11% of people between 20 and 40 have CVD, while 37% between 40 and 60, 71% of people between 60 and 80, and 85% of people over 80 have CVD.
- The average age of death from coronary artery disease in the developed world is around 80 while it is around 68 in the developing world.
- Diagnosis of disease typically occurs seven to ten years earlier in men as compared to women.

# Risk factors

- Modifiable

- Obesity = *BMI >30 OR waist circumference >35 inches (88 cm) in women and >40 inches (102 cm)*
- Insulin resistance/diabetes
- High cholesterol
- High blood pressure
- Being physically inactive
- Smoking
- Sleep apnoea
- Eating an unhealthy diet
- Clinical depression
- High stress levels

# Complications of cardiovascular disease

- Heart failure
- Arrhythmias
- Myocardial infarction
- Stroke
- Kidney failure
- Peripheral artery disease and limb gangrene

What is new?

Hypertension

# Diagnosis

- New hypertension guidelines (JNC 8) have lowered the threshold for the diagnosis and treatment of hypertension.

## Blood Pressure Categories



BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
<b>NORMAL</b>	<b>LESS THAN 120</b>	<b>and</b>	<b>LESS THAN 80</b>
<b>ELEVATED</b>	<b>120 – 129</b>	<b>and</b>	<b>LESS THAN 80</b>
<b>HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1</b>	<b>130 – 139</b>	<b>or</b>	<b>80 – 89</b>
<b>HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2</b>	<b>140 OR HIGHER</b>	<b>or</b>	<b>90 OR HIGHER</b>
<b>HYPERTENSIVE CRISIS (consult your doctor immediately)</b>	<b>HIGHER THAN 180</b>	<b>and/or</b>	<b>HIGHER THAN 120</b>

# Treatment

- In the general population ***younger*** than 60 years, initiate ***pharmacologic*** treatment to lower BP at 140/90 or higher and treat to a goal BP of lower than 140/90 mm Hg.
- In the general population ***aged 60 years or older***, initiate ***pharmacologic*** treatment at blood pressure 150/90 mmHg. Treat to a goal BP lower than 150/90 mm Hg.
- In the population aged 18 years or older with ***diabetes***, initiate ***pharmacologic*** treatment to lower BP at 140/90 or higher and treat to a goal BP of lower than 140/90 mm Hg.

# Treatment

- Emphasis on lifestyle modification
  - Low salt diet
  - Weight loss
  - Daily exercise
  - Diet low in refined carbohydrates and high in fiber, including fruits and vegetables

- The main objective of hypertension treatment is to attain and maintain goal BP.
- If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug.
- The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided.
- Do not use an ACEI and an ARB together in the same patient.
- We may need to use more than 3 drugs to reach goal BP

# When to refer?

- Once Blood pressure is elevated > 140/90mmHg
- Benefits:
  - Investigations can be done to assess co-morbidities, complications or identify possible causes, and treatment offered accordingly.
  - Patients' progress can be followed up

Cholesterol

# Guidelines

- 2018 — New cholesterol guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) highlight more personalized risk assessments and new cholesterol-lowering drugs for people at the highest risk for cardiovascular disease.
- The updated guidelines reinforce the importance of healthy living, lifestyle modification and prevention.
- Having high cholesterol at any age increases CVD risk significantly. Therefore, even at a young age, people should follow a heart-healthy lifestyle, as well as understand and maintain healthy cholesterol levels.

- In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statins or maximally tolerated statins to decrease ASCVD risk. Reduce LDL-C levels by  $\geq 50\%$ .
- In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dl (1.8 mmol/L) to consider addition of non-statins to statins
- In patients with severe primary hypercholesterolemia (LDL-C level  $\geq 190$  mg/dl [ $\geq 4.9$  mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy.
- In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.
- In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels  $\geq 70$  mg/dl ( $\geq 1.8$  mmol/L), at a 10-year ASCVD risk of  $\geq 7.5\%$ , start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

# Diet

- Eggs are now considered not to significantly raise cholesterol levels.
- Some studies show an individual can eat up to 12 eggs per week with no appreciable effects on serum cholesterol!!!
- Moderation is key.
- It is thought that the methods used in cooking the eggs matter; thus boiled or poached eggs are healthier than omelets or fried eggs because of the added fat content

# Risk assessment apps

- Individualized care is now being recommended for elevated cholesterol management.
- To aid in this, mobile phone/computer apps have been developed to calculate the lifetime cardiovascular disease risk of each individual patient.
- The risk calculator introduced in the 2013 guidelines remains an essential tool to help healthcare providers identify a patient's 10-year risk for CVD.
- Because the calculator uses population-based formulas, the guidelines now urge doctors to talk with patients and provide a more personalized perspective of a person's risk.
- Examples: WHO CV risk calculator ASCVD plus app

# New drugs

- New class of drugs may change the face of lowering LDL cholesterol. These drugs are known as the PCSK9 Inhibitors.
- The PCSK9 inhibitors are a class of injectable drugs that have been shown to dramatically lower LDL cholesterol levels -- by up to 60% in some cases -- when combined with a statin.
- PCSK9 inhibitors are monoclonal antibodies.
- They bind to and inactivate proprotein convertase subtilisin kexin 9 (PCSK9) located in the liver
- PCSK9 inactivates the receptors on the liver cell surface that transport LDL into the liver for metabolism.
- PCSK9 blockade causes more receptors to be available to capture LDL for break down and removal from circulation.
- Drawback: Expensive \$14,000 per annum in the US, injectable

# When to refer?

- Elevated cholesterol with ASCVD risk  $>7.5\%$  Or patients with established ASCVD regardless of cholesterol levels

Diabetes

# Guidelines

- Emphasis on heart health and cardiovascular protection.
- Physicians are encouraged to prescribe more “Cardio protective” medications
- All glycemic targets should be individualized
- Optimal level of glycated hemoglobin (HbA1c) is  $\leq 6.5\%$

# Criteria for the diagnosis of diabetes

- Fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.\*
- OR
- 2-h PG  $\geq 200$  mg/dL (11.1 mmol/L)
- OR
- HbA1C  $\geq 6.5\%$  (48 mmol/mol)

# New medications

- **SGLT2 inhibitors (Gliflozins):**
  - They act by inhibiting sodium-glucose transport protein 2 (SGLT2) located in the renal tubules of the kidneys which are responsible for reabsorbing glucose back into the blood.
  - As a result, more glucose is excreted in the urine. SGLT-2 inhibitors have been shown to be effective at lowering hemoglobin A1c levels, improving weight loss and lowering blood pressure.
  - They carry a low risk of hypoglycemia (low blood sugar levels).

- Gliflozins have been found to exhibit
  - Cardioprotective
  - Renoprotective
  - Anti-hyperlipidemic
  - Anti-atherosclerotic
  - Anti-obesity
  - Anti-neoplastic
  - Hepatoprotective
  - Renoprotective effects in in vitro, pre-clinical, and clinical studies.
- These effects have been attributed to a variety of its pharmacodynamic actions such as natriuresis, deactivation of renin-angiotensin-aldosterone system, alterations in energy homeostasis, glycosuria, lipolysis, anti-inflammatory, and anti-oxidative actions

- They are usually well tolerated. SGLT-2 inhibitors may be used in the treatment of type 2 diabetes and act independently of beta-cell function in the pancreas.
- Adverse effects:
  - Urinary tract infections
  - Osmotic Diuresis
- Examples
  - Canagliflozin (Invokana)
  - Dapagliflozin (Farxiga)
  - Empagliflozin (Jardiance)

# Inhaled insulin:

Fast acting, taken only at mealtimes. It comes in 4-unit and 8-unit cartridges that is used in an inhaler like device.

## Pros

- Fewer injections for the patient
- Easier administration
- The lungs provide a large vascular area for quicker absorption of the drug.
- Better adherence to treatment regimens

## Cons

- Possible damage to lung tissue
- The need for lifestyle changes is still necessary
- Higher costs
- Due to the nature of inhaled medications appropriate dosage can be an issue.
- Patient participation and correct inhalation maneuvers
- Loss of the drug in the device chamber or in the upper airway

- Side effects
  - Sudden or serious lung problems
  - Hypoglycemia
  - Cough
  
- Contraindications
  - Insulin allergies
  - Smokers or those exposed to second hand smoke on a constant basis
  - COPD
  - History of lung cancer
  - Asthma

# Glucagon-like peptide-1 receptor agonists:

- Also known as GLP-1 receptor agonists or incretin mimetics, are agonists of the GLP-1 receptor.
- Binding of GLP-1 to the receptor on the beta cell results in stimulation of insulin secretion.
- GLP-1 also has potential effects on beta cell mass by stimulation of beta cell proliferation, and inhibition of beta cell apoptosis.
- GLP-1 inhibits glucagon secretion
- Inhibits hepatic glucose production
- Decreases gastrointestinal motility and promotes satiety
- Studies show cardioprotection
- Chronic administration of GLP-1 receptor agonists leads to weight loss
- They have a lower risk of causing hypoglycemia.
- Injectable
- Examples: Exenatide

# Insulin

- 42hour long acting insulin Insulin degludec
- Given once a day
  
- Pros:
- Alternate day dosing can be done
- Sugar control is maintained even if patient skips a dose

# When to refer

- Diabetes treatment goes beyond sugar control and there are a lot of parameters to be monitored and clinical features to consider when prescribing for these patients.
- All diabetics should be referred once the diagnosis is made and sugar is not controlled by lifestyle alone.

Obesity

- Diet, exercise, and behavioral modification should be included in all obesity management approaches for body mass index (BMI) of 25 kg/m<sup>2</sup> or higher.
- Other tools, such as
  - Pharmacotherapy for BMI of 27 kg/m<sup>2</sup> or higher with comorbidity or BMI over 30 kg/m<sup>2</sup>
  - Bariatric surgery for BMI of 35 kg/m<sup>2</sup> with comorbidity or BMI over 40 kg/m<sup>2</sup>

Should be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when this is possible.

# Medication

- Few medications are available for the management of obesity.
- Generally, the medications approved by the US Food and Drug Administration (FDA) for obesity are intended for patients with a BMI of 30 or above (obese) **OR** of 27 or above (overweight) with a weight-related risk factor (eg, diabetes, hypertension).
- All are indicated as adjuncts to caloric restriction, increased physical activity, and behavior modification.
- Currently, the 3 major groups of drugs used to manage obesity are as follows:
  - Centrally acting medications that impair dietary intake
  - Medications that act peripherally to impair dietary absorption
  - Medications that increase energy expenditure

- Most medications for obesity are approved for short-term use only.
- Obesity is a chronic medical condition, and as with similar chronic conditions (eg, diabetes, hypertension), after therapeutic agents are stopped, the relapse rate is high.
- Some examples of obesity medications include:
  - Orlistat
  - Lorcaserin (a fixed-dose combination of immediate-release phentermine and extended-release topiramate),
  - A fixed-dose combination of bupropion and naltrexone .
- The list of potential anti-obesity agents being investigated has increased considerably with the explosion in knowledge of the pathogenesis of obesity.
- Improved understanding of the neuro-circuitry of the feeding-satiety cycle has provided many potential targets for designer therapeutic agents under development.

Heart failure

# Exercise

- Exercise training is an evidence-based adjunct treatment modality for patients with heart failure.
- The benefits of exercise training are clinically translated into left ventricular anti-remodeling effects, increased exercise capacity and reduced morbidity and mortality.
- Cardiopulmonary exercise testing is mandatory to assess exercise capacity objectively and to define training intensity.
- Ideally, a patient-tailored exercise training program is prescribed instead of a “one size fits all” approach.
- Increasing long-term adherence and reaching the frailest patients are challenging goals for future initiatives in the field.

# Exercise guidelines

- General exercise guidelines for patients with congestive heart failure include 20 to 30 minutes of aerobic exercise performed three to five times each week. Patients are generally advised to exercise for as long as they can, gradually increasing duration of exercise to reach this goal.
- The American Heart Association also recommends gradually warming up and cooling down to avoid strain on the heart.
- Strength training exercises for major muscle groups at least two times each week. Gradually increase the resistance as strength increases.

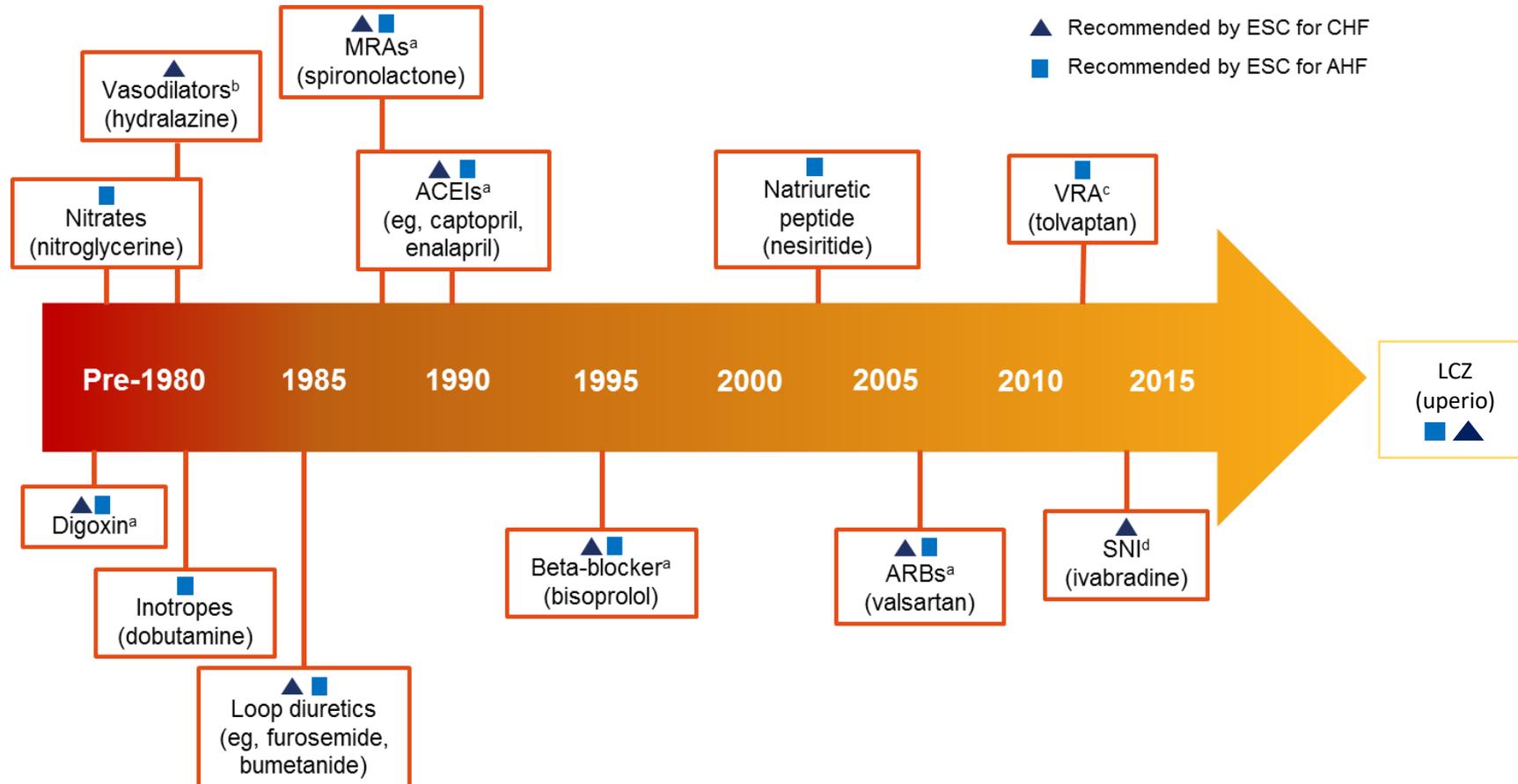
# Benefits

- Exercise training reduces neurohormonal stimulation, the production of proinflammatory cytokines and natriuretic peptide overexpression.
- Significant decrease in the peripheral organ injuries encountered in chronic heart failure, with a reduction in vascular resistance and improvements in endothelial dysfunction and the oxidative capacity of peripheral muscles.
- Ultimately, exercise training leads to a notable improvement in ventilatory capacity.
- Improvements in symptoms at rest, exercise capacity and quality of life.

# Medication

- Sacubitril/valsartan
- Bromocriptine in Peripartal cardiomyopathy

# Evolution of heart failure therapy



Only the first approval time for each therapeutic class is shown

<sup>a</sup>Recommended for AHF after stabilisation; <sup>b</sup>Recommendation for treatment of hypertension in patients with symptomatic HF (NYHA functional class II-IV) and LV systolic dysfunction; <sup>c</sup>Tolvaptan may be used to treat patients with resistant hyponatremia; <sup>d</sup>European Medical Agency has approved ivabradine for use in patients with a heart rate  $\geq 75$  bpm. May also be considered in patients with a contraindication to  $\beta$ -blockers.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; MRA: mineralocorticoid receptor antagonist; SNI: sinus node If channel inhibitor; VRA: vasopressin receptor antagonist

# EU and US product labels for sacubitril/valsartan

	ESC guideline recommendations <sup>1</sup>	Sacubitril/valsartan EU LABEL <sup>2</sup>
Class I B	Sacubitril/valsartan is recommended as a <b>replacement for an ACEi</b> to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi, a beta-blocker and an MRA	Sacubitril/valsartan is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction
	US focused update recommendations <sup>3</sup>	Sacubitril/valsartan US LABEL <sup>4</sup>
Class I BR	The clinical strategy of inhibition of the renin-angiotensin system with ACEi (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR <b>ARNI (Level of Evidence: B-R)</b> in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality	Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction  Sacubitril/valsartan is usually administered in conjunction with other heart failure therapies, in place of an ACEi or other ARB
Class I BR	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, <b>replacement by an ARNI</b> is recommended to further reduce morbidity and mortality	

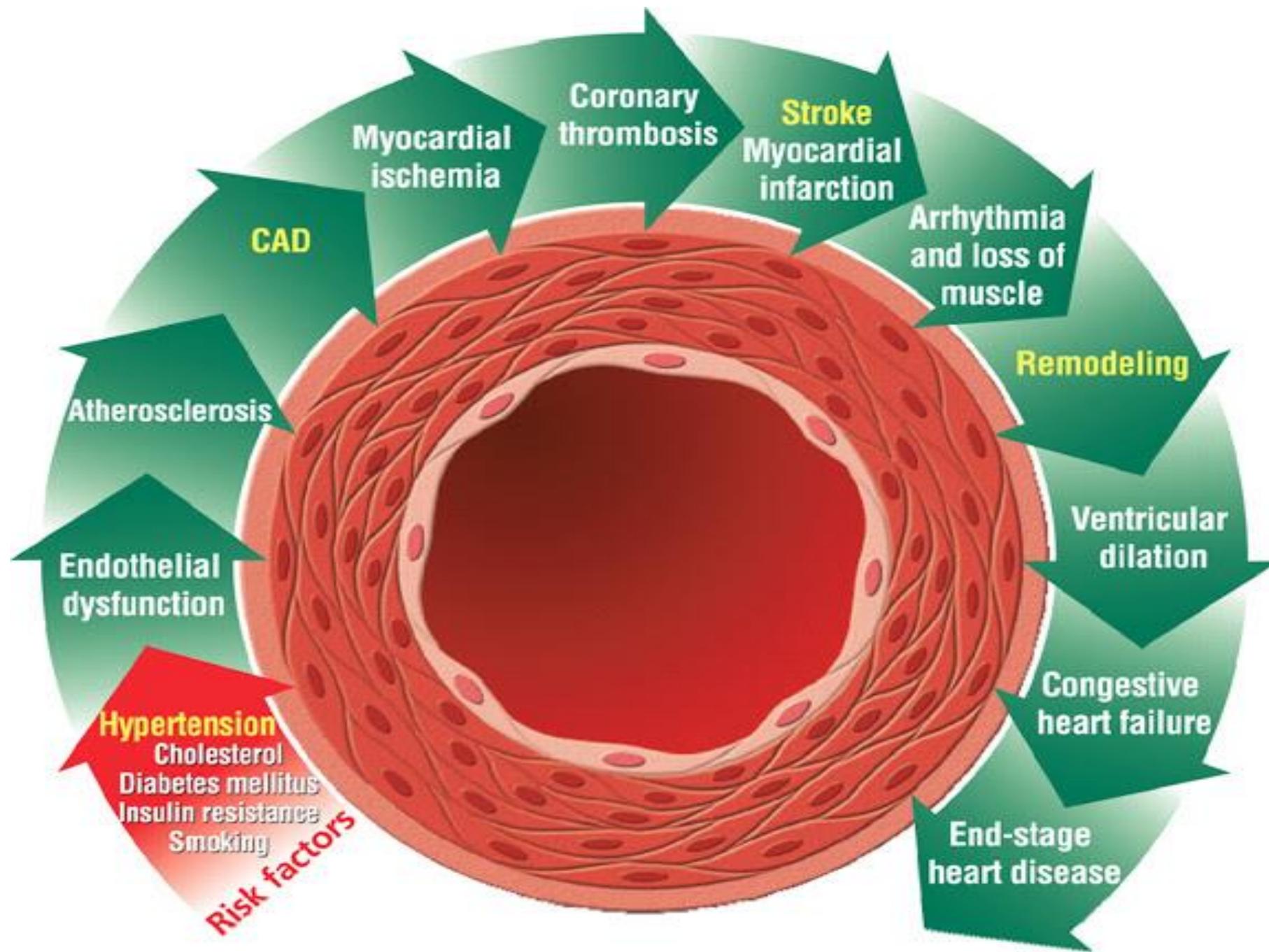
ACC, American College of Cardiology; AHA, American Heart Association; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker, ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFSA, Heart Failure Society of America; HFrEF, HF with reduced ejection fraction; NYHA, New York Heart Association

1. Ponikowski et al. Eur Heart J 2016;37:2129–2200; 2. Entresto (sacubitril/valsartan) [EU SmPC]; 3. Yancy et al. J Am Coll Cardiol. Published 21 May 2016. doi:10.1016/j.jacc.2016.05.011; 4. Entresto (sacubitril/valsartan) [US Full Prescribing Information]

# Peripartum cardiomyopathy

- Peripartum cardiomyopathy (PPCM) is a life-threatening, pregnancy-associated heart disease that develops towards the end of pregnancy or in the first months following delivery in previously healthy women.
- Oxidative-stress mediated cleavage of prolactin into a toxic 16-kDa prolactin fragment as a major factor driving the disease. This induces detrimental but potentially reversible effects on heart function.
- Bromocriptine, which blocks prolactin release, was initially tested in a PPCM mouse model where it efficiently prevented the onset of PPCM.
- Randomised trials further strengthen the role of bromocriptine in addition to standard heart failure therapy in clinical practice.

# The role of the Community Pharmacist in Cardiovascular disease management



- Pharmacists can improve access to routine screenings. Blood pressure, blood sugar, body mass index, cholesterol, and refer as appropriate.
- Patient counselling and encouragement on drug and lifestyle therapy adherence. Personalized follow up may be necessary (texts, emails and calls).
- Provide a friendly face to further counsel patients on their medical condition.
- Stocking good quality medication at an affordable price.
- Flexible opening times.
- Giving feedback to doctors on prescriptions and patient buying patterns.
- Documenting side effect patterns of medications

# Summary

- Cardiovascular disease is a leading cause of morbidity and mortality all over the world.
- Treatment of these diseases keep evolving.
- Prevention of cardiovascular disease as well as non drug management cannot be overemphasized.
- Collaboration between the doctor and the pharmacist is important for optimal patient care and treatment adherence.
- Our collective goal is to reduce the burden of cardiovascular disease in our communities as well as worldwide.

Thank you

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