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MEDICAL NOTES POWERHOUSE

# *Medical* Notes Powerhouse

The Complete High-Yield Notes for NEET SS & INI SS-ET

## *Cardiology*

**05** VOLUME
of 10 · Volume V · CH 243–294

**52** CHAPTERS

**7** SECTIONS

**10** VOLUME SET

SECTIONS IN THIS VOLUME

- CV Approach & Diagnostics
- EP & Arrhythmias
- Heart Failure & CMs
- Valvular Heart Disease
- Pericardium & Tumours
- Coronary Artery Disease
- HTN & Vascular

Sources Harrison's Principles of Internal Medicine, 22nd Edition

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SECTION I

# CV Approach & Diagnostics

*Clinical evaluation, ECG, imaging and cardiac catheterisation*

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# CH 243 · Approach to the Patient with Possible CV Disease — ...

*Opening chapter to CV section: scope of the problem, natural history, cardinal symptoms, NYHA functional classification, NYHA diagnostic schema, family history, ECG role, and approach to murmurs. Exam essentials = NYHA classes I–IV + the 4-element NYHA*

## Magnitude of the Problem

- CV diseases = **most prevalent serious disorders** in industrialized nations; rising in developing world.
- **Age-adjusted CHD mortality ↓ by 2/3** over past 4 decades in US (risk-factor reduction + better Rx).
- Still **~700,000 deaths/yr in US** from CV disease; **~1/3 sudden**.
- Diagnosed in **~50% of US adults**.
- **~19 million CV deaths/yr globally**.
- **Threats to progress**: obesity, T2DM, metabolic syndrome — may reverse gains in CHD age-adjusted mortality.
- CV disease = **leading cause of death in BOTH men and women**. Absolute CV deaths ↓ in men but ↑ **in women** in recent decades.
- **Women-specific**: inflammation, obesity, T2DM, metabolic syndrome more prominent; CAD often microvascular (not epicardial); exercise ECG less accurate for epicardial obstruction.

## Natural History

- **Acute presentations** in previously asymptomatic patient — MI; HCM/long-QT presenting as syncope or sudden death.
- **Risk-factor recognition** long before event → opportunity for prevention.
- **Chronic insidious course** in valvular disease, idiopathic DCM — gradual ↑ dyspnea/HF symptoms, punctuated by late acute deteriorations.
- Understanding natural history → tailor diagnostics, therapy, and prognostic counselling.

## Cardiac Symptoms — 4 Mechanisms

- Symptoms in heart disease arise from **4 underlying processes**:
- **(1) Myocardial ischemia** — supply/demand mismatch
  - → **Chest discomfort** (Chap 15).
- **(2) Contraction/relaxation disturbance** (pump failure)
  - → **Fatigue** (forward); ↑ **upstream pressure** → peripheral edema (Chap 43) / pulmonary congestion + dyspnea (Chap 39).
- **(3) Obstruction to flow** (e.g., valvular stenosis)
  - → Symptoms mimicking myocardial failure (Chap 264).
- **(4) Arrhythmia / rate abnormality**
  - → **Palpitations** (Chap 45), dyspnea, hypotension, **syncope** (Chap 23) — abrupt onset, often abrupt offset.

### Symptoms are non-specific

**Table — Cardinal CV symptoms have non-cardiac mimics**

| Symptom | Cardiac cause | Non-cardiac mimics |
|---|---|---|
| Dyspnea | HF, valvular dz | Pulmonary dz, marked obesity, anxiety |
| Chest discomfort | Myocardial ischemia | GERD, MSK, PE, dissection, anxiety |
| Edema | HF (untreated) | Renal disease, hepatic cirrhosis |
| Syncope | Arrhythmia, AS, HCM | Neurogenic (vasovagal), neurologic |

### Exertional pattern — the diagnostic clue

- **Cardiac dyspnea/chest discomfort** = brought on by **exertion**, relieved by rest.
- Opposite pattern (symptoms at rest, remit with exertion) is **rarely cardiac**.
- Always probe the **activity threshold** that provokes symptoms.

### The asymptomatic patient

- May present only with: **murmur**, **elevated BP**, abnormal ECG, or imaging finding.
- First clinical event in asymptomatic CAD may be **SCD, MI, or stroke** — hence global CAD risk assessment is mandatory.
- Tools: clinical risk score + lipid panel ± hsCRP/biomarkers.

> **CLINICAL PEARLS**
>
> **Exertion-relieved** chest discomfort → think **non-cardiac** (e.g., MSK, anxiety).
> First CAD event = often catastrophic. **Asymptomatic ≠ low-risk** — calculate global risk.
> **Women** with angina: think coronary **microvascular** dysfunction; exercise ECG less reliable.

## NYHA Complete Cardiac Diagnosis — 4 Elements

1. **Underlying etiology** — congenital, hypertensive, ischemic, inflammatory?
2. **Anatomic abnormalities** — which chambers (hypertrophy/dilatation)? Which valves (stenosis/regurgitation)? Pericardial involvement? Prior MI?
3. **Physiologic disturbances** — arrhythmia present? HF? Ischemia?
4. **Functional disability** — what level of activity provokes symptoms? (Use NYHA class).

> **NEET SS HIGHLIGHTS**
>
> **NYHA diagnosis = 4 parts**: etiology, anatomy, physiology, functional class.
> Mnemonic: **E-A-P-F** (Etiology → Anatomy → Physiology → Function).
> Functional class alone is **insufficient** — without etiology + anatomy + physiology you cannot plan Rx or prognosticate.

### Worked example — exertional chest discomfort

- Identifying **ischemia** alone is insufficient.
- Must define the **anatomic substrate** (CAD vs. AS) + **contributory physiology** (anemia, thyrotoxicosis, SVT) before therapy or prognosis is planned.
- **Severity of disability** dictates tempo + extent of workup and choice of therapy.

## NYHA Functional Classification

Table 243-1 — NYHA Functional Class

| Class | Activity limitation | Symptoms |
|---|---|---|
| I | None | No symptoms with ordinary exertion |
| II | Slight | Ordinary activity causes symptoms |
| III | Marked | Less-than-ordinary activity causes symptoms; **asymptomatic at rest** |
| IV | Any activity | Symptoms **at rest** |

❤ NEET SS HIGHLIGHTS

❤ **NYHA I** = no limitation. **II** = slight (ordinary). **III** = marked (less-than-ordinary). **IV** = symptoms at rest.
❤ **III vs. IV** = absence vs. presence of **rest** symptoms.
❤ NYHA III: **asymptomatic at rest** is a defining feature.

## Laboratory Workup — 5 Categories

1. **ECG** (Chap 247).
2. **Noninvasive imaging** — CXR, echo, radionuclide, CT, PET, cardiac MRI (Chap 248).
3. **Blood tests** — risk markers (**lipids, hsCRP**) and functional markers (**BNP/NT-proBNP**).
4. **Invasive testing** when indicated — cardiac catheterization + coronary angiography (Chap 249).
5. **Genetic testing** for monogenic dz — **HCM, Marfan, LQTS** (ion-channel genes).

## Family History

- Familial clustering common in CV disease.
- **Monogenic (Mendelian)** single-gene defects:
  - **HCM** (Chaps 266–270).
  - **Marfan syndrome** (Chap 425).
  - **Long-QT syndrome** → SCD (Chap 259).
- **Polygenic disorders** — major CAD risk factors:
  - Premature CAD, essential HTN, T2DM, hyperlipidemia.
  - Familial transmission less obvious but still useful for risk/prognosis.
- Familial clustering may also be **environmental/behavioral**: salt/calorie intake, smoking.

## Assessing Functional Impairment

- Don't just record **'dyspnea'** — quantify the activity level + rate that provokes it.
- **Two-flight dyspnea in a marathoner > one-flight dyspnea in a sedentary patient** in significance.
- Always consider **baseline activity** (work + recreation) before grading severity.
- **Current therapy matters** — HF symptoms on optimal diuretics/GDMT are **far graver** than identical symptoms untreated.
- Anchor severity to **change over time**: 'what could you do 6–12 months ago that you cannot do now?'

## Role of ECG

- ECG **should be recorded** in known/suspected heart dz.
- ECG **establishes diagnosis** only for:
  - **Arrhythmias.**
  - **Conduction abnormalities.**
  - **Ventricular hypertrophy.**
  - **Acute MI.**
- Otherwise = **nonspecific.** Wide range of normal; affected by age, body habitus, serum electrolytes.
- Interpret ECG **in context** of other cardiac findings — never in isolation.

## Approach to the Heart Murmur

- **Systematic evaluation** of murmur attributes:
- **8 features:**
  - **Timing** (systolic / diastolic / continuous).
  - **Duration.**
  - **Intensity** (grade I–VI).
  - **Quality** (harsh, blowing, rumbling, musical).
  - **Frequency** (high / low pitch).
  - **Configuration** (crescendo, decrescendo, crescendo-decrescendo, plateau).
  - **Location** (point of maximal intensity).
  - **Radiation.**
- Interpret with history + general PEx + rest of cardiac exam (Chap 246).

### Benign vs. pathologic — quick filter

- Most murmurs are **midsystolic, soft (grade I–II/VI).**
- Such a murmur in an **asymptomatic child / young adult** without other findings → **benign**, no echo needed.
- **Echo required** for any: grade ≥ III, holosystolic, late systolic, **diastolic**, or **continuous** murmur, OR if other signs/symptoms of cardiac disease, OR abnormal ECG / CXR.

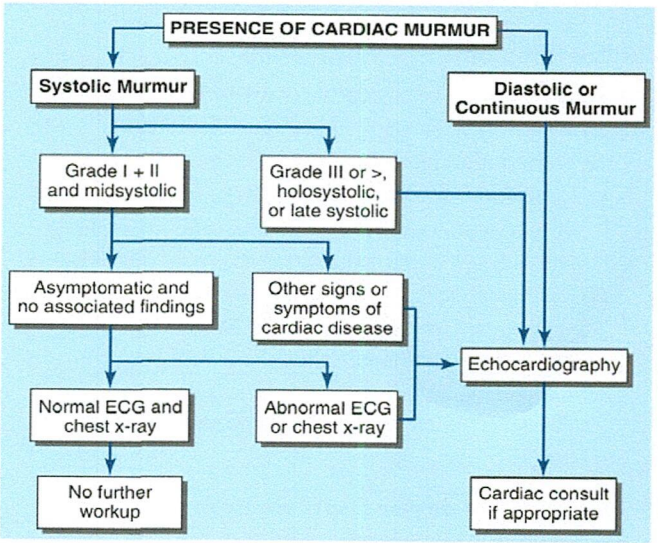



*Fig 243-1 — Approach to evaluation of a heart murmur. Grade I–II midsystolic + asymptomatic + normal ECG/CXR → no further workup. Grade ≥ III, holo/late systolic, diastolic/continuous, or any associated finding → **echocardiography ± cardiology consult**.*

## CLINICAL PEARLS

- **Diastolic or continuous murmur = always pathologic** → echo.
- **Grade ≥ III** systolic, **holosystolic**, or **late systolic** → echo.
- Soft midsystolic in young + asymptomatic + normal ECG/CXR → reassurance, **no echo**.
- Any associated CV symptom or abnormal ECG/CXR mandates echo regardless of grade.

## LAST MINUTE REVISION

► CV dz = leading cause of death in **both sexes**. ~700k US deaths/yr, ~1/3 sudden.
► Age-adjusted CHD mortality **↓ 2/3** over 4 decades — threatened by obesity/T2DM/metabolic syndrome.
► **Women**: microvascular CAD more common; exercise ECG less sensitive.
► **4 mechanisms of cardiac symptoms**: ischemia, pump failure, obstruction, arrhythmia.
► Cardiac symptoms = **exertional**; rest-only symptoms relieved by exertion → think non-cardiac.
► **NYHA diagnosis = E-A-P-F** (etiology, anatomy, physiology, function).
► **NYHA I** = no limitation; **II** = slight; **III** = marked, **asymptomatic at rest**; **IV** = symptoms at rest.
► **5 lab categories**: ECG, noninvasive imaging, blood tests, invasive (cath), genetic.
► **Genetic testing** for monogenic dz: HCM, Marfan, LQTS.
► ECG **diagnostic only** for: arrhythmia, conduction, LVH/RVH, acute MI. Otherwise nonspecific.
► **Murmur 8 attributes**: timing, duration, intensity, quality, frequency, configuration, location, radiation.
► **Echo needed**: any diastolic/continuous murmur; systolic grade ≥III, holo/late systolic; any associated CV finding.
► Grade I–II midsystolic, asymptomatic young, normal ECG/CXR → **no echo**.
► **Polygenic CAD risk factors**: premature CAD, HTN, T2DM, hyperlipidemia.

## MCQ CORNER

**Q1.** A 64 y/o man with HF has dyspnea climbing one flight of stairs but is comfortable at rest. He is on optimal GDMT. Which NYHA class?
A. Class I
B. Class II
✓ **C. Class III**
D. Class IV
► *Symptoms with less-than-ordinary exertion but asymptomatic at rest = NYHA III. Class IV requires symptoms at rest.*

**Q2.** A 19 y/o asymptomatic college athlete has a grade II/VI midsystolic murmur at the LSB. ECG and CXR are normal. Next step?
A. Transthoracic echocardiography
B. Stress echo
✓ **C. Reassurance, no further workup**
D. Cardiology referral for cardiac MRI
► *Grade I–II midsystolic murmur in an asymptomatic young patient with normal ECG/CXR = benign flow murmur. No echo needed (Fig 243-1).*

**Q3.** Which of the following ECG findings is diagnostically established by ECG alone, per the NYHA framework?
A. Mitral stenosis
✓ **B. Acute myocardial infarction**
C. Aortic regurgitation
D. Hypertrophic obstructive cardiomyopathy
► *ECG establishes diagnosis only for arrhythmias, conduction abnormalities, ventricular hypertrophy, and acute MI. Valvular/structural diagnoses require imaging.*

**Q4.** Which of the following is a monogenic (Mendelian) cardiac disorder requiring genetic counselling?
A. Essential hypertension
B. Type 2 diabetes mellitus
✓ **C. Hypertrophic cardiomyopathy**
D. Hyperlipidemia (familial combined)
► *HCM, Marfan syndrome, and long-QT syndrome are classic monogenic CV disorders. HTN, T2DM, and most hyperlipidemias are polygenic.*

**Q5.** A 52 y/o woman presents with exertional angina. Stress ECG is non-diagnostic. The most likely mechanism that explains the limited diagnostic accuracy of exercise ECG in this patient is:
✓ **A. Microvascular coronary dysfunction common in women**
B. Higher prevalence of LBBB at baseline in women
C. Better collateral circulation in women
D. Lower epicardial CAD prevalence at her age
► *Coronary microvascular dysfunction is more common in women and contributes to lower diagnostic accuracy of exercise ECG for epicardial obstruction in women.*

### ✦ MNEMONIC

**EAPF** *NYHA Complete Cardiac Diagnosis*

- **E** — **E**tiology — congenital / HTN / ischemic / inflammatory
- **A** — **A**natomy — chambers, valves, pericardium, prior MI
- **P** — **P**hysiology — arrhythmia, HF, ischemia
- **F** — **F**unctional class — NYHA I–IV

*Use for every cardiac patient — diagnosis is incomplete without all 4.*

**TIDQ-FCLR** *8 attributes of a murmur*

- **T** — **T**iming (systolic / diastolic / continuous)
- **I** — **I**ntensity (grade I–VI)
- **D** — **D**uration
- **Q** — **Q**uality
- **F** — **F**requency (pitch)
- **C** — **C**onfiguration
- **L** — **L**ocation (PMI)
- **R** — **R**adiation

*Systematic evaluation per Chap 246 — combine with general PEx.*

### ◉ UPDATES

◉ Global CV mortality estimate **~19 million/yr** (rising in low/middle-income countries).
◉ Obesity, T2DM, and metabolic syndrome may **reverse** the age-adjusted CHD mortality decline.
◉ Genetic testing increasingly available for **HCM, Marfan, LQTS** — incorporate into routine FHx where suggestive.
◉ Recognize **sex differences** in CAD: microvascular dysfunction in women; ↓ accuracy of exercise ECG.

# CH 244 · Basic Biology of the CV System — Development, Vascu...

*Foundation chapter — embryology of heart and great vessels, vascular cell biology, vascular smooth-muscle Ca signaling, sarcomere mechanics, excitation–contraction coupling, Frank-Starling, preload/afterload/contractility, pressure-volume loops, diastolic function,*

## Cardiac Development

- Heart forms **early in embryogenesis** — first functioning organ.
- Origin: **cardiac crescent** of lateral splanchnic mesoderm → migrate to midline → **linear heart tube** (single endocardial + single cardiomyocyte layer).
- Linear tube → **chamber specification + asymmetric looping** → presumptive atria + ventricles.
- **Two heart fields**:
  - **1st heart field** = linear heart tube.
  - **2nd heart field** (pharyngeal mesoderm) → adds myocardium to **inflow + outflow poles**; gives rise to **RA, RV, OT**. Marker: **Islet-1**.
- Different embryonic origins explain **right- vs. left-sided** regional disease susceptibility.
- **Endocardial cushions** (cardiac jelly = hyaluronic acid-rich ECM) → valves; via **epithelial-mesenchymal transformation** of endocardial cells.
- **Truncus arteriosus → aorta + pulm artery**; septated by neural-crest-derived mesenchyme.
- **Neural crest cells**: orchestrate aortic arch remodeling + truncal septation; sensitive to **vitamin A and folate** deficiency → aortic arch anomalies.
- **Smooth muscle origins**: aortic arch + ductus + carotids = **neural crest**; descending aorta = lateral plate mesoderm; proximal outflow = 2nd heart field.
- **Coronaries**: derive from **proepicardial organ** (septum transversum derivative, also gives fibrous diaphragm + liver).

### Conduction system development

- Differentiates from cardiomyocyte precursors.
- **SA node** ← sinus venosus precursors; **AV node** ← AV canal.
- Proximal = **slow conducting** (SA, AV nodes); distal = **fast** (His, bundle branches, Purkinje).
- **AV node decremental conduction** = delays atrial→ventricular transmission and protects ventricles from rapid atrial rates.
- Developmental defects → **congenital heart block, WPW pre-excitation**.

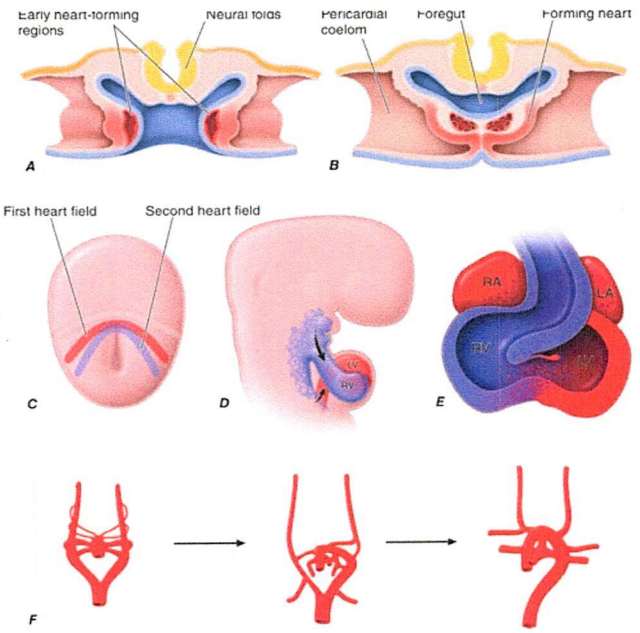



*Fig 244-1 — Cardiac development. (A,B) Bilateral heart-forming regions fuse at midline. (C-E) 1st heart field forms linear tube; 2nd heart field contributes inflow/outflow poles, much of RV/OT, and parts of atria. (F) Symmetric aortic arches remodel asymmetrically under neural-crest control.*

**♥ NEET SS HIGHLIGHTS**

- ♥ **1st heart field** = linear tube; **2nd heart field** (Islet-1) = inflow/outflow + RA/RV.
- ♥ **Neural crest** = aortic arch + ductus + carotid SMC; needs **vit A + folate**.
- ♥ **Cardiac jelly** = hyaluronic acid (cushion) → valves via EMT.
- ♥ **Coronaries** from **proepicardial organ**.
- ♥ **SA node** ← sinus venosus; **AV node** ← AV canal.

## Blood Vessel — Ultrastructure

- **Capillary** = endothelial monolayer + basement membrane + discontinuous **pericytes** (SMC-like).
- **Trilaminar arterial wall**:
  - **Intima** — endothelial monolayer.
  - **Media** — VSMC syncytium ± elastic laminae.
  - **Adventitia** — ECM with fibroblasts, mast cells, nerve terminals.
- **Veins**: thin media, thicker adventitia.
- **Arterioles** (small muscular) → regulate **BP + regional flow**.
- **Medium muscular arteries** → site of **atherogenesis**.
- **Elastic arteries** (e.g., aorta) → concentric SMC bands + elastin lamellae; internal + external elastic laminae; **vasa vasorum** nourishes media.

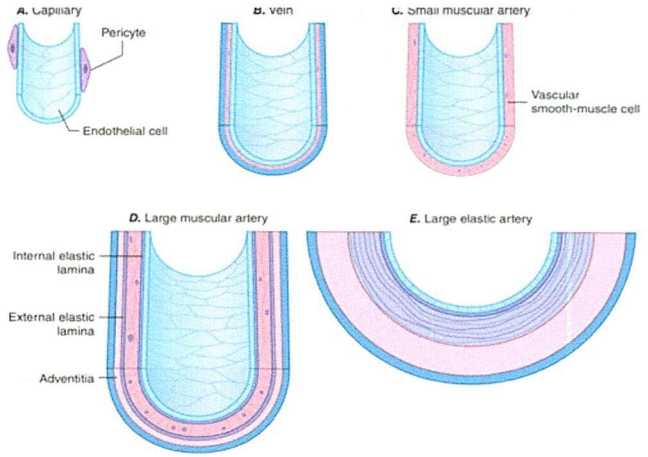



*Fig 244-2 — A) Capillary = endothelial tube + pericytes. B) Vein (thin media). C) Small muscular artery. D) Large muscular artery. E) Elastic artery — concentric SMC/elastin + internal & external elastic laminae + vasa vasorum.*

## Endothelial Cell — Homeostatic vs. Dysfunctional

**Table 244-1 — Endothelial functions in health and disease**

| Function | Homeostatic | Dysfunctional |
|---|---|---|
| Vasomotor | Vasodilation > vasoconstriction | Impaired dilation, vasoconstriction |
| Thrombosis | Antithrombotic, profibrinolytic | Prothrombotic, antifibrinolytic |
| Inflammation | Anti-inflammatory | Pro-inflammatory |
| Proliferation | Anti-proliferative | Pro-proliferative |
| Redox | Antioxidant | Pro-oxidant |
| Barrier | Selective permeability | Impaired barrier (capillary leak) |

### Endothelial vasoactive output

- **Dilators**: prostacyclin (PGI2), **NO**, EDHF, $H_2O_2$.
- **Constrictor**: **endothelin-1**.
- Key trigger = **laminar shear stress** → maintains homeostasis; measured clinically by **flow-mediated dilatation** (FMD).
- Excess **superoxide ($O_2^-$)** — e.g., from Ang II — inactivates NO → endothelial dysfunction.

### Endothelial role in inflammation, thrombosis

- Endotoxin/cytokines → adhesion molecules.
- **Acute bacterial infection** → granulocyte recruitment.
- **Chronic inflammation** (TB, atherosclerosis) → monocyte recruitment.
- Inflammatory stimuli / endotoxin / Ang II / hyperglycemia → ↑ **PAI-1** + **tissue factor** → procoagulant state (sepsis-DIC).
- EC injury: complement lysis, allograft arteriopathy (HLA), **TTP/HUS**.
- EC secretes **heparan sulfate** → inhibits SMC proliferation; injury releases **PDGF** → SMC migration/proliferation (atheroma).

## Vascular Smooth Muscle Cell

- Contraction/relaxation in muscular arteries sets **BP, regional flow, LV afterload**.
- **Venous tone** → capacitance + preload.
- Adult VSMCs rarely replicate without injury/inflammation.
- Proliferation/migration drives **atherosclerosis stenosis**, **arteriolar remodeling in HTN**, and **pulm HTN from L→R shunts**.
- VSMC secretes bulk of vascular ECM — excess collagen/GAGs → **stiffness** ↑ afterload (poor outcome with aging).

### VSMC contraction — $Ca^{2+}$-dependent

- ↑ cytoplasmic [$Ca^{2+}$] = principal trigger (membrane influx + SR release).
- **L-type VDCC** opens with depolarization → '$Ca^{2+}$ sparks' → SR release.
- Agonist (NE, ET-1, Ang II) → **PLC** → **DAG + $IP_3$**:
  - **DAG** → activates PKC.
  - **$IP_3$** → SR $IP_3R$ → SR $Ca^{2+}$ release.
- **Contraction** = phosphorylated myosin light chain (MLC).
- **MLCK** ($Ca^{2+}$/calmodulin) activates ATPase → contraction.
- **MLCP** (phosphatase) reverses → relaxation.
- **RhoA / Rho-kinase** inhibits MLCP → '**$Ca^{2+}$ sensitization**'.
- **Relaxation pathways**: NO → **sGC** → **cGMP** → **PKG**; ANP → **pGC** → **cGMP**; β-agonist → **AC** → **cAMP** → **PKA**.

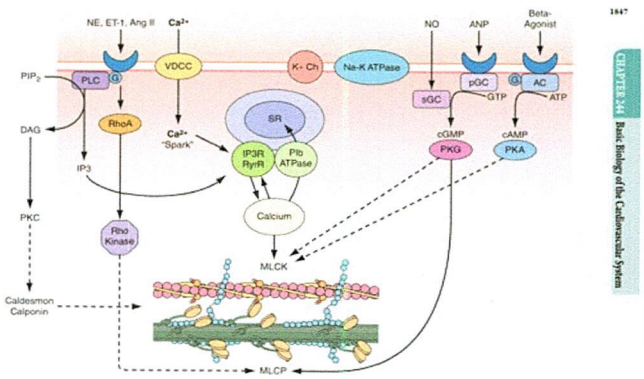



*Fig 244-4 — VSMC contraction. Agonists (NE, ET-1, AngII) → PLC → IP3 (SR release) + DAG → PKC. VDCC + $Ca^{2+}$ sparks raise [$Ca^{2+}$]. MLCK contracts, MLCP relaxes. cAMP (β-agonist) and cGMP (NO, ANP) drive relaxation.*

### Neural / humoral control

- **α1** (large arteries) + **α2** (small arteries/arterioles) → constriction (NE).
- **β2** → cAMP-dependent relaxation.
- **Muscarinic (ACh)**: directly on VSMC → constriction; on EC → NO-mediated **relaxation**.
- **Nitrergic neurons** release NO directly.
- Peptidergic NTs: SP, VIP, CGRP, ATP.
- Baroreceptors (aortic arch, carotid) + chemoreceptors + cutaneous thermoreceptors → autonomic reflex modulation.

**CLINICAL PEARLS**

- **Acetylcholine** paradox: directly constricts VSMC, but via EC NO it **net dilates** arteries — used to test endothelial function.
- **Rho-kinase** = $Ca^{2+}$-sensitization; inhibitors (fasudil) explored in pulm HTN/Raynaud.
- **FMD** = noninvasive endothelial function index (post-occlusive brachial artery dilatation).

### Arteriogenesis vs. angiogenesis

- **Angiogenesis** = new capillary growth; driven by **VEGF, FGF**; semaphorins pattern tubes.
- **Arteriogenesis** = expansion of pre-existing collaterals after arterial occlusion.
- **True vascular regeneration** (all 3 layers) does **not occur** in adult mammals.

## Cardiomyocyte — Ultrastructure

- Length **60–140 µm**; diameter **17–25 µm**.
- Multiple **myofibrils** = chains of **sarcomeres**.
- Sarcomere = unit between two **Z-lines**; length **1.6–2.2 µm**.
- **A band** = fixed length 1.5 µm (thick filaments).
- **I band** = thin filaments only; shortens during contraction.
- Thick filament = **myosin** (~10 nm diameter, ~300 molecules); has globular head with **ATPase**.
- Thin filament = **actin double helix** on **tropomyosin**, with **troponins C / I / T** at intervals.
- **Titin** = giant elastic protein, myosin → Z-line; sets **passive stiffness**.
- **Dystrophin** = links sarcomere to membrane (adherens junctions); mutated → DMD/BMD cardiomyopathy.



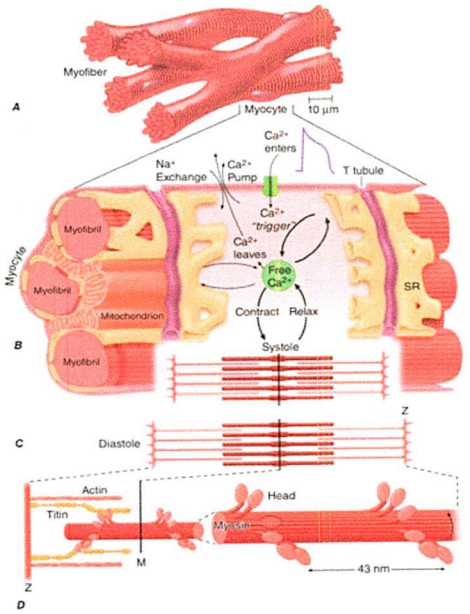



*Fig 244-5 — Cardiomyocyte & sarcomere. (A) Branching myocytes, T-tubule + SR. (B–C) Actin–myosin overlap in systole vs. diastole. (D) Myosin heads engage actin; titin tethers thick filament to Z-line.*

## Contractile Process — Cross-Bridge Cycle

1. **ATP hydrolysis** on myosin head → energized cross-bridge (Pi, ADP bound).
2. **$Ca^{2+}$ binds troponin C** → tropomyosin shifts → exposes actin sites → **active complex**.
3. **Power stroke** — ADP dissociates → low-energy **rigor complex** (the 'rowing motion').
4. **New ATP binds** myosin → detaches from actin → cycle continues until [$Ca^{2+}$] falls.

- **Sliding filament theory**: A band constant; thin filaments slide into A band; I band + sarcomere shorten.
- Cycling rate = function of **myosin ATPase activity** → sets contraction velocity.
- **Rigor mortis** = no ATP → cannot detach myosin → persistent stiffness.
- Sarcomere/cytoskeletal protein mutations → HCM, DCM, ARVC; sensitize to toxic/peripartum cardiomyopathies.

## Excitation–Contraction Coupling

- Resting $V_m$ = **−80 to −100 mV**; $Na^+$-$K^+$-ATPase maintains gradients.
- **Phase 2 plateau**: L-type $Ca^{2+}$ channels open → small $Ca^{2+}$ entry.
- Entry triggers **$Ca^{2+}$-induced $Ca^{2+}$ release** from SR via **RyR2** (ryanodine receptor 2) — RyR2 mutations → CPVT.
- Cytoplasmic $Ca^{2+}$ binds **troponin C** → contraction.
- **Relaxation pathways** ($Ca^{2+}$ removal):
  - **SERCA2A** SR pump (ATP-dependent) — $Ca^{2+}$ stored on **calsequestrin**.
  - Sarcolemmal **$Na^+/Ca^{2+}$ exchanger** (NCX).
  - Plasma-membrane $Ca^{2+}$ ATPase (minor).
- **Phospholamban (PLB)** = SERCA2A brake; PKA-phosphorylated PLB releases SERCA2A → faster relaxation (**lusitropy**).
- **β-AR signaling**: Gs → AC → cAMP → PKA → phosphorylates L-type Ca channel + RyR2 + PLB → ↑ rate of contraction, peak force, AND ↑ rate of relaxation.
- Cytoplasmic [$Ca^{2+}$] = principal **inotropic state** determinant.
- **Digitalis** inhibits $Na^+/K^+$-ATPase → ↑ intracellular Na → ↓ Ca extrusion via NCX → ↑ $Ca^{2+}$ → ↑ contractility.



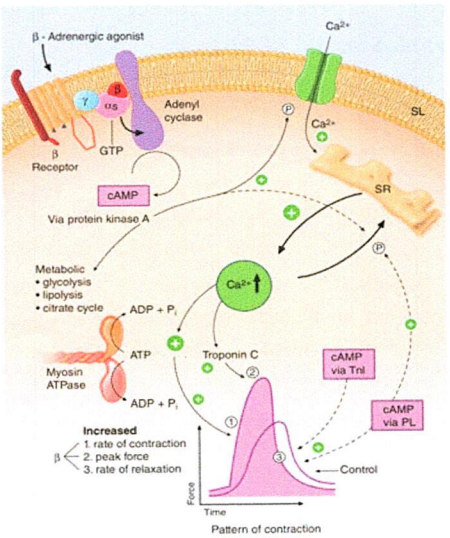



*Fig 244-7 — β-adrenergic positive inotropy + lusitropy. Gs → AC → cAMP → PKA → phosphorylates L-type Ca channel (↑ Ca entry) + phospholamban (↑ SR uptake) → ↑ rate of contraction, peak force, AND rate of relaxation.*



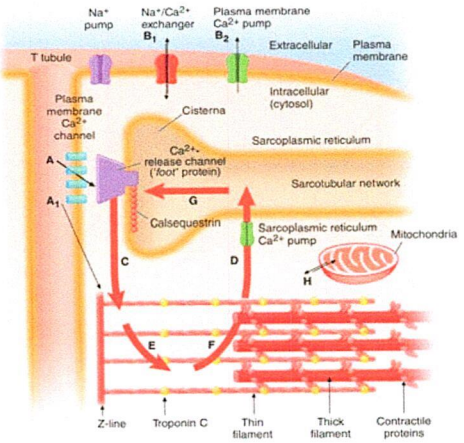



*Fig 244-8 — Excitation-contraction coupling. Plasma membrane $Ca^{2+}$ entry (A) → trigger $Ca^{2+}$. SR release (C) → troponin C binding (E) drives systole. SERCA (D) + NCX/PMCA (B1/B2) reduce cytosolic $Ca^{2+}$ for relaxation. Calsequestrin stores SR $Ca^{2+}$.*

### ♥ NEET SS HIGHLIGHTS

♥ **RyR2** = cardiac SR $Ca^{2+}$ release channel. Mutated in **CPVT**.
♥ **SERCA2A** + **phospholamban** set relaxation rate (lusitropy).
♥ **NCX** = main $Ca^{2+}$ extrusion; **digoxin** raises $Ca^{2+}$ via Na/K-ATPase block → ↑ inotropy.
♥ **Troponin C** = $Ca^{2+}$ binding; **Troponin I** = inhibitor; **Troponin T** = tropomyosin binding.
♥ **Titin** sets passive stiffness; **Dystrophin** links sarcomere to sarcolemma.
♥ β-AR effects: ↑ **inotropy, chronotropy, lusitropy, dromotropy**.

## Frank-Starling — Preload

- Stroke volume depends on **3 factors: preload, afterload, contractility**.
- **Preload** = sarcomere length at onset of contraction; optimal at **~2.2 µm**.
- **Starling's law:** contraction force  end-diastolic length (~EDV).
- Ventricular function curve: plot stroke work vs. EDP.
- **Curve shift:**
  - ↑ **contractility** → shifts **up and left**.
  - ↓ **contractility** → shifts **down and right**.

I. Myocardial fibrosis ↓
J. Chronic overexpression of neurohormones ↓
K. Ventricular remodeling ↓
L. Chronic and/or excessive myocardial hypertrophy ↓

[a]Arrows indicate directional effects of determinants of contractility. [b]Contractility rises initially but later becomes depressed.

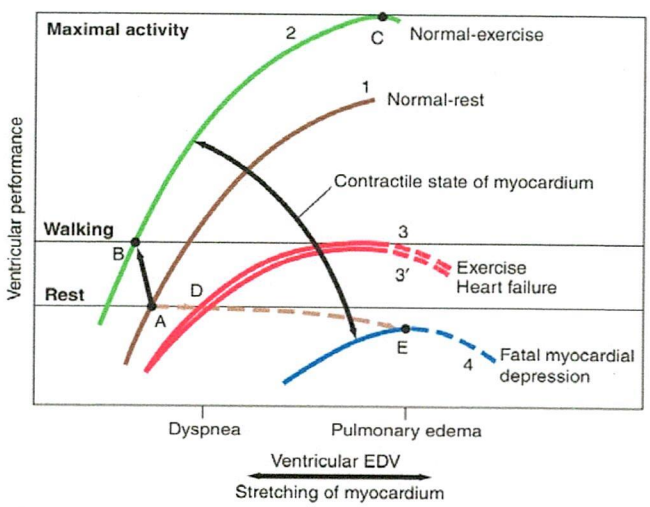



*Fig 244-9 — Family of Starling curves. Curve set by contractility; operating point on a curve set by preload. Exercise + sympathetic stimulation moves operating point up + curve up/left. Decompensated HF descending limb causes pulmonary edema.*

## Afterload

- **Afterload** = wall tension during ejection; opposes shortening.
- **Laplace's law:** wall tension = (P × r) / (2 × h).
- **↑ in dilated LV; ↓ in hypertrophied LV** at same aortic P (concentric hypertrophy reduces wall stress).
- Determined by aortic pressure, ventricular volume + wall thickness, and arterial compliance.
- Vicious cycle: ↓ contractility → ↑ EDV → ↑ afterload (Laplace) → further ↓ output.
- **Vasodilators** (afterload reduction) → ↑ cardiac output in HFrEF.

## Determinants of stroke volume (Table 244-2)

**Table 244-2 — Determinants of Stroke Volume**

| Component | Determinants |
|---|---|
| **Preload** | Blood volume; distribution (posture, intrathoracic / pericardial pressure, venous tone, skeletal muscle pump); atrial contraction |
| **Afterload** | SVR; arterial compliance; arterial blood volume; ventricular wall tension (radius, thickness) |
| **Contractility** | Intracellular [$Ca^{2+}$]; adrenergic tone; catecholamines; HR; inotropes; ischemia; cell death; sarcomere/cytoskeletal mutations; fibrosis; chronic neurohormonal overactivity; remodeling; hypertrophy |

## Cardiac Response to Exercise

- **Preload ↑** — hyperventilation, muscle pump, venoconstriction → ↑ venous return.
- **Contractility ↑** — sympathetic + circulating catecholamines + tachycardia.
- **Afterload ~stable / slightly ↑** — muscle vasodilation offsets vasoconstriction elsewhere.
- Net result: cardiac output up to **5×** basal with only modest ↑ BP, with little change in EDV/EDP.

## Assessment of Cardiac Function

- Resting CO/SV often normal even late in HF — insensitive.
- **Ejection fraction** = SV/EDV; normal **67 ± 8%**.
- Normal **LVEDV index ~75 ± 20 mL/m²**; **LVESV index ~25 ± 7 mL/m²**.
- Imaging: echo, radionuclide, cardiac MRI — quantify EDV/ESV/EF, regional motion, filling.
- EF, CO, volumes all depend on **loading conditions**: hypovolemia or acute HTN can lower EF without intrinsic dysfunction.
- **ESPVR** (end-systolic pressure-volume relation) = load-independent contractility index.
- **CPET** (cardiopulmonary exercise testing) → max $O_2$ delivery = surrogate for cardiac reserve.

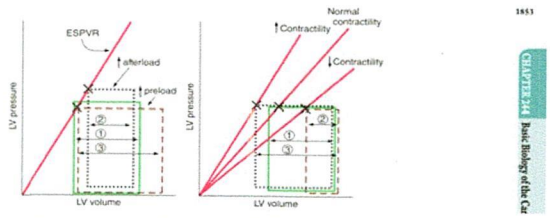



*Fig 244-11 — Pressure-volume loops. LEFT: ↑ preload (1→3) raises SV; ↑ afterload (1→2) lowers SV; ESPVR unchanged (no Δ contractility). RIGHT: ↑ contractility shifts ESPVR LEFT (↑ SV, ↓ ESV at any pressure); ↓ contractility shifts ESPVR RIGHT.*

## Diastolic Function

- Filling determined by **active relaxation** (SERCA-mediated $Ca^{2+}$ reuptake) + **passive stiffness**.
- Relaxation slowed by **ischemia** (↓ ATP for SERCA).
- Stiffness ↑ in:
  - Hypertrophy.
  - Fibrosis.
  - Infiltration (**amyloid**).

- Pericardial constraint (constriction).

- **Doppler mitral inflow:** E (early) > A (atrial) is normal.
- Impaired relaxation: E ↓, A ↑ → **E/A reversal.**
- Worsening dz → **'pseudonormalization'** (rising LA pressure mimics normal pattern) → **restrictive pattern** (tall E, short DT).

## Cardiac Metabolism

- ATP supports contraction + ionic/biochemical homeostasis.
- Heart consumes **~15% of total body $O_2$ / ATP.**
- Determinants of $MVO_2$: **wall tension, HR, contractility.**
- Fuel preference (descending): **FFAs > glucose > lactate > amino acids > ketones.**
- Glucose sources: plasma + myocardial glycogen (glycogenolysis).
- Ischemia: glycolytic ATP becomes important — but anaerobic metabolism inefficient + lactate-acidotic.

### ◷ LAST MINUTE REVISION

► **Heart fields:** 1st = linear tube; 2nd (Islet-1) = inflow/outflow + RV/RA.
► Neural crest → aortic arch SMC + truncal septation; needs vit A + folate.
► Cardiac jelly = HA → endocardial cushions → valves via EMT.
► Coronaries = proepicardial organ; SA ← sinus venosus, AV ← AV canal.
► **Endothelium:** dilates via NO/PGI2/EDHF; constricts via ET-1; assessed by FMD.
► **VSMC contraction:** ↑Ca → calmodulin → **MLCK** → MLC phosphorylation; relaxes via cGMP (NO/ANP) + cAMP (β2).
► Rho-kinase = $Ca^{2+}$ sensitization (inhibits MLCP).
► Sarcomere: A band fixed, I band shortens, Z-Z = sarcomere; optimal length **2.2 µm.**
► **Troponins:** C ($Ca^{2+}$), I (inhibitor), T (tropomyosin); cTnT/cTnI = MI biomarkers.
► Titin = passive stiffness; dystrophin links sarcomere to sarcolemma.
► **EC coupling:** L-type Ca → SR Ca release via **RyR2** → troponin C → contraction.
► Relaxation: **SERCA2A** (+ **PLB** brake), NCX, PMCA.
► β-AR (Gs→AC→cAMP→PKA) → ↑ inotropy + lusitropy + chronotropy + dromotropy.
► Digoxin: blocks Na/K-ATPase → ↑ Na → ↓ NCX → ↑ Ca → + inotropy.
► **Starling:** SV ↑ with EDV; contractility shifts curve up-left.
► **Laplace:** T = Pr/2h; dilation ↑ wall stress, hypertrophy ↓ it.
► **Normal EF** = 67 ± 8%; LVEDVi 75 ± 20 mL/m²; LVESVi 25 ± 7.
► **ESPVR** = load-independent contractility index.
► Exercise → CO ↑ up to 5× basal with modest BP rise (muscle vasodilation).
► Heart fuel: FFA > glucose > lactate > AA > ketones; ~15% body $O_2$.
► Diastolic stiffness ↑: hypertrophy, fibrosis, amyloid, pericardial constraint.
► Mitral inflow E/A reversal → pseudonormalization → restrictive (worsening filling).

### ✎ MCQ CORNER

**Q1.** A neonate has truncus arteriosus with aortic arch interruption. The embryologic structure most likely impaired is:
A. First heart field
✓ **B. Cardiac neural crest**
C. Proepicardial organ
D. Endocardial cushions
► *Cardiac neural crest cells orchestrate aortic arch remodeling and truncoaortic septation. Maternal vitamin A or folate deficiency interferes with this. First heart field = linear tube; proepicardial organ = coronaries; cushions = valves.*

**Q2.** A 70 y/o has dilated LV with EF 25%. Per Laplace's law, increased afterload primarily results from:
A. Increased aortic pressure
B. Increased ventricular radius
C. Decreased wall thickness
✓ **D. All of the above**
► *Wall tension = (P × r)/(2h). Dilated LV (↑ r) and thinned wall (↓ h) raise wall stress at any aortic pressure. Vasodilators reduce afterload and improve CO in HFrEF.*

**Q3.** A patient with HF on β-blocker therapy. β-blockade reduces myocardial work primarily by which mechanism?
A. Inhibiting $Na^+/K^+$-ATPase
✓ **B. Reducing PKA-mediated L-type Ca channel and phospholamban phosphorylation**
C. Increasing NCX activity
D. Blocking sGC-mediated cGMP
► *β-AR signaling (Gs→AC→cAMP→PKA) phosphorylates L-type Ca channels and phospholamban, increasing inotropy and lusitropy. β-blockade reduces this — lowers HR, contractility, $MVO_2$.*

**Q4.** Mitral inflow Doppler reveals E/A reversal with prolonged deceleration time. The most likely diastolic abnormality is:
A. Normal filling
✓ **B. Impaired relaxation**
C. Pseudonormalization
D. Restrictive filling
► *Early stage diastolic dysfunction: relaxation impaired → ↓ E, compensatory ↑ A (atrial kick), prolonged DT. Pseudonormalization comes next as LA pressure rises.*

**Q5.** Which cardiac structural protein, when mutated, classically causes hypertrophic cardiomyopathy?
A. Dystrophin
✓ **B. β-myosin heavy chain (MYH7)**
C. Lamin A/C
D. Plakoglobin
► *MYH7 (β-MHC) and MYBPC3 are the most common sarcomere genes causing HCM. Dystrophin → DMD/BMD; lamin A/C → DCM with conduction disease; plakoglobin → ARVC.*

### ✦ MNEMONIC

**C-I-T** *Troponins on thin filament*
**C** — Calcium binding — TnC
**I** — Inhibitor of actomyosin — TnI (released in MI)
**T** — Tropomyosin binding — TnT (released in MI)
*cTnI and cTnT = clinical MI biomarkers.*

**PACE** *β-adrenergic effects on myocardium*
**P** — Positive inotropy (force ↑)
**A** — Accelerated relaxation = lusitropy
**C** — Chronotropy (HR ↑)
**E** — Enhanced AV conduction = dromotropy
*All via Gs → AC → cAMP → PKA. β-blockade reverses all four.*

**Pr/2h** *Laplace's law for ventricular wall stress*
**P** — intra-cavitary Pressure
**r** — ventricular radius
**h** — wall thickness (divides)
*Dilation ↑ stress; concentric hypertrophy ↓ stress at any pressure.*

### UPDATES

◉ **SGLT2 inhibitors** in HFrEF/HFpEF — improve diastolic function and outcomes regardless of EF.
◉ **Sacubitril/valsartan (ARNI)** — neprilysin inhibition raises BNP/cGMP-based vasodilator natriuretic signaling.
◉ **Mavacamten** — selective myosin inhibitor for obstructive HCM (sarcomere-targeted Rx).
◉ **Genetic testing** now standard for HCM, ARVC, LQTS, DCM — sarcomere/cytoskeletal/ion-channel panels.
◉ **Strain imaging (GLS)** — sensitive early marker of myocardial dysfunction before EF falls.

# CH 245 · Epidemiology of CV Disease — Epidemiologic Transiti...

*CVD = global #1 cause of death. Five-stage epidemiologic transition; HIC vs. LMIC patterns; behavioral + metabolic risk factors (tobacco, diet, inactivity, lipids, BP, obesity, DM); genetic risk (PGS, CHIP, Lp(a)); COVID-19 impact; prevention strategies.*

## Scope — CVD = Global #1 Killer

- **2022**: CVD = **>19 million deaths/year** worldwide = **33%** of all deaths.
- Before 1900: infections + malnutrition = leading causes; CVD <10%.
- **HIC vs. LMIC** CVD rates have **converged** — same death rate now.
- **LMICs = 85% of world population** → drive global CVD trends.
- **2019**: CHD = 16.2% of all deaths globally (largest YLL contributor at 10%); stroke moved from 3rd → **2nd** largest cause (11.6%).
- Together **CHD + stroke = >25% of global deaths**.

## Epidemiologic Transition — 5 Stages

**Table 245-1 — Five stages of the epidemiologic transition**

| Stage | Era / driver | Dominant CVD pattern | CVD % all deaths |
|---|---|---|---|
| **1. Pestilence & Famine** | Pre-1900 agrarian | Rheumatic HD, nutritional/infectious cardiomyopathy | <10% |
| **2. Receding Pandemics** | Public-health infrastructure | RHD, HTN-HD, stroke (esp. hemorrhagic) | 10–35% |
| **3. Degenerative / Man-made** | Urbanization, smoking, diet shift | **CHD**, ischemic stroke peak | 35–65% |
| **4. Delayed Degenerative** | Preventive Rx, lifestyle, statins | ↑ age at first event; CHD > stroke | <50% (declining) |
| **5. Inactivity & Obesity** | Sedentary, caloric excess, DM2 | Age-adj CVD mortality plateau / rising | Rising |

- Driver = **industrialization + urbanization + lifestyle**; affects every region.
- **HICs** = stages 4–5; CHD > stroke (2- to 5-fold).
- **Eastern Europe/Central Asia** = stage 3 peak — **highest CVD death rate ~55%**; affects working-age population.
- **South Asia / India** = transition Western-style; rheumatic HD still important.
- **Sub-Saharan Africa** = stage 1, RHD still endemic.

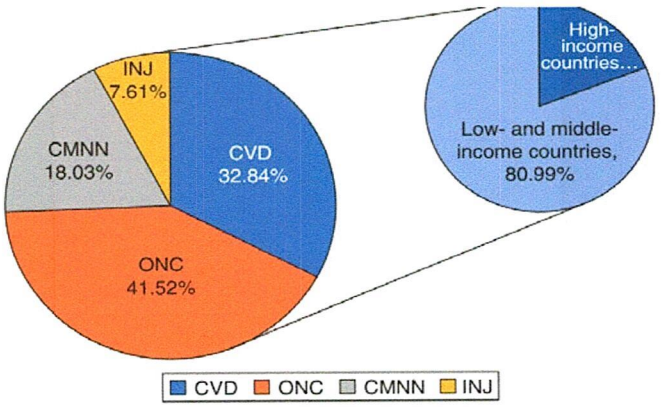



*Fig 245-1 — Global deaths by cause (2019). CVD = 32.84%; ONC = 41.52%; CMNN (communicable/maternal/neonatal/nutritional) = 18.03%; injuries = 7.61%. LMICs contribute ~81% of all deaths.*

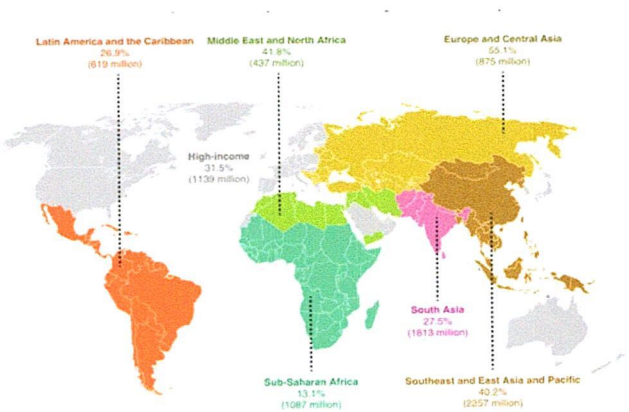



*Fig 245-2 — CVD as % of total deaths by World-Bank economic region. Highest: **Europe & Central Asia 55.1%**; Middle East/N. Africa 41.8%; SE Asia/Pacific 40.2%; HIC 31.5%; Latin America 26.9%; Sub-Saharan Africa 13.1%.*

## Global Trends

- **HICs**: CVD death rate ↓ **50–60%** over past 60 yrs; rate of decline slowing.
- **LMICs**: CVD deaths ↑ **~15% over 20 yrs**; absolute deaths climbing due to aging + population growth.
- 1990 → 2019: **absolute CVD deaths ↑ 54%**, but **age-adj rate ↓ 32%**.
- **US fifth phase**: age-adj death rate declines tapered: 3%/yr (70s-80s) → 2% (90s-2010) → minimal (2010-19) → **↑ in 2020–21** (first rise since early 1960s).
- **Drivers of US plateau**: rising DM2 + obesity; smoking decline stalled; HTN control worsening (since 2016). Offset by ↓ cholesterol from statins.

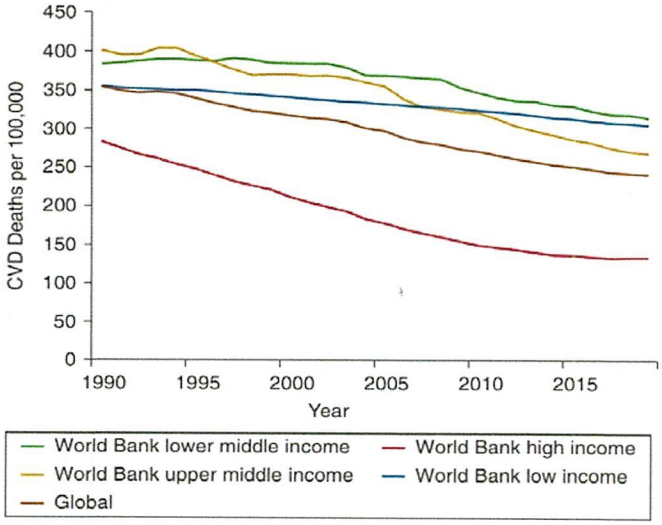



*Fig 245-3 — Age-standardized CVD death rate per 100,000 (1990–2019). All World-Bank income groups declining; declines steepest in HICs, slowest in low-income.*

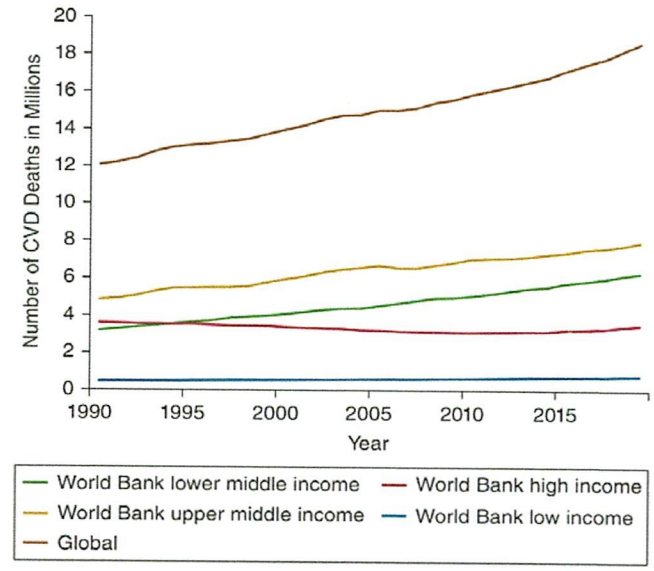



*Fig 245-4 — Absolute number of CVD deaths 1990–2019 by World-Bank income. **Total CVD deaths rising globally** despite age-adjusted rate decline — driven by LMIC population aging + growth.*

**CLINICAL PEARLS**

- Eastern Europe/Central Asia = **highest regional CVD mortality (~55%)** globally.
- **Japan**: traditionally high stroke, low CHD — diet-related; CHD now rising as diet Westernizes.
- Western Europe shows a **north-south gradient** — N (Finland, Ireland, Scotland) > S (France, Spain, Italy = Mediterranean).
- **Rheumatic HD** remains major in South Asia + sub-Saharan Africa.

## Behavioral Risk Factors

### Tobacco

- **>1.3 billion users**; **~8.7 million deaths/yr** (15.4% of all deaths).
- **3.2 million tobacco deaths are CVD.**
- Smoking rates: HIC 21.6% > middle 19.5% > low 11.2%; global avg 22.3%.
- **Secondhand smoke** → ~598,000 CVD deaths/yr in non-smokers.
- Smoking bans → **immediate + long-term benefit.**

### Diet

- Total calories ↑ with development.
- Key shift = ↑ **saturated animal fat** + ↑ hydrogenated/**trans** fats + ↑ simple carbs + ↓ plant-based foods.
- Fat = <20% calories in rural China/India, <30% in Japan, >35% in US.

### Physical inactivity

- Mechanization → agricultural → industrial/office work.
- Inactivity responsible for **1.3 million deaths in 2019.**
- Global inactivity prevalence ~28% (steady 2001-2016).

## Metabolic Risk Factors

### Lipids

- **High LDL-C** → 41% of ischemic HD deaths + 9% stroke deaths = **~4 million deaths/yr.**
- Global mean TC declining 0.07-0.08 mmol/L per decade (driven by HIC statin use).
- **Lipoprotein(a) [Lp(a)]** = independent CVD risk; elevated in ~20% globally; **African > South-Asian/East-Asian > Caucasian**; ↑ lipid accumulation, endothelial dysfunction, prothrombotic.
- **PCSK9 inhibitors** lower Lp(a); specific anti-Lp(a) agents in development.

### Hypertension

- Risk begins at **SBP >110–115 mmHg.**
- 2015: 3.47 billion adults SBP ≥110–115; **874 million** SBP ≥140.
- SBP ≥140 accounts for 25% of those with ↑ BP but **73% of BP-related deaths.**
- **53% of stroke + 53% of CHD deaths** attributable to ↑ BP → ~10.8 million deaths/yr (2019).
- **HIC HTN deaths ↓**; LMIC HTN deaths ↑.
- **US BP control declining since 2016**; many MICs now outperform HICs.
- **Undiagnosed HTN in Asia** → high prevalence of **hemorrhagic stroke.**
- Urbanization → ↑ BP (India urban 33.8% vs. rural 14.5–31.7%).

### Obesity

- **2025**: ~892 million obese adults globally (~16.1% prevalence).
- High BMI → **5.0 million deaths/yr** (7.1% all-cause); **CVD = leading cause** (1.95 million).
- Rising fastest in **LMICs** (steeper trajectories than HICs).
- **Women > men** in obesity prevalence globally.
- Highest male obesity: US, S/C Latin America, Australasia, C/W Europe.
- Highest female obesity: S/N Africa, Middle East, C/S Latin America, US.
- Lowest: S/SE Asia, E/C/W Africa.

### Diabetes mellitus (mostly T2DM)

- **~476 million** with DM globally; projected **~693 million by 2045.**
- Prevalence ↑ **~130% (M) / 121% (F)** from 1990 → 2017.
- **~50% undiagnosed; 80% live in LMICs.**
- Highest regional prevalence: **Middle East / North Africa** 8.7%; lowest = East Asia/Pacific 5.8%.

## COVID-19 Impact on CVD

- **Delayed presentation** for ACS / stroke → worse outcomes.
- Obesity + DM worsened COVID outcomes.
- **Reduced HTN + dyslipidemia control** from limited provider access.
- Contributed to **2020-21 CVD death rate ↑** in US.