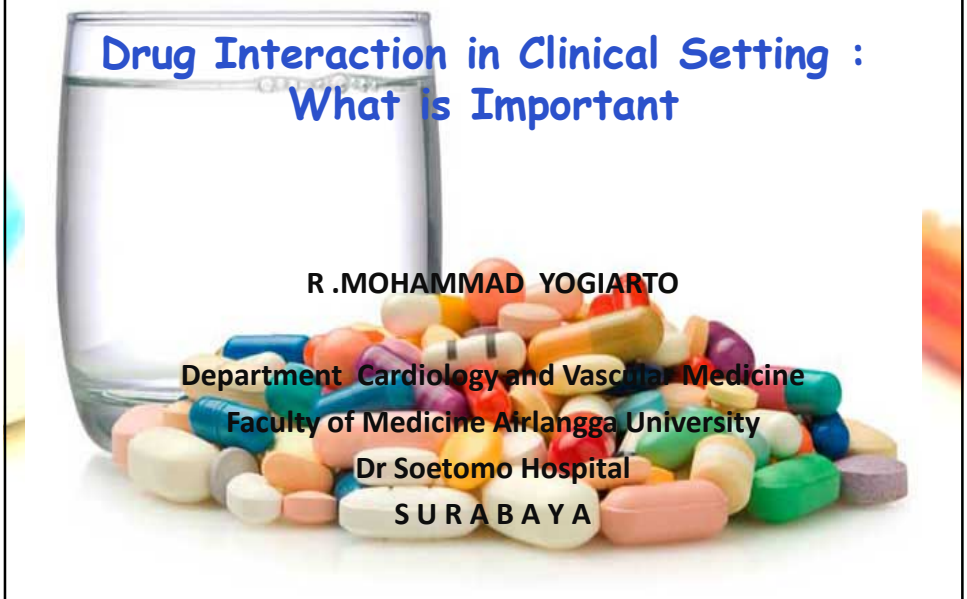
Drug Interaction in Clinical Setting : What is Important



R .MOHAMMAD YOGIARTO

Department Cardiology and Vascular Medicine
Faculty of Medicine Airlangga University
Dr Soetomo Hospital
S U R A B A Y A

Doctor should elicit a **detailed drug history** of the patient and record all the medication that he/ she is currently on.

Definition

- ***Drug interaction*** **is defined as the pharmacological activity of *one drug* is altered by the concominant use of *another drug* or by the presence of some *other substance.***

Drug interactions: Are they really important?

- Metaanalysis of 39 prospective clinical trials has proved:
- Adverse Drug Reactions are 4th most frequent cause of death
- Lazarou et al: JAMA 1998

- Analysis of USA National Drug Register has proved:
- The cause of 2/3 of ADRs are drug interactions
- Phillips et al: JAMA 2001

Every Drug Interaction is Harmful ????

NO

- Several drug interactions are deliberately employed **in therapeutics**, e.g.
  - **ACE inhibitors + diuretics** to treat hypertension or
  - **Sulfamethoxazole + Trimethoprim** to treat bacterial infection or
  - **Furosemide + amiloride** to prevent hypokalaemia.
  - **Ca channel Blocker + ACEI/ARB**

Risk Factor

- Poly pharmacy
- Multiple prescribers
- Multiple pharmacies
- Specific population
- Specific illness
- Narrow therapeutic index drugs

(eg. Cyclosporine, digoxin, insulin, lithium, antidepressant, warfarin)

Prescribing to Avoid Adverse Drug Reactions

- Interactions can occur before or after administration of drugs
- Pharmacokinetic interactions
  - GI tract
  - Plasma
  - Liver
  - Kidney
- Pharmacodynamic interactions
  - Can occur at target organ
  - Can be systemic (e.g., blood pressure)

MECHANISM OF DRUG INTERACTIONS

- **Drug interactions can be broadly divided into**
  - **Pharmaceutical Interaction**
    - **During dosage form preparation or at time of administrations.**
    - **Dissolving the drug in solvent,**
    - **Mixing drugs in powder, solution or injection forms.**
  - **Pharmacokinetic (ADME)**
    - **Absorption (Complex or Chelate formation, Altered stomach pH, Ionization, GIT motility, First Pass Metabolism)**
    - **Distribution (Protein binding)**
    - **Metabolism (Enzyme induction/inhibition)**
    - **Excretion (Altered pH, Ionization, Entero-hepatic recirculation)**
  - **Pharmacodynamic (At receptor or tissue level)**

Different kinds of drug interactions

Drug interactions: → **PHARMACOKINETIC**, **PHARMACODYNAMIC**

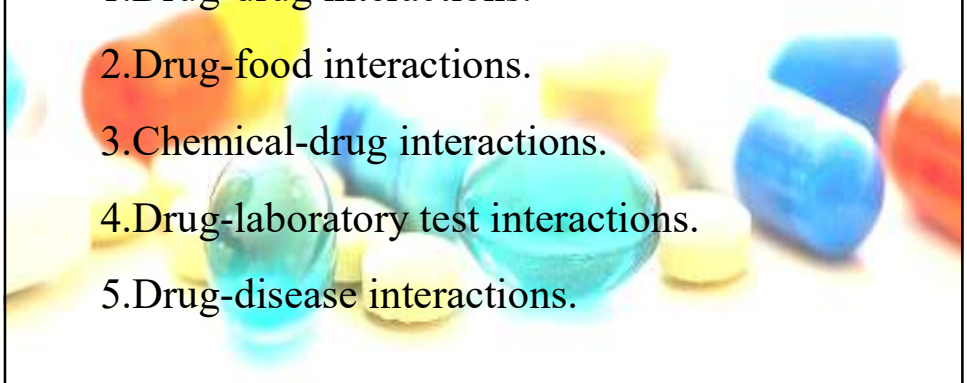
- **Interaction drug - drug**
- **Interaction drug - alcohol**
- **Interaction drug - foods (and soft drinks)**
- **Interaction drug – food supplements**

All these kinds are divided into:

Drug interactions:
- **clinically relevant**
- **not clinically relevant**

Types of Drug Interactions

1. Drug-drug interactions.
2. Drug-food interactions.
3. Chemical-drug interactions.
4. Drug-laboratory test interactions.
5. Drug-disease interactions.



Effect of Drug Interactions

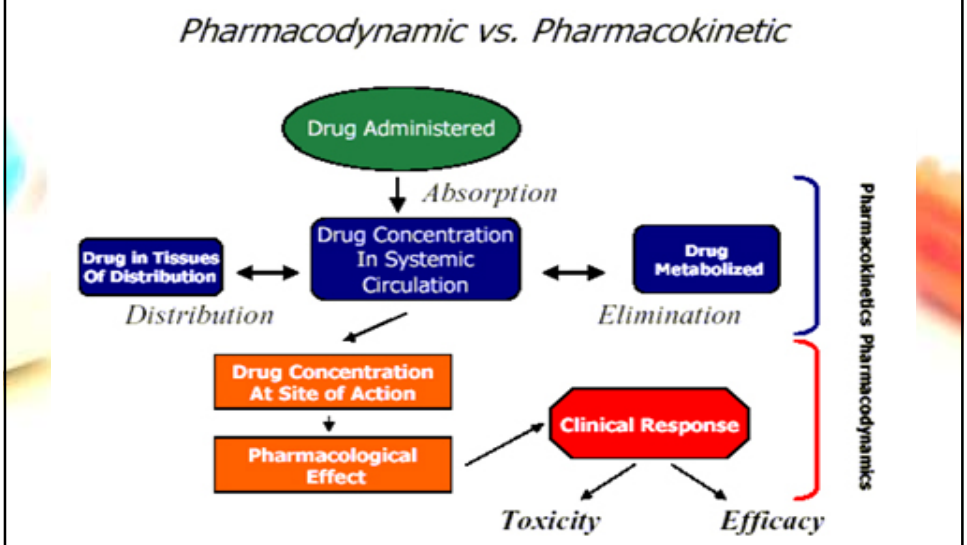
- **Drug interaction can result in**
  - **Increased effect – Additive or Synergistic effect**
  - **Decreased effect – Antagonistic effect**
- **Drug interactions usually happen unexpectedly and result in adverse drug reactions**
- **Drug interactions for good therapeutic effects are usually used intentionally and their results are already known by physicians**

Effects of drug interactions

- These can be desirable, adverse or inconsequential.
- Majority of drug interactions are desirable or inconsequential.
- Clinically desirable drug interactions can form part of therapeutic regimens when two or more drugs with different

(e.g to lower elevated blood pressure.)

Mechanism

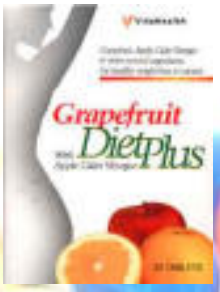


Drug interaction mechanisms

- Mechanisms of drug interactions- pharmacokinetic and pharmacodynamic.
- ***Pharmacokinetic***

1. Chemical interactions
2. Interactions affecting oral availability
3. Protein binding interactions.
4. Interactions due to altered biotransformation
5. Interactions due to altered renal excretion.

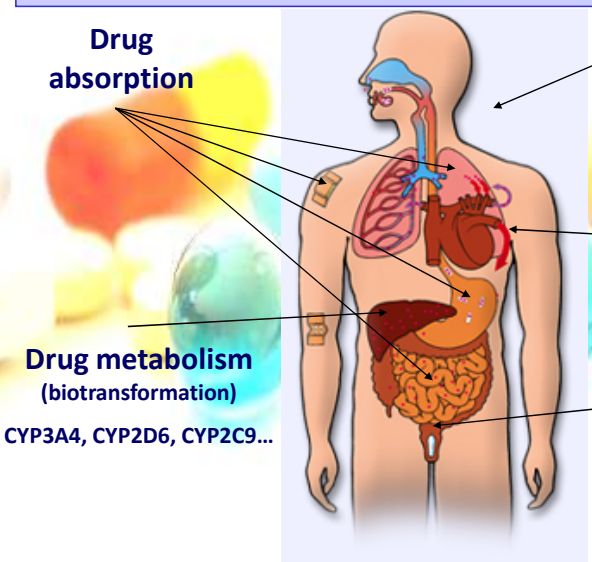
Drug-Food interactions



- Grapefruit juice and Terfenadine
- Grapefruit juice and cyclosporin
- Grapefruit juice and felodipine
- Grapefruit contains : furanocoumarin compounds that can selectively inhibit CYP3A4

Pharmacokinetic Interactions

Pharmacokinetic drug interactions



Pharmacokinetic Interactions

- Most drug interactions involve an alteration in the pharmacokinetics of the drug
- Probably no 'overlap' in the therapeutic effects of the two drugs
- Difficult to predict
  1. Absorption
  2. Distribution
  3. Metabolism
  4. Excretion

Drug Absorbtion

- Drug interactions can either delay the onset of drug action or increase or decrease the amount of drug absorbed
- Rate of drug absorption is a concern when a fast onset of absorption is necessary
- An example of this would be analgesics. A rapid response is often desired when the patient is in pain
- This is important because it can ultimately affect drug levels.

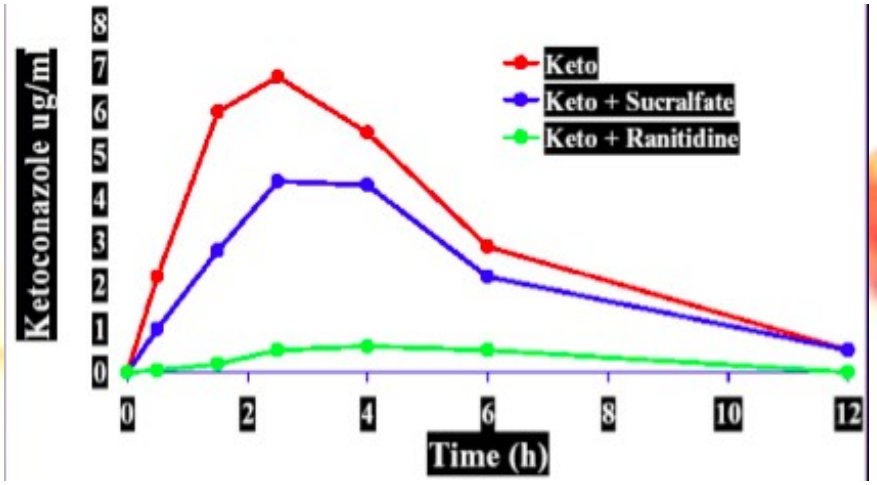
Drug Absorbtion

OBJECT DRUG	PRECIPITANT DRUGS	INFLUENCE ON OBJECT DRUG
ABSORPTION INTERACTION *1.COMPLEXATION & AbSORPTION*		
CEPHROFLOXACINE, PENCILLAMINE	ANTACIDS,FOOD & MINERALS SUPPLEMENTS CONTAINING AL,Mg,Fe,Zn & Ca IONS	FORMATION OF POORELY SOLUBLE AND UNABSOBABLE COMPLEX WITH SUCH HEAVY METAL IONS.
2.ALTERATION OF GI PH		
SULPHONAMIDES, ASPIRIN FERROUS SULPHATE	ANTACIDS SODIUM BICARBONATE,CALCIUM CARBONATE	ENHANCED DISSOLUTION AND ABSORPTION RATE. DECREASED DISOLLUTION AND HENCE ABSORPTION.
3.ALTERATION OF GUT MOTILITY		
ASPIRIN DIAZEPAM, LEVODOPA, MEXILETINE	METOCLOPRAMIDE	RAPID GASTRIC EMPTYING,INCREASED RATE OF ABSORPION.
LEVODOPA, LITHIUM CARBONATE, MEXILETINE	ANTI CHOLINERGICS	DELAYED GASTRIC EMPTYING;DECREASED RATE OF ABSORPTION.

Drug Absorbtion

OBJECT DRUG	PRECIPITANT DRUGS	INFLUENCE ON OBJECT DRUG
4.ALTERATION OF GI MICROFLORA		
DIGOXIN	ANTI BIOTICS	INCREASED BIOAVAILABILITY DUE TO DESTRUCTION OF BACTERIAL FLORA THAT INACTIVATES DIGOXIN IN LOWER INTESTINE.
5.MALABSORPTION SNDROME		
VITAMIN A,B_{12},DIGOXIN	NEOMYCIN	INHIBITION OF ABSORPTION DUE TO MAL.

Drug Absorbtion



Distribution Interactions

- There is an important factor : Vd
- Protein binding interactions :
  - **unbound** molecules remain free and pharmacological **active**
  - **Bound** molecules are pharmacological **inactive**
- The major mechanism for distribution interaction is alteration in protein-drug binding.

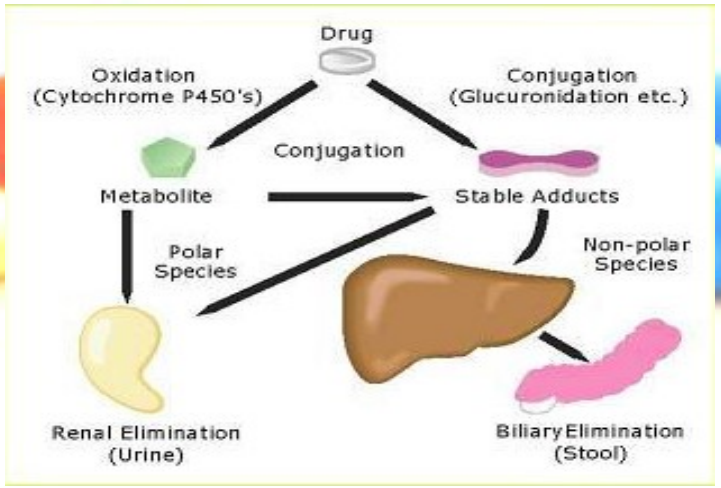
Distribution Interactions

- Only drugs with **low** Vd will be affected.
  ex: **Warfarin** (99% bound) and **Phenytoin** (90% bound)

Competitive displacement interactions		
Displaced drug	***Displacer***	
Anti coagulants	Phenylbutazone, chloral hydrate, phenytoin	Increased clotting time. increased risk of hemorrhage.
Tolbutamide	Sulphonamides	Increased hypoglycemic effect.

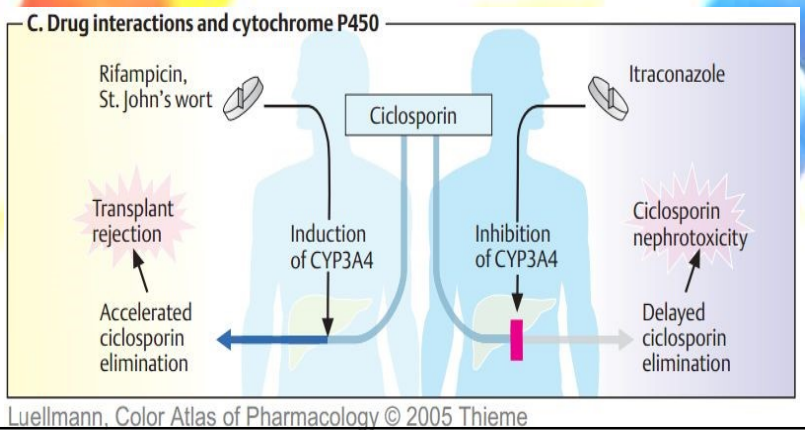
Metabolism

- Pathways of drug interaction



Metabolism

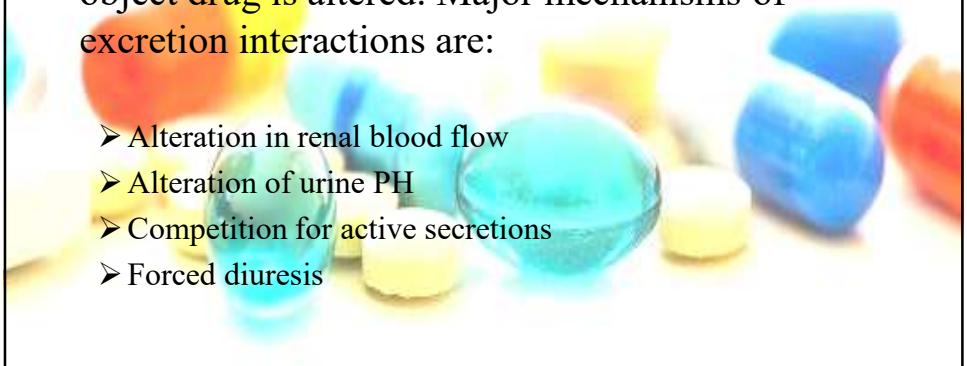
- Types of drug metabolism interaction :
  - Enzyme induction
  - Enzyme inhibition



Luellmann, Color Atlas of Pharmacology © 2005 Thieme

Excretion

- Are these where the excretion pattern of the object drug is altered. Major mechanisms of excretion interactions are:
  - ➢ Alteration in renal blood flow
  - ➢ Alteration of urine PH
  - ➢ Competition for active secretions
  - ➢ Forced diuresis



Excretion

EXCRETION INTERACTIONS		
1.CHANGES IN ACTIVE TUBULAR SECRETION		
PENCILLIN,CEPHALOSPORINS,NALIDIXIC ACID	PROBENICID	ELEVATED PLASMA LEVELS OF ACIDIC DRUGS
2.CHANGES IN URINE PH		
AMPHETAMINE	ANTACIDS,THIAZIDESACETAZOLAMIDE	INCREASED PASSIVE REABSORPTION OF BASIC DRUGS.INCRESED RISK Of TOXICITY
3.CHANGES IN RENAL BLOOD FLOW		
LITHIUM BICARBONATE	NSAIDS	DECREASED RENAL CLEARANCEOF LITHIUM.RISK OF TOXICITY

Pharmacodynamic Interactions

- Are those in which the activity of the object drug at its site of action is altered by the precipitant.

✧ Direct pharmacodynamic interactions

✧ Indirect pharmacodynamic interactions

Direct Pharmacodynamic Interactions

- In which drugs having similar or opposing pharmacological effects are used concurrently

- **The three consequences of direct interactions are:**
  1. Antagonism.
  2. Addition or summation
  3. Synergism or potentiation

*D*irect Pharmacodynamic Interactions

✧ **Antagonism:**

The interacting drugs have opposing actions
Ex: Beta-blocker plus salbutamol

✧ **Addition or Summation:**

The interacting drugs have similar actions and the resultant effect is the some of individual drug responses

Ex:Two beta-blockers, Morphine plus diazepam

✧ **Synergism or potentiation:**

It is an enhancement of action of one drug by another

Indirect Pharmacodynamic Interactions

- In which both the object and the precipitant drugs have unrelated effects, but latter in some way alerts the effects of the former
- Ex: salicylates decrease the ability of the platelets to aggregate thus impairing the Homeostasis if warfarin induced bleeding occurs

Consequences of Drug Interactions

The consequences of drug interactions may be:

- Major: Life threatening
- Moderate: Deteriotion of patients status
- Minor: Little effect

Reducing The Risk of Drug Interactions

1.Identify the patients risk factors.

2.Take through drug history.

3.Be knowledge about the actions of the drugs being used.

4.Consider therapeutic alternatives.

5Avoid complex therapeutic regiments when possible.

6.Educate the patient.

7.Monitor therapy.

Prevention of adverse drug interactions

1 .Document all drugs including herbal prearations, OTC,recreational drugs that the patient is taking.

2 .Understand the pharmacokinetics and pharmocodymics of the drugs given ,keeping in mind the important mechanisms of drug interations.

3 .Minimize the number of drugs given to any patient an try to ensure that the benefits outweigh the risks for each.

4 .Be particularly vigilant with patients taking low therapeutic index drugs.

Prevention of adverse drug interactions cont.

5 .Be cautious in high risk clinical settings.ICU specialists need to remember interactions all the time.

6 .Whenever a patients course deteriorates, look out for a possible adverse drug interaction.IF the deterioration is due to drug therapy,it probably is reversible.

7 .Use textbooks of drug interactions or modern software programs to search for possible drug induced effects you may not have considered.

8 .Always be vigilant for previously undescribed interactions,particularly when prescribing new or unfamiliar drugs.

Summary

- Multimorbidity and polypharmacy increase clinical workload, drug interaction
- There should be **more comprehensive** in managing complex multi-morbidity, polypharmacy and other aspects of medicines management.
- **Doctors, nurses and pharmacists need to work coherently as a team,** to have holistic management

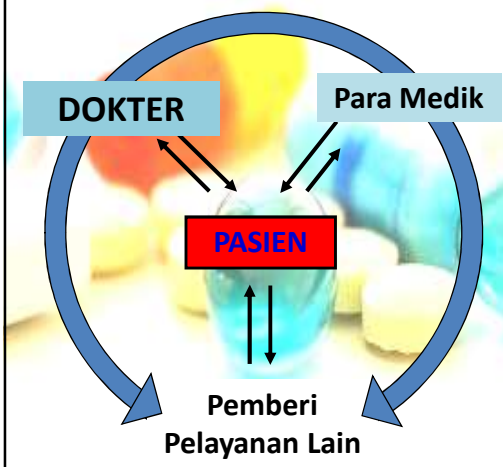
Medicine Optimisation & Polypharmacy Challenges..

- Time, resources, manpower – doctors, nurses, pharmacists
- Importance of formal medication review
- Multidisciplinary assessment (vs. specialism)
- 'One-stop shop' reviews
- Getting evidence of improved patient outcome
- Shared decision-making (and recording)
- Coding accuracy for decision support
- Adaptive guidelines
- Alert fatigue
- Use of "order sentences" & stating what medication is for
- Interfaces, and integrated care; care homes

Clinical Pharmacists in The Team

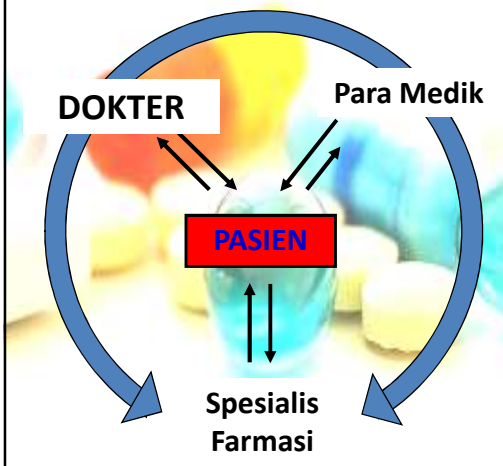
- **Reviewing** systems – repeat prescriptions, drug monitoring protocols, response to hazard/warnings
- Significant event reviews, **audits**
- **Identifying** and targeting those on high risk drugs at risk (polypharmacy, multimorbidity, frail etc.)
- Post discharge and reconciliation reviews
- Support to **home care**
- Medication reviews – medicines optimisation

Holistic approach in management patient with Cardiovascular Disease



- Lebih berpusat pada Pasien
- Semua Pemberi Pelayanan harus bekerja sama
- Ada kerja sama dengan Pasien
- Tidak ada pemberi pelayanan yang mendominasi secara terus-menerus

Holistic approach in management patient with Cardiovascular Disease



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Thank
you