Physiological Changes and Comorbidities Associated with Aging: Relation to Risk of Cancer Therapy Toxicity

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Aging and Cancer

- Cancer Biology and Aging
- Comorbidity and Aging
- Pharmacology of Anti-Neoplastic Agents in the Elderly
- Toxicity of Anti-Neoplastic Agents in the Elderly

Overlap in Natural Aging Processes and Cancer

- Cellular senescence
  - Triggered by cellular stresses
  - Controlled by tumor suppressor pathways
- Genomic instability
  - Age-dependent accumulation of somatic mutations
  - Aging results from chronic increase in level of DNA damage
- Telomere loss
- Autophagy

Finkel et al. Nature. 448; 2007, 767-774.

Cancer Biology and Aging

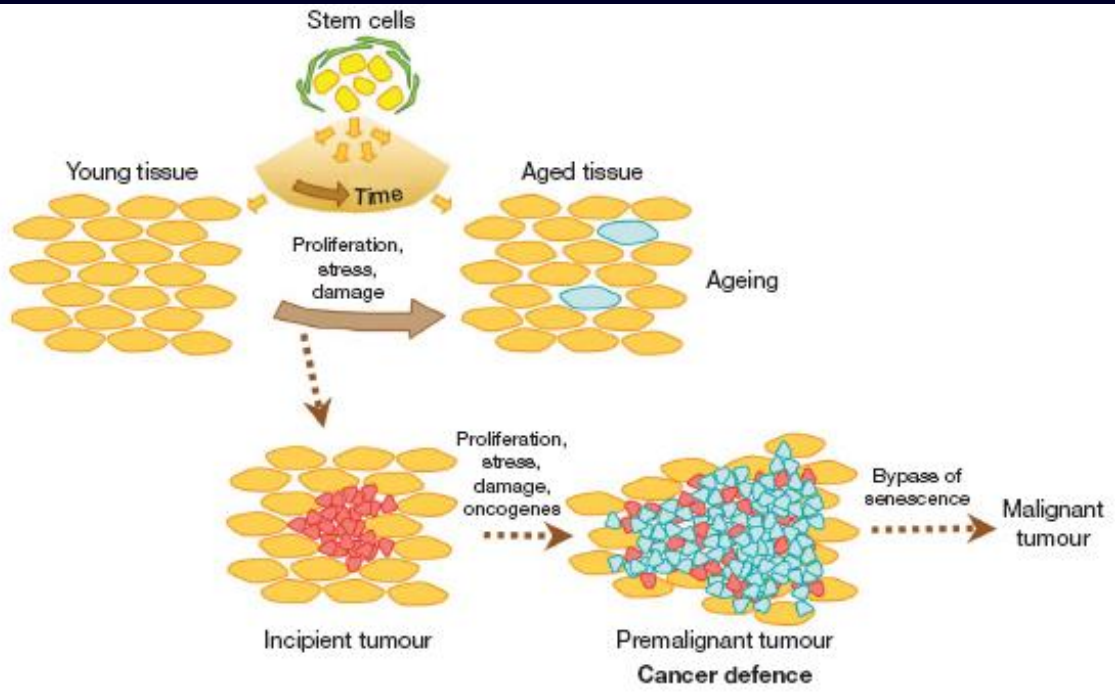


Figure 1 | The potential interplay between stem cells, stress, ageing and cancer. During normal ageing, stem cells accumulate damage and subsequent stress-dependent changes (for example, de-repression of the *CDKN2a* (*INK4a/ARF*) locus or telomere shortening). This leads to the increasing abundance of senescent cells (large blue cells) within differentiated tissues. Incipient tumours, arising directly from stem cells or from more committed cells, undergo rapid proliferation (small red cells). These pre-malignant tumour cells rapidly accumulate damage, in part owing to the presence of oncogenes, leading to a higher proportion of tumour cells becoming senescent (small blue cells). Tumour progression to full malignancy is favoured when tumour cells acquire mutations that impair the senescence program (for example, mutations in *Trp53* or *CDKN2a*).

Finkel et al. Nature 2007; 767.

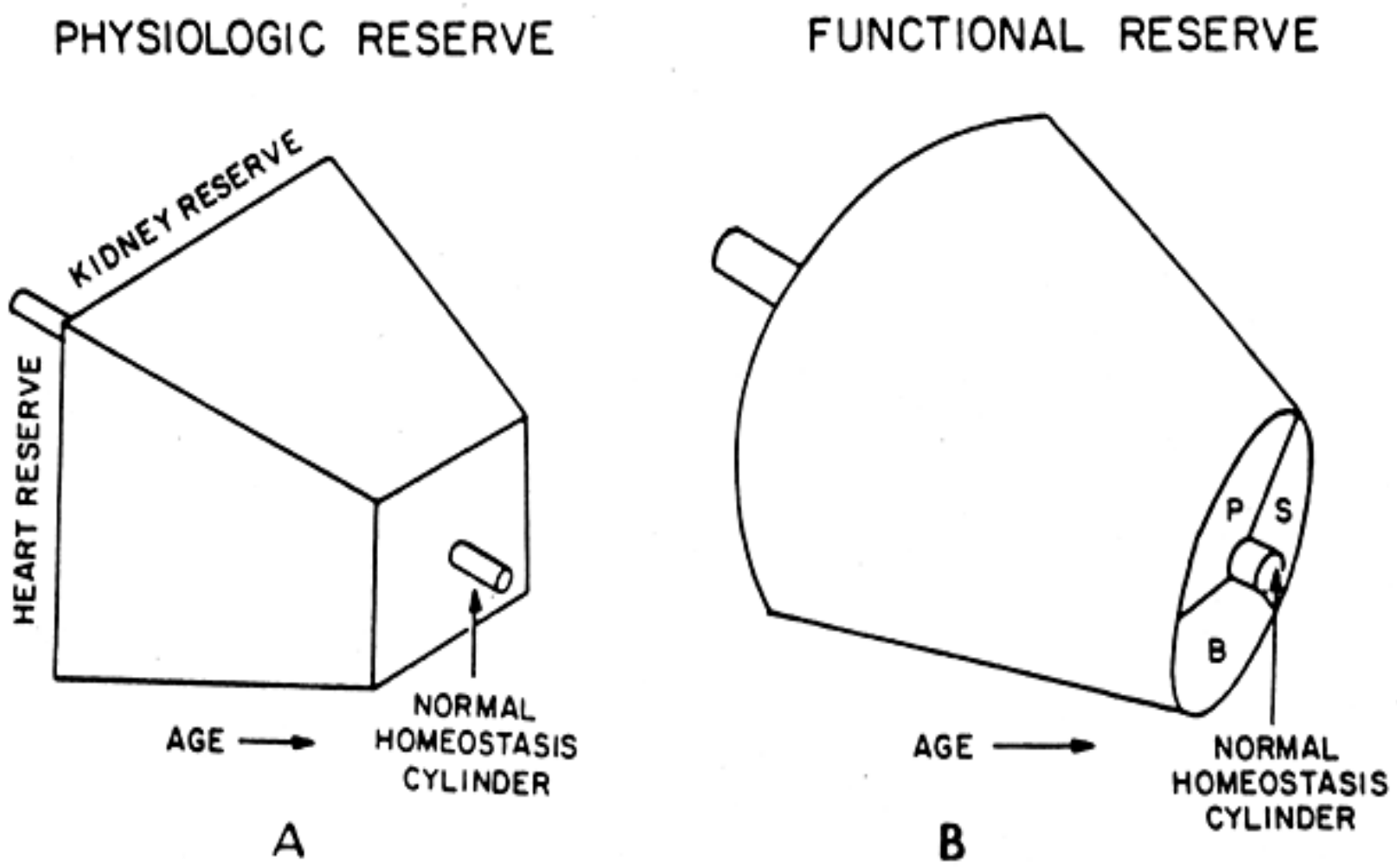
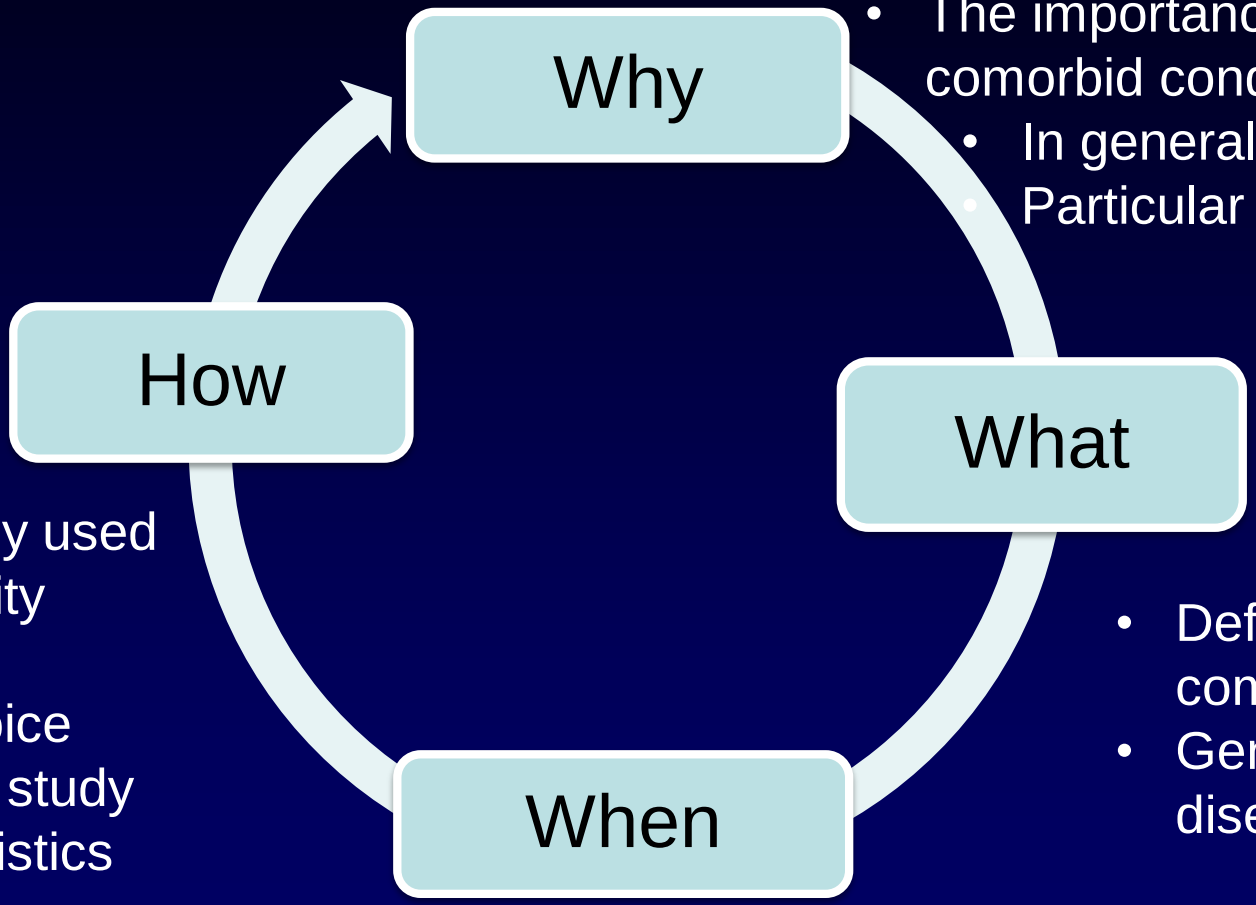


Figure 2. Functional aging. *A*, The Fries and Crago model of diminishing area of physiologic reserve due to the decline function. A stress to the individual that carries outside the outer envelope will result in death. (Reproduced with permiss Fries JF and Crapo LM: Vitality and Aging. Implications of the Rectangular Curve. San Francisco, W. H. Freeman, 1981, p. 3 expanded model representing the diminishing area of functional reserve due to the decline in biopsychosocial functions. Th homeostasis cylinder represents the physical and instrumental activities of daily living (see text). Death will occur when f reserves decrease to a point less than that amount required by the homeostatic cylinder or when a stress exceeds the comp functional reserves.

Comorbidity Measures – *what is the what?*



- The importance of comorbid conditions
  - In general
  - Particular to cancer

- Definitions of comorbidity
- Generic vs. disease-specific

- Situations in which it may be important to measure comorbidity

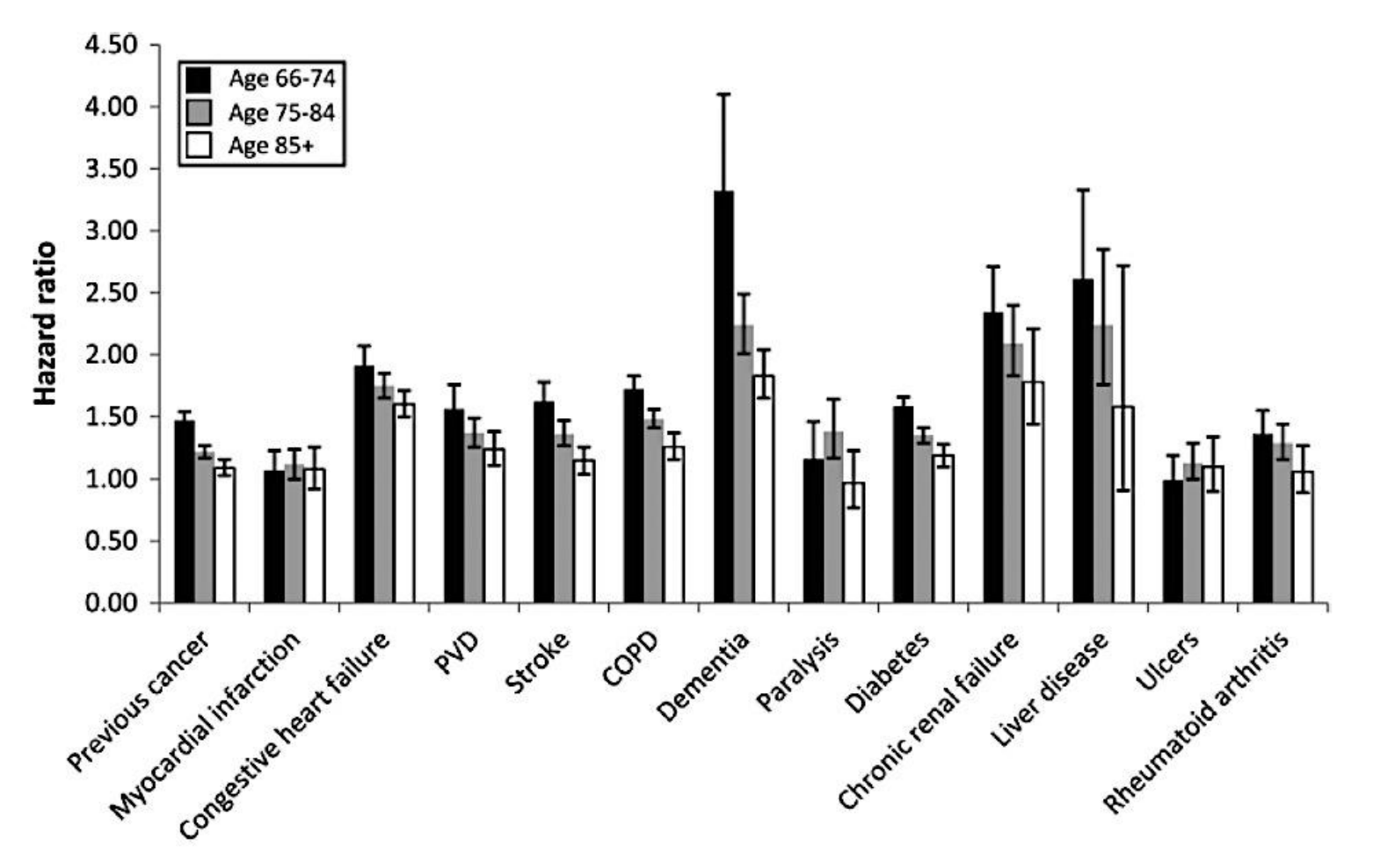
- Commonly used comorbidity indices
- Index choice based on study characteristics

Comorbidity in Cancer

- A coexisting medical condition that exists along with an index condition that has implications for an outcome
- No gold standard for measurement
- Particular importance in cancer
  - Confounder or mediator of effect
  - Outcome of interest
  - Distinguish from toxicity

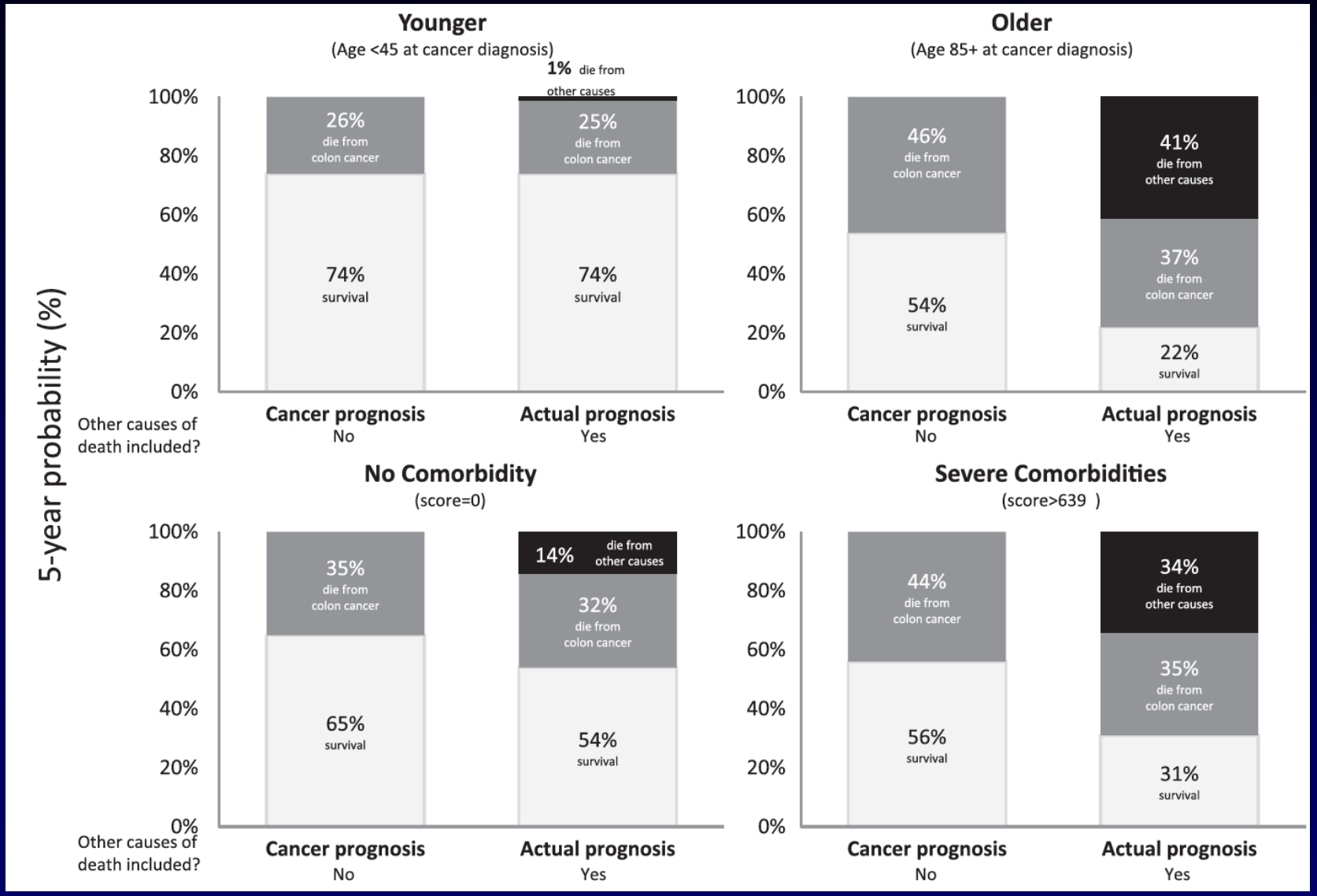
Sorensen HT. Clin Epi 2013:5 (suppl1):1-2.
Ritchie CS. J Oncol Practice 2011;7:371-4.

What to Measure: Individual Comorbidities vs. a Summated Index



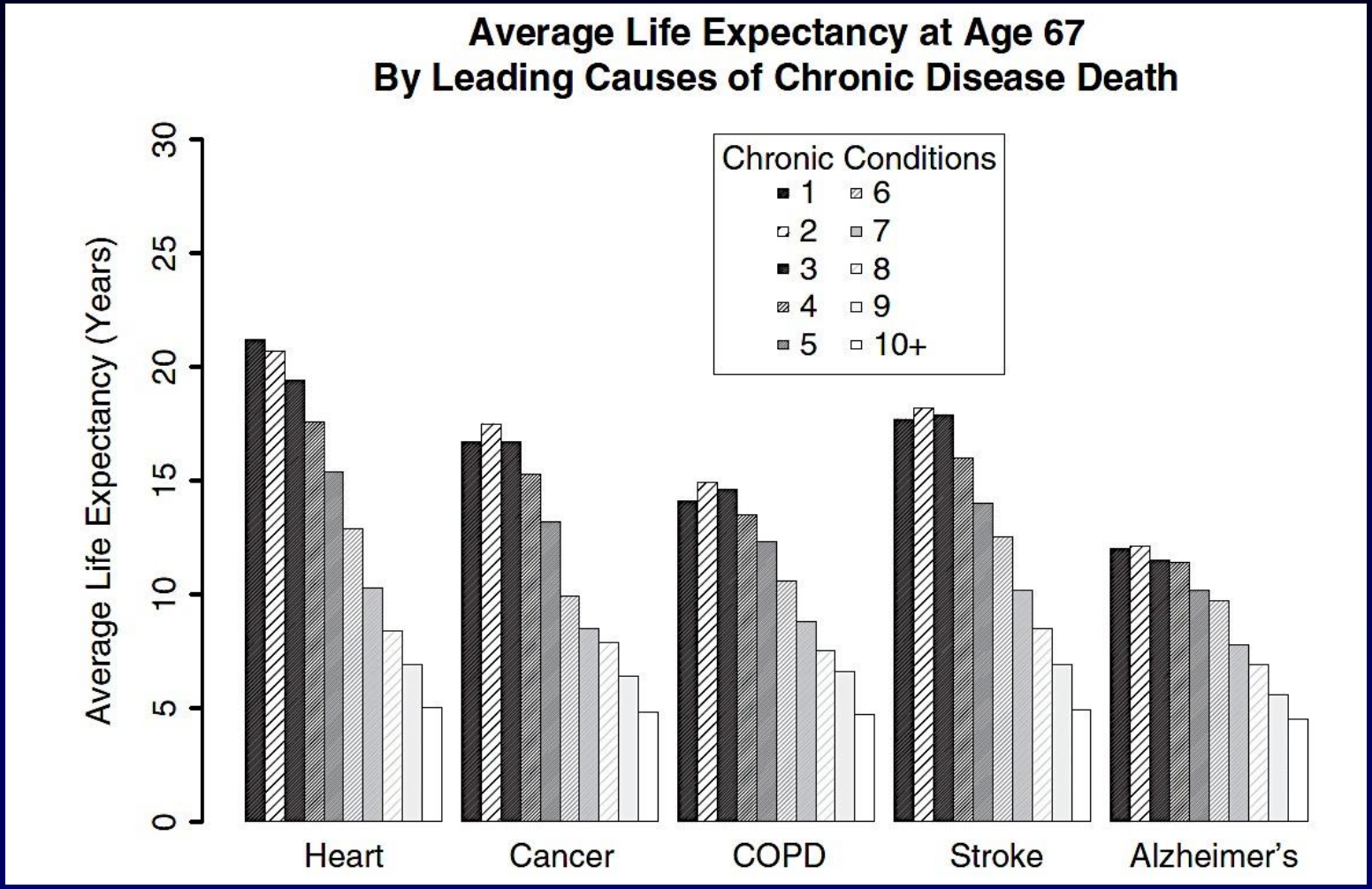
Patnaik JL et al. J Natl Cancer Inst. 2011 Jul 20; 103(14): 1101–1111.

Comorbidity and Prognosis



Howlander, JNCI Monographs, 2014;49:255-264

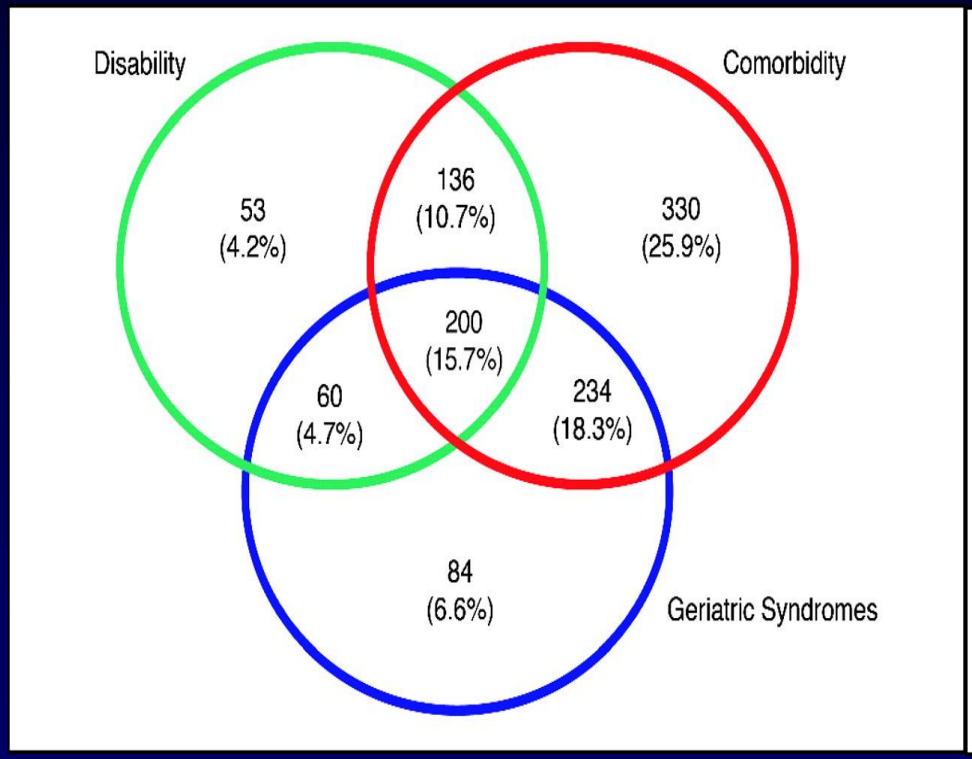
Impact of Number of Chronic Conditions on Life Expectancy



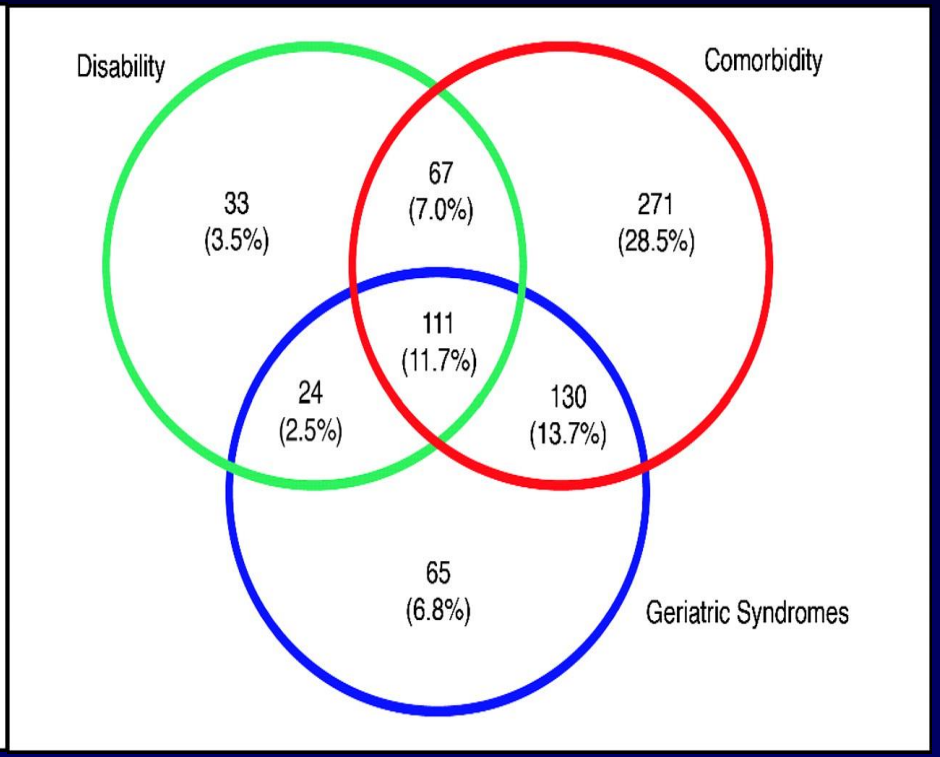
DuGoff EH, et al. Med Care 2014;52:688-94.

Comorbidity ≠Disability ≠ Geriatric Syndromes

Colorectal Cancer



Breast Cancer



Koroukian, S. M. et al. *J Clin Oncol*; 24:2304-2310 2006

What is Multimorbidity?

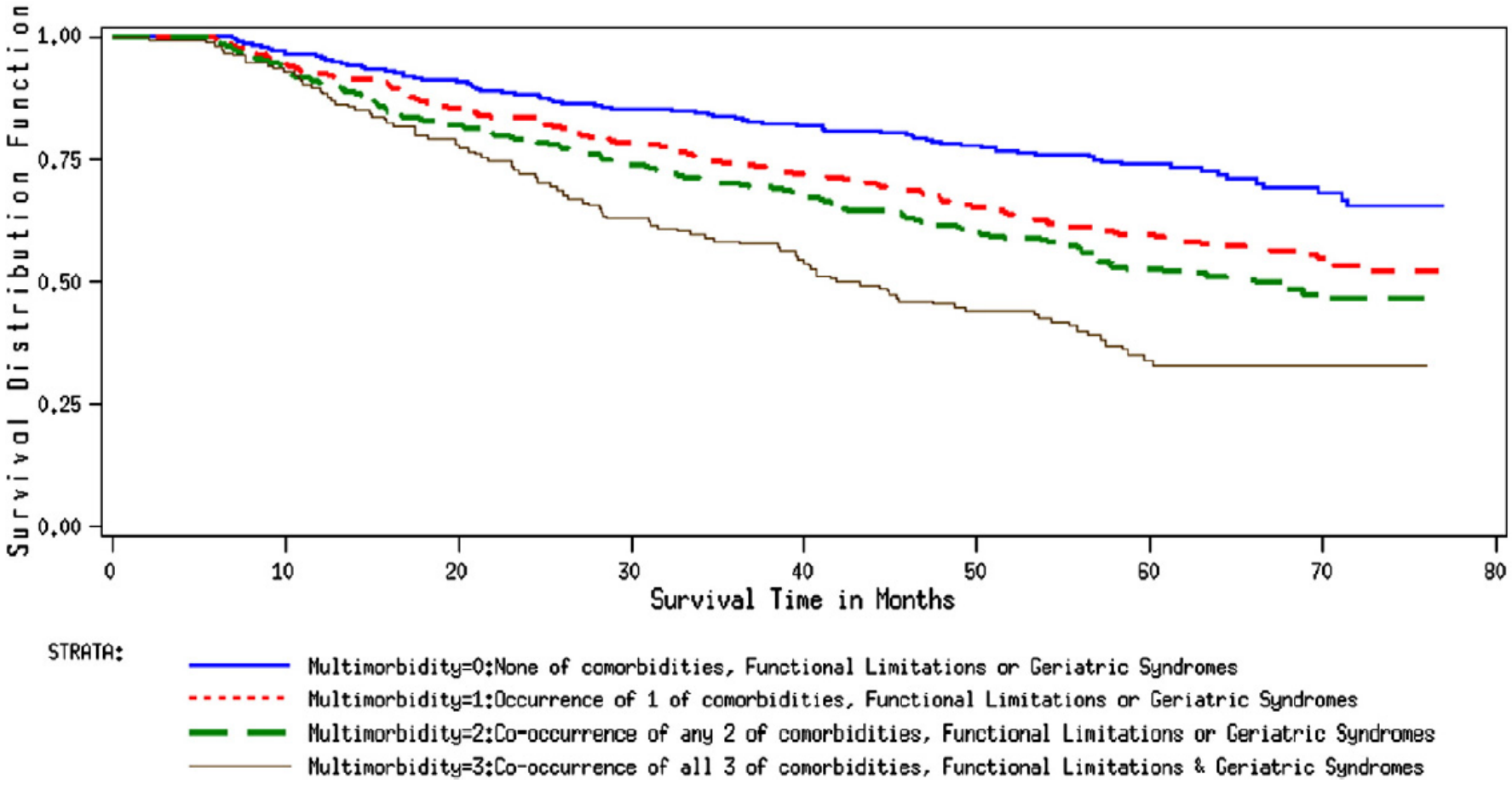
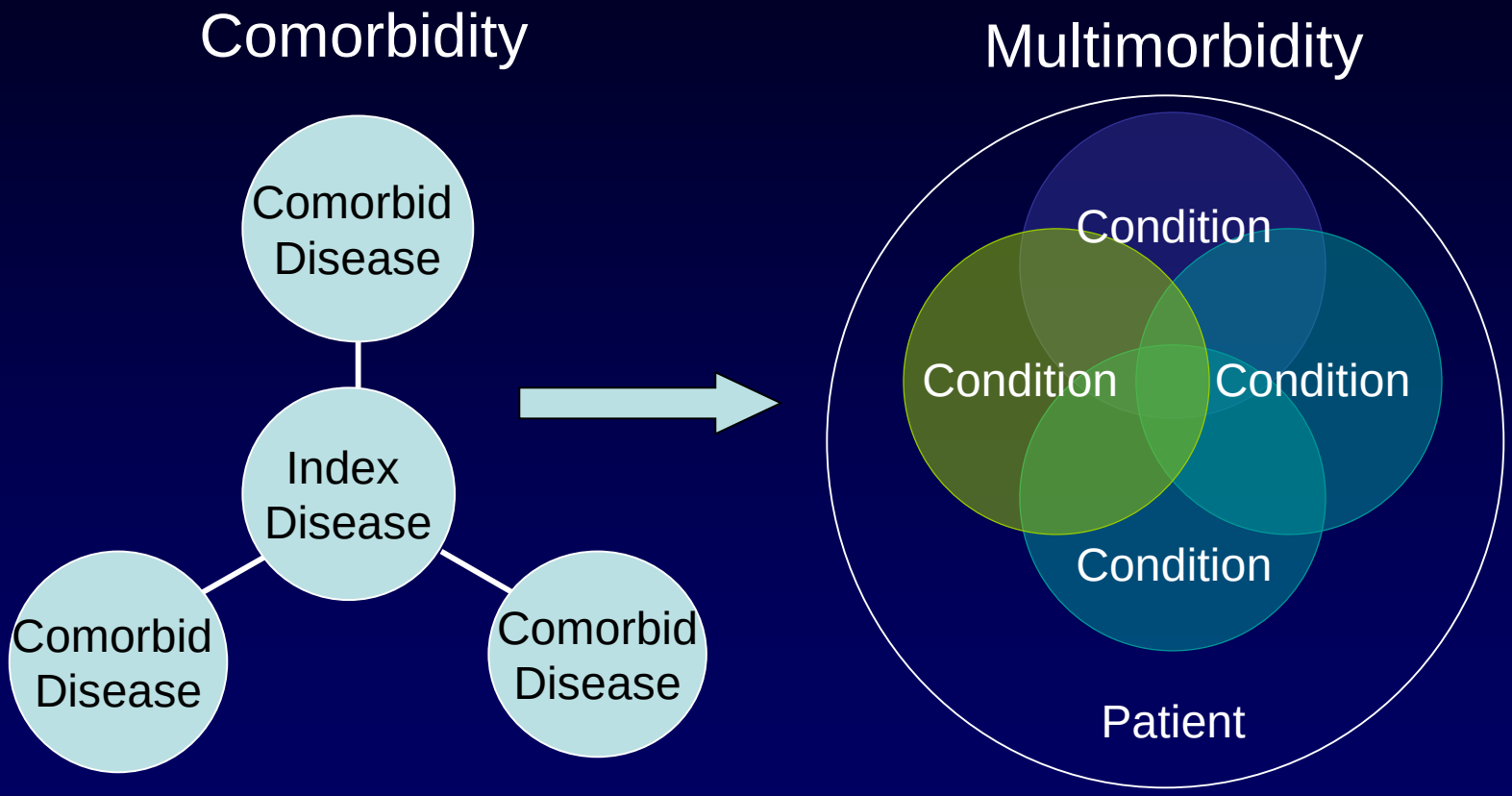


Fig. 1 – Overall survival by Multimorbidity. Log-Rank chi-square = 58.3 p < 0.0001.

Koroukian S, et al. J Geriatr Oncol 2011;2:200-8.

More than half of people 65 and older have 3+ chronic conditions



Boyd, CM, Fortin M. Public Health Reviews, 2011.

Importance of Multimorbidity

Brendan Smialowski (NY Times)

- *Increased risk of*:
  - Death
  - Institutionalization
  - Increased utilization of healthcare resources
  - Decreased quality of life
  - Higher rates of adverse effects of treatment or interventions
- *Almost all existing "guidelines" have single disease focus*
- *Best approaches to decision-making and clinical management of older adults with multimorbidity* ***remain unclear***

AGS Expert Panel on the Care of Older Adults with Multimorbidity. J Am Geriatr Soc 2012;60:1957-68

AGS

Pharmacologic Processes Affected by Aging

- Absorption
- Distribution
- Metabolism
- Excretion

Aging and Absorption

- Amount absorbed (*bioavailability*) is not changed
- Peak serum concentrations may be higher or lower, and delayed
- Exceptions: drugs with extensive first-pass effect (bioavailability may increase because less drug is extracted by the liver, which is smaller with reduced blood flow)
- Factors that may affect absorption
  - Reduced gastric secretion
  - Reduced gastric emptying time
  - Reduced gastrointestinal motility
  - Diminished splanchnic blood flow
  - Decreased absorption surface
  - Concomitant medications, ie. H2 blockers, antacids

Effect of Aging on Distribution

- Doubled fat content
- Decreased intracellular water
- Increased volume of distribution (Vd)
- Lowered peak concentration and prolonged terminal $t_{1/2}$
- Reduced albumin concentrations
  - (etoposide and taxanes are highly protein bound)
- Displacement of protein-bound drugs by other medications

Aging and Metabolism

- Metabolic clearance of a drug by the liver may be reduced because:
  - Aging decreases liver blood flow, size, and mass, and
  - The liver is the most common site of drug metabolism

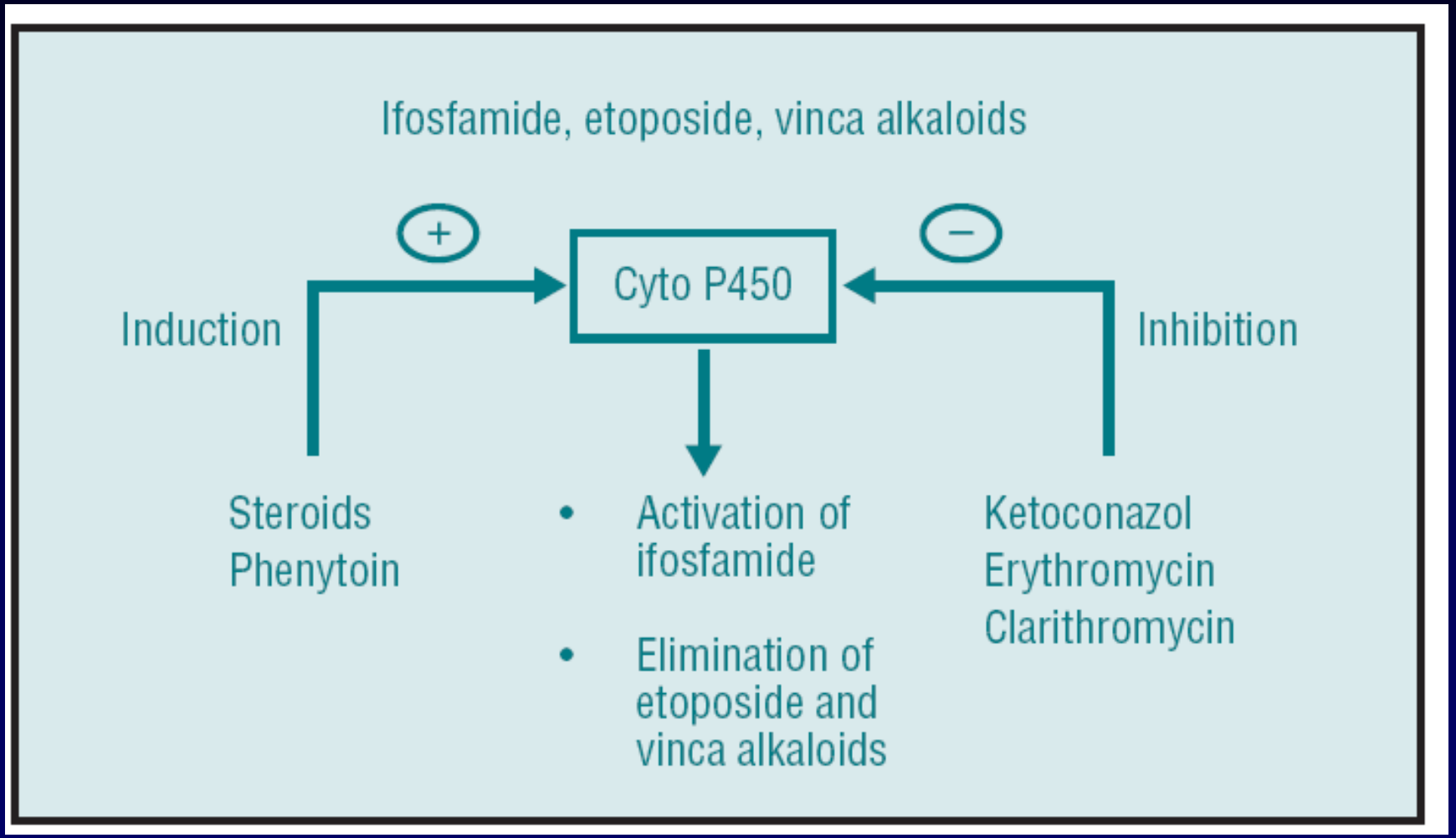
Hepatic Metabolism

- Reduced blood flow to liver
- Decreased liver size
- Age related changes in P450 microsomal systems
  - 32% decline after age 70
- Polypharmacy
  - P450 inhibitors (e.g., grapefruit juice)
  - P450 inducers (e.g., phenobarbital)

Agents for which Hepatic Dysfunction is Important in Dosing

- Gemcitabine
- Docetaxel
- Paclitaxel
- Vinorelbine
- Anthracyclines
- Ifosfamide

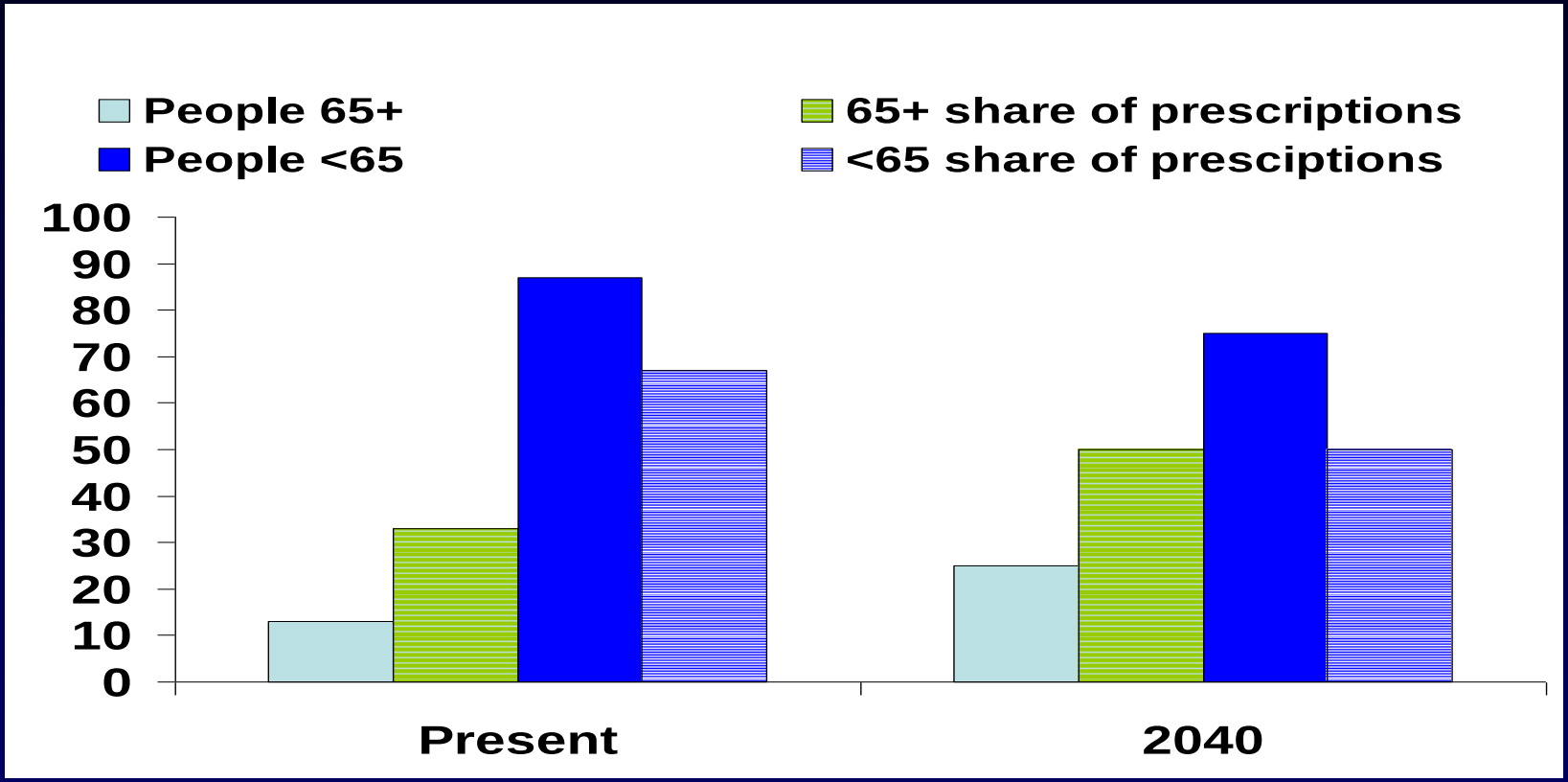
Role of Cytochrome P450



Cytochrome P-450 and Drug Interactions

- Effects of aging and clinical implications are still being researched
- CYP3A4 is involved in more than 50% of drugs on the market
- CYP3A4 is induced by rifampin, phenytoin, and carbamazepine and is inhibited by macrolide antibiotics, nefazodone, itraconazole, ketoconazole, and grapefruit juice

Polypharmacy



Now, people age 65+ are 13% of US population,
buy 33% of prescription drugs.
By 2040, will be 25% of population, will buy 50% of prescription drugs

Risk Factors for Adverse Drug Events

- 6 or more concurrent chronic conditions
- 12 or more doses of drugs/day
- 9 or more medications
- Prior adverse drug reaction
- Low body weight or low BMI
- Age 85 or older
- Estimated CrCl < 50 mL/min

Common Drug-Drug Interactions

Combination	Risk
ACE inhibitor + diuretic	Hypotension, hyperkalemia
ACE inhibitor + potassium	Hyperkalemia
Antiarrhythmic + diuretic	Electrolyte imbalance, arrhythmias
Benzodiazepine + antidepressant, antipsychotic, or benzodiazepine	Confusion, sedation, falls
Calcium channel blocker + diuretic or nitrate	Hypotension
Digitalis + antiarrhythmic	Bradycardia, arrhythmia

Before Starting a New Medication, Consider:

- Is this medication necessary?
- What are the therapeutic end points?
- Do the benefits outweigh the risks?
- Is it used to treat effects of another drug?
- Could 1 drug be used to treat 2 conditions?
- Could it interact with diseases, other drugs?
- Does patient know what it’s for, how to take it, and what ADEs to look for?

Key Concepts Regarding Drug Elimination

- **Half-life:** time for serum concentration of drug to decline by 50%

- **Clearance:** volume of serum from which the drug is removed per unit of time (eg, L/hour or mL/minute)

Effects of Aging on the Kidney

↓ kidney size

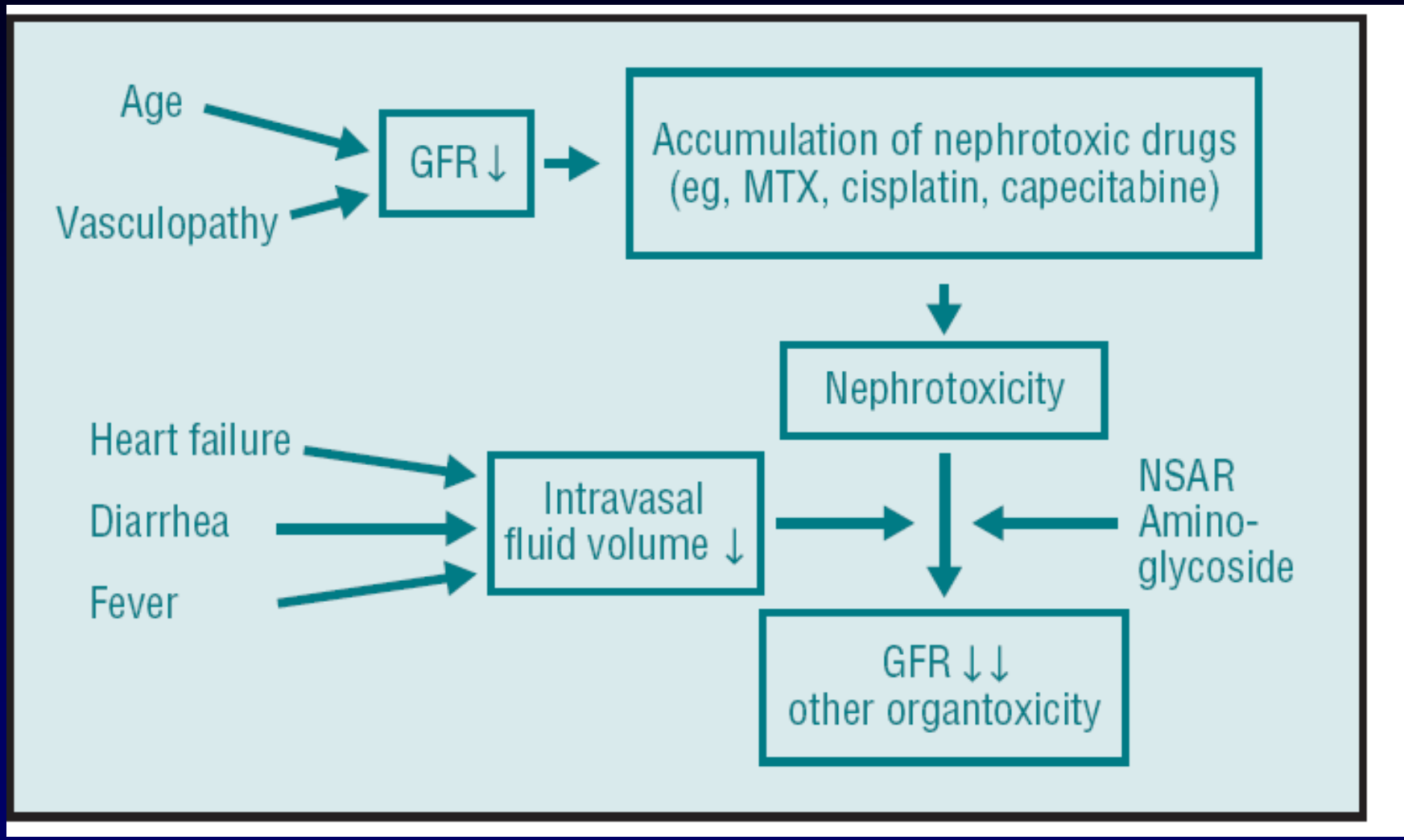
↓ renal blood flow

↓ number of functioning nephrons

↓ renal tubular secretion

Result: Lower glomerular filtration rate

Renal Toxicity



Serum Creatinine Does Not Represent Creatinine Clearance

↓ lean body mass → lower creatinine production

and

↓ glomerular filtration rate (GFR)

Result: In older persons, serum creatinine stays in normal range, masking change in creatinine clearance (CrCl)

Determining Creatinine Clearance

Measure

- Time-consuming
- Requires 24-h urine collection
- 8-h collection may be accurate but not widely accepted

Estimate

- Usually done with the Cockroft and Gault equation *(see next slide)*

Crockroft and Gault Equation

$$\frac{(\text{Ideal weight in kg})\,(140 - \text{age})}{(72)\,(\text{serum creatinine in mg/dL})} \times (0.85 \text{ if female})$$

Sample Creatinine Clearance Calculations (Female)

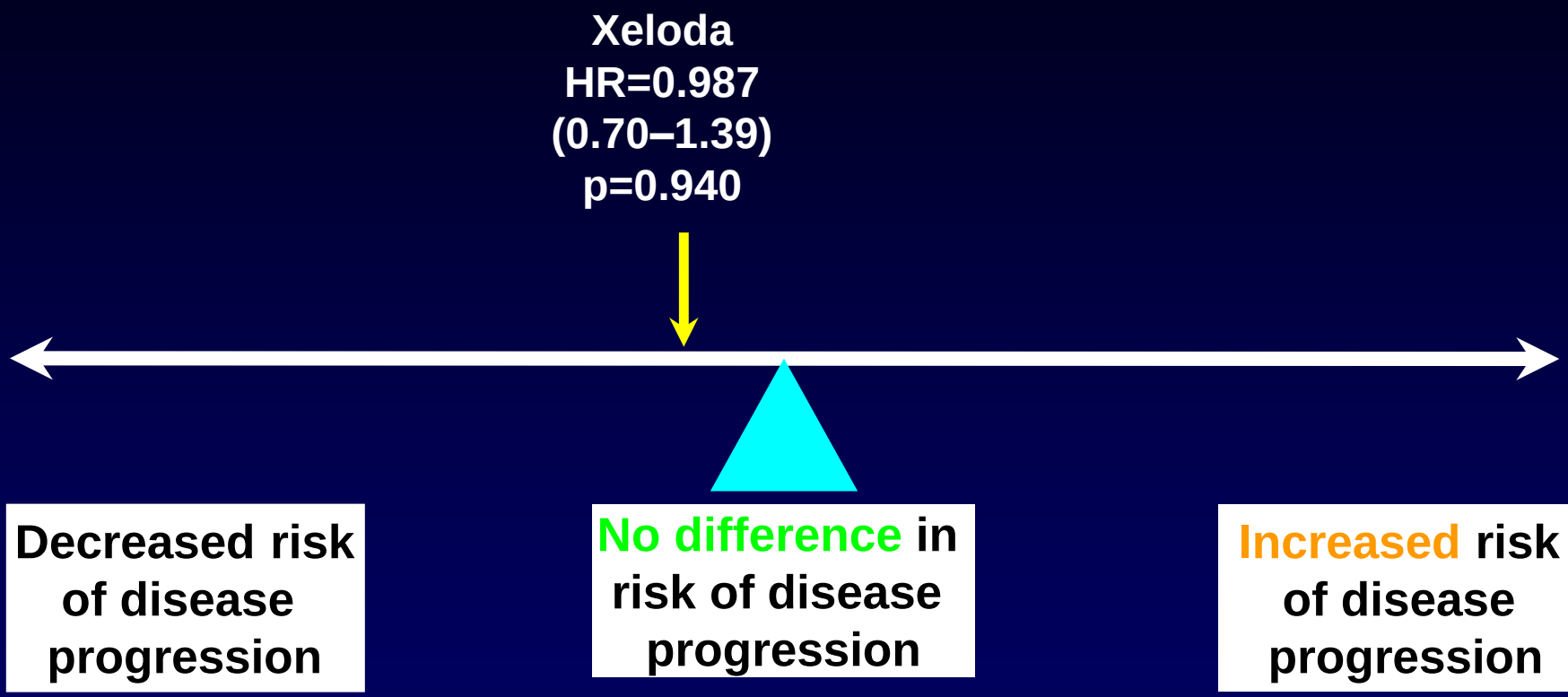
Age	Weight (kg)	Serum Cr	CrCl (cc/min)
70	70	1.0	58
70	70	1.5	39
70	70	2.0	29
70	50	2.0	21
80	70	1.0	50
80	70	2.0	25
80	50	2.0	18

Capecitabine: Tolerability data Led to Renal Impairment Guidelines

Renal impairment	Calculated creatinine clearance (mL/min)	Starting dose (mg/m^2 twice daily)
None	>80	1,250
Mild	51–80	1,250†
Moderate	30–50	950†
Severe	<30	Contra-indicated

Poole C et al. Cancer Chemother Pharmacol 2002;49:225–34

Capecitabine Efficacy is Maintained Following Adjustments to Individual Tolerable Dose



HR = hazard ratio for disease progression in patients with versus without dose reduction

O'Shaughnessy et al

Who Will Receive a Lower Starting Dose?

- Recommended starting dose for patients with moderate renal impairment is 75% of the standard starting dose (950mg/m^2 twice daily)
- Since calculated creatinine clearance is driven by age, elderly patients will typically receive this lower starting dose

Cassidy J et al. Ann Oncol. 2002

Elderly Patients With Cancer: Adapting to Renal Function

- Elderly patients are at greater risk for chemotherapy-induced toxicities
- Reluctance to give standard chemotherapy treatment often results in undertreatment
- Adapting to renal function allows safe and equipotent drug usage

Age-Related Pharmacodynamic Changes

- Toxicity differences (e.g., fluorpyrimidines)
- Tumor resistance to chemotherapy (e.g., increased incidence of MDR-1)
- Changes in sensitivity due to:
  - Anoxia of neoplastic cells
  - Reduced cell proliferation

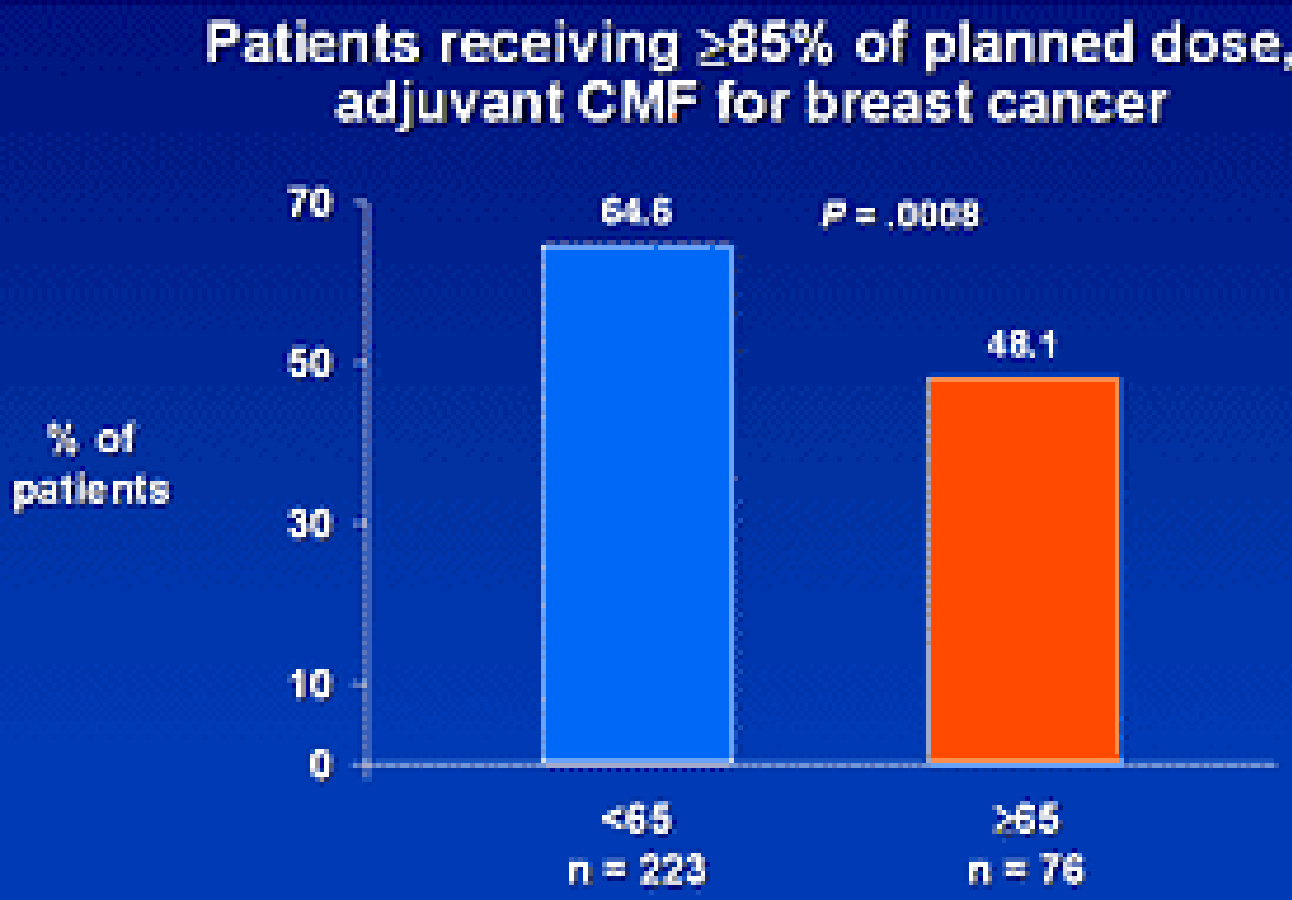
Toxicity is More Common and Severe in the Elderly

- Hematologic
- Cardiomyopathy
- Mucositis

Hemotologic Toxicity and Age: Non-Hodgkin's Lymphoma

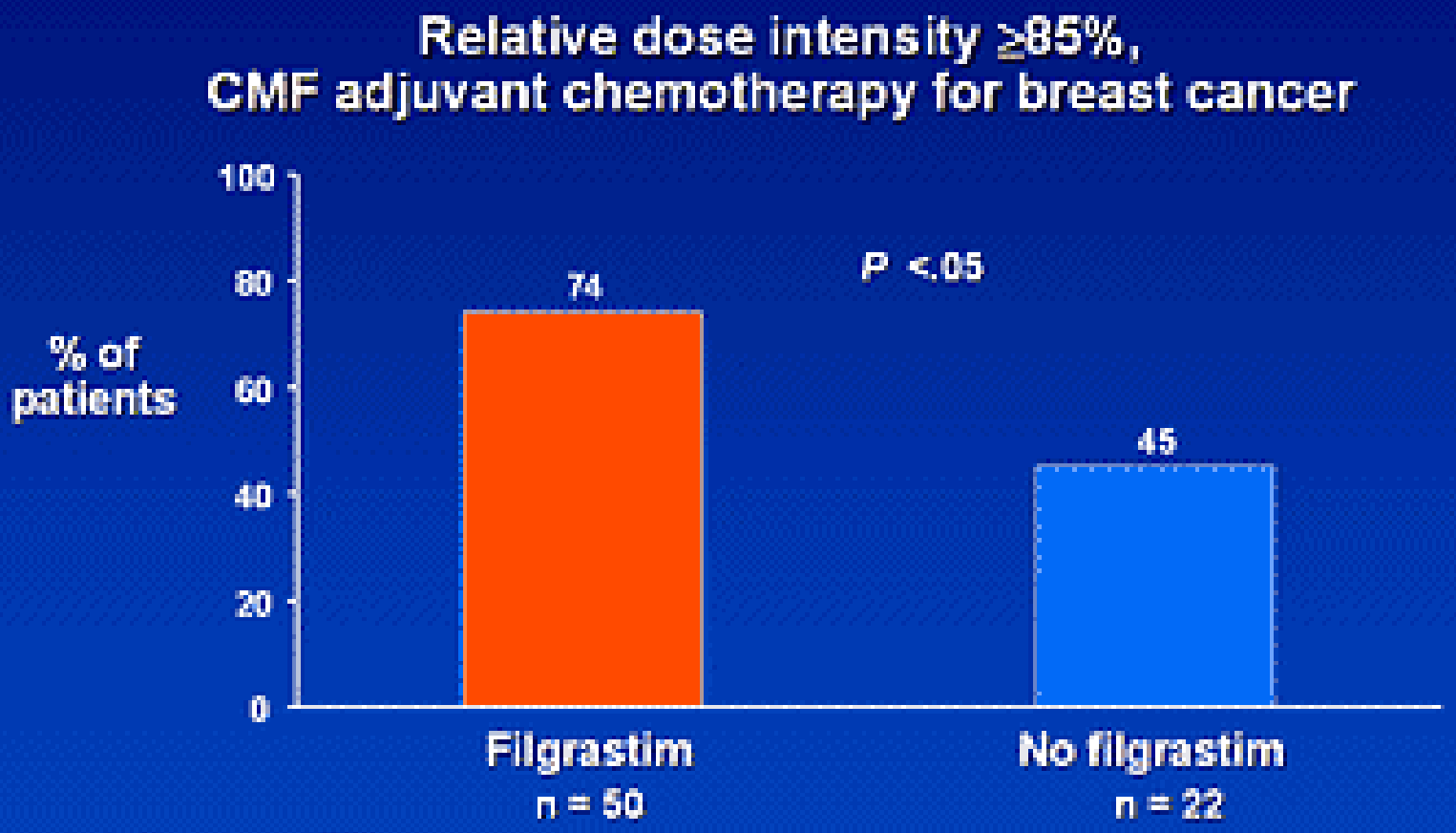
- Studies of patients ≥ 70 with NHL treated with CHOP or CHOP-like regimens
  - Higher incidence of grade 3, 4 neutropenia
  - Two-fold increase in neutropenic infections
  - Increased incidence of anemia and thrombocytopenia

Fewer Older Patients (=65) Receive Full-Dose Adjuvant Chemotherapy for Breast Cancer



Crivellari et al. *J Clin Oncol*, 2000.

Filgrastim Helps Maintain Chemotherapy Dose Intensity in Breast Cancer



de Graaf et al. *Oncology*, 1998.

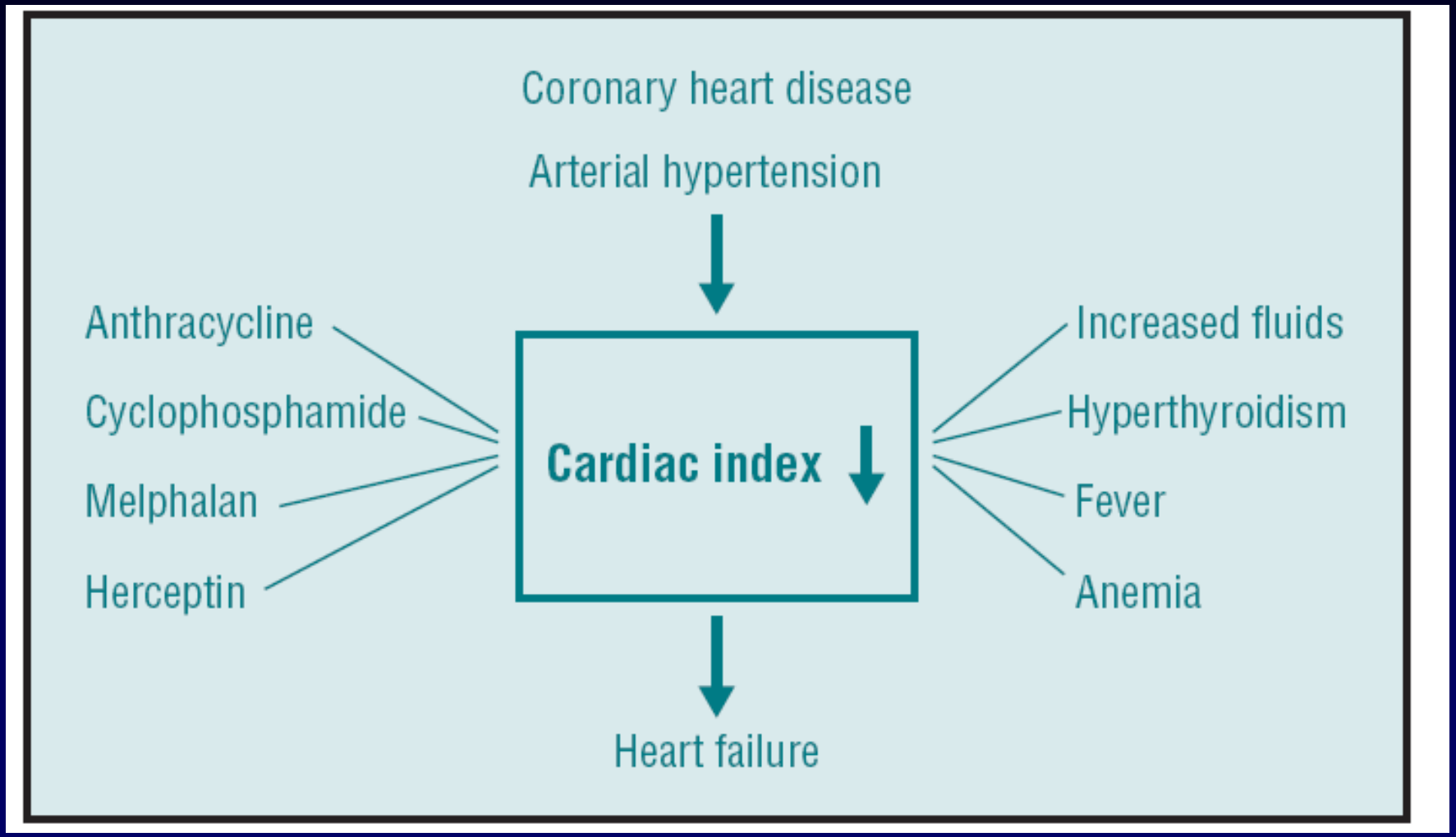
Chemotherapeutic Agents Associated with Mucositis

- Methotrexate: Severe with prolonged infusion and impaired renal function
- 5-FU: More severe with higher dose and frequent schedules
- Doxorubicin: May be severe and ulcerative; increased with liver disease
- Bleomycin: May be severe and ulcerative
- Vinblastine: Frequently ulcerative

Prevention and Treatment of Mucositis

- Oral cyrotherapy
- Dose and schedule selection
- Rapid correction of dehydration
- Treatment of secondary infection

Cardiac Toxicity



Anthracycline cardiotoxicity

- Age is a risk factor due to decreased myocardial reserve
- Alternative approaches to toxicity prevention with dose of doxorubicin ≥ 600 mg/m2
- MUGA scans have limited predictive value
- Myocardial damage is rare ≤ 300 mg/m2

Prevention of Cardiotoxicity

- Cytoprotective Agents
- Alternative schedules
- Monitor LVEF and clinical symptoms
- Alternative drugs (e.g., mitoxantrone, epirubicin, liposomal anthracyclines)

Prevention of Toxicity

- Patient selection
- Treatment planning
- Dosing taking into account comorbidity and physiology
- Supportive care drugs
- Chemotherapy protectors
- Scheduling changes

Conclusion: Prevention of Toxicity

- Chemotherapy doses should be adjusted to renal function and physiology
- Successive doses should be adjusted according to toxicity
- In patients over 70 years, primary prophylaxis with hematopoietic growth factors should be considered depending on regimen
- Primary goal of treating frail patients is palliation