

What patient CV risk factors should be excluded from what types of oncologic agents?

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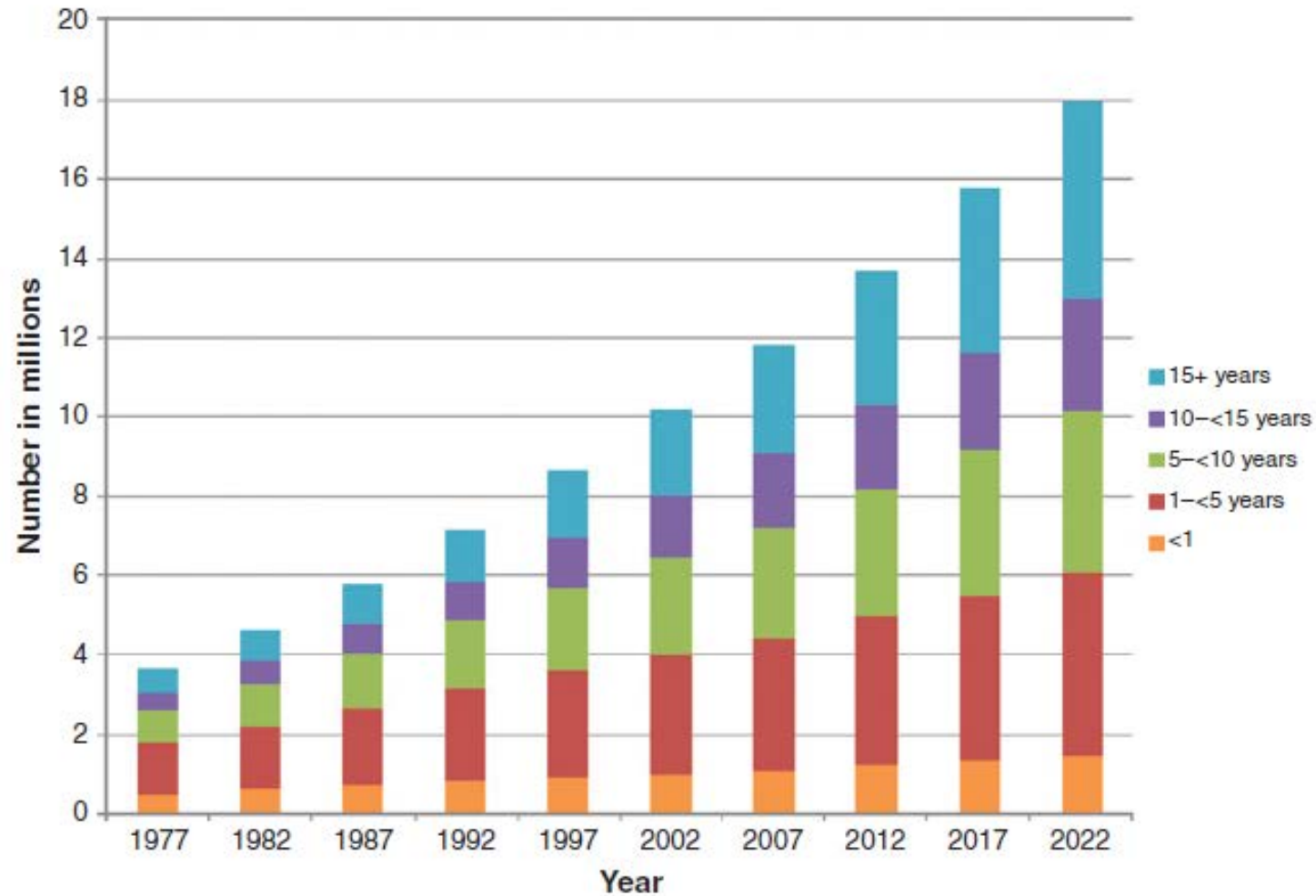


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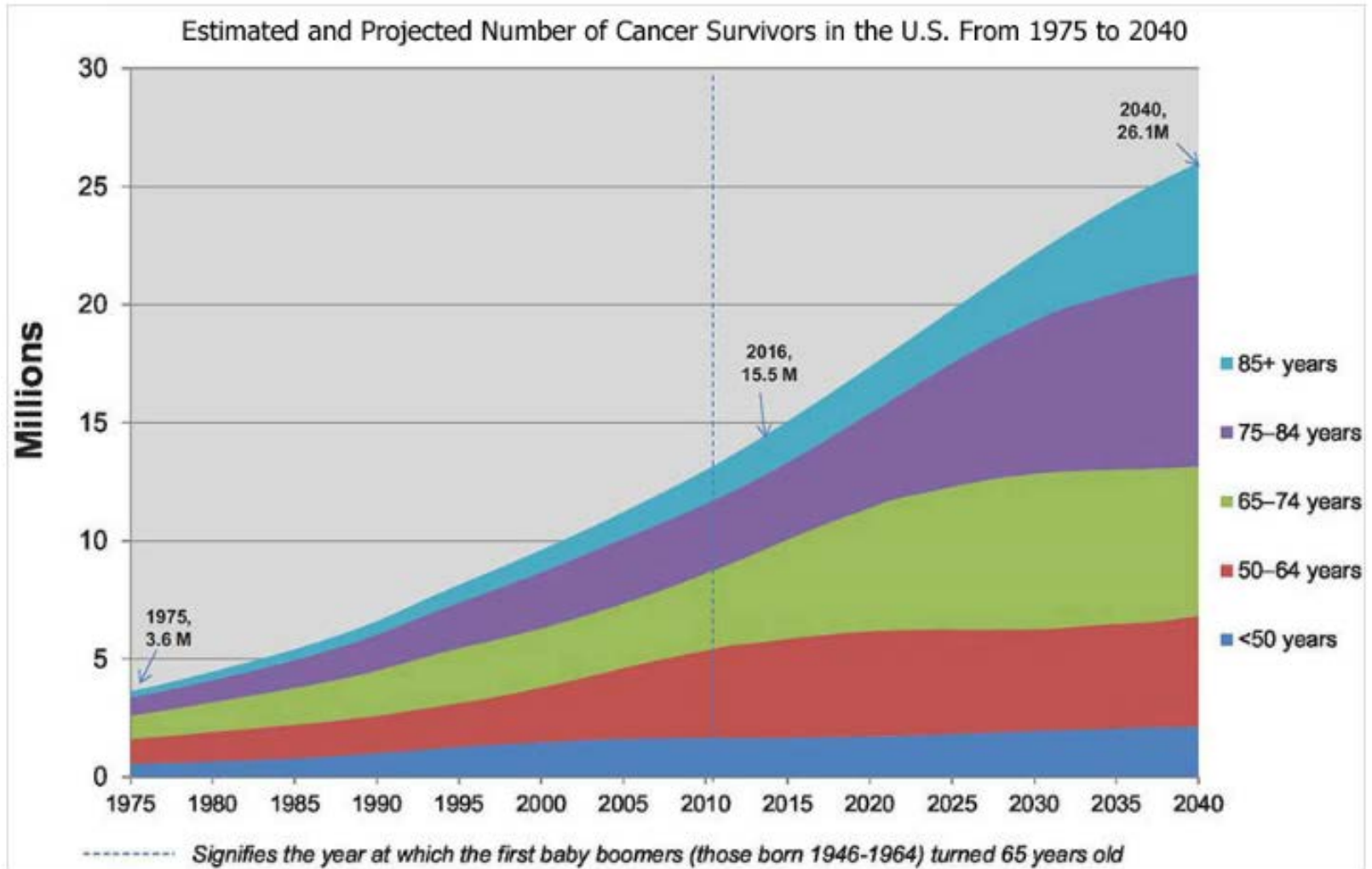
Disclosures

- Consultant
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- Research Support
 - Singulex
 - Beckman

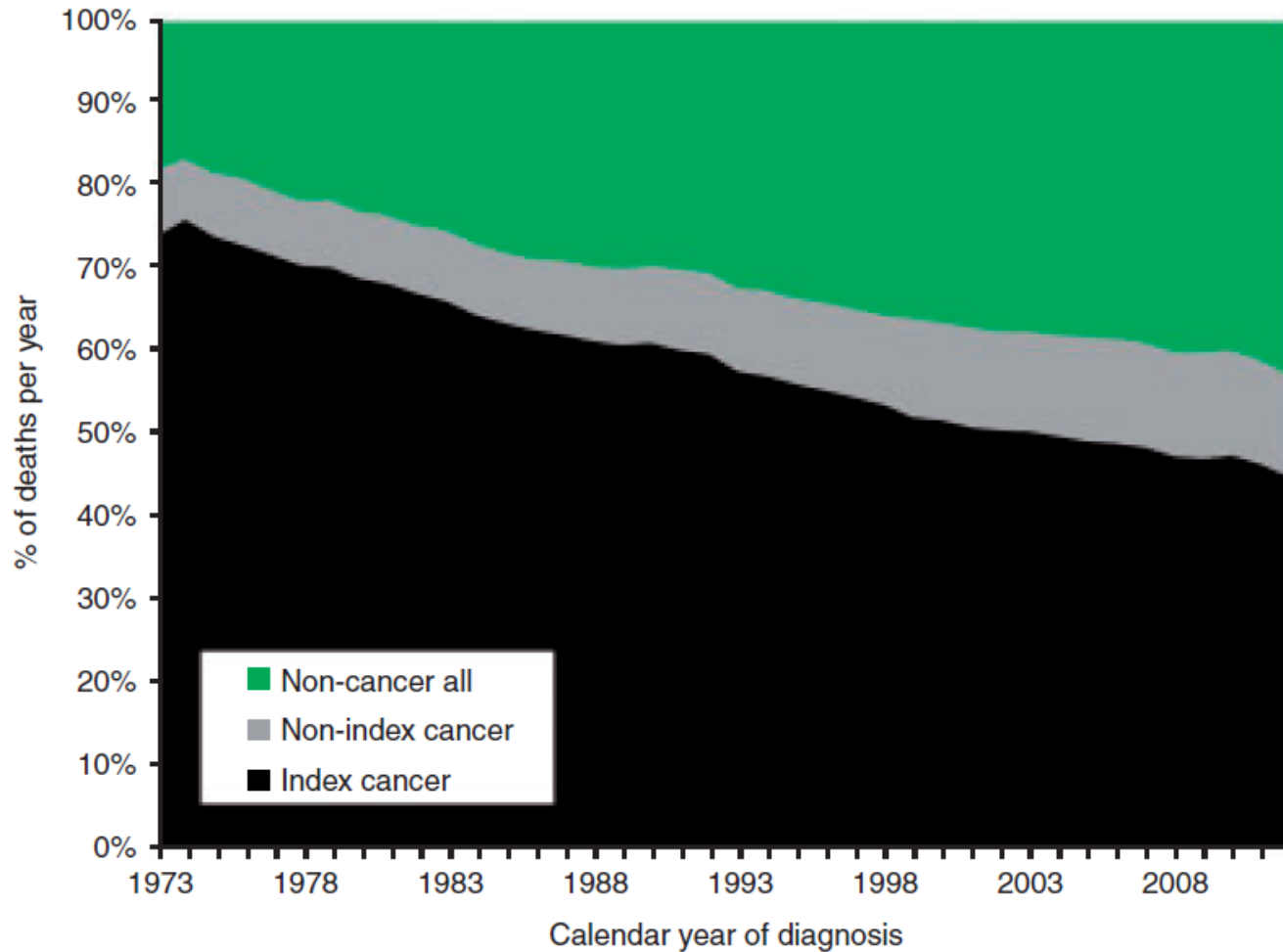
Cancer Survivorship in the US



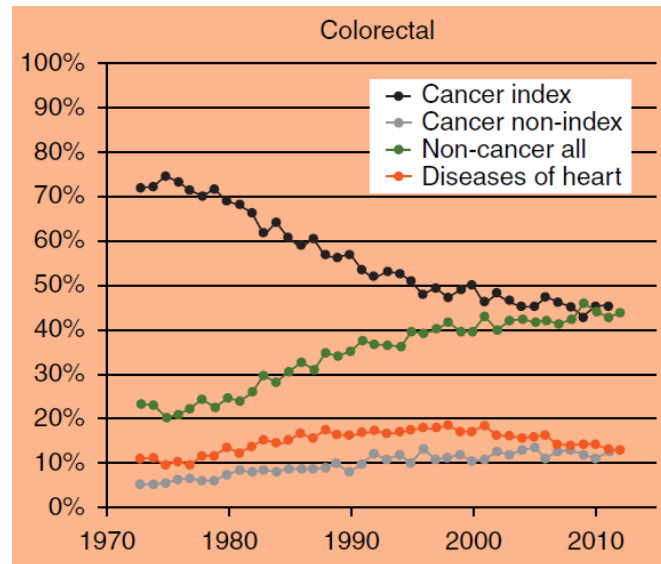
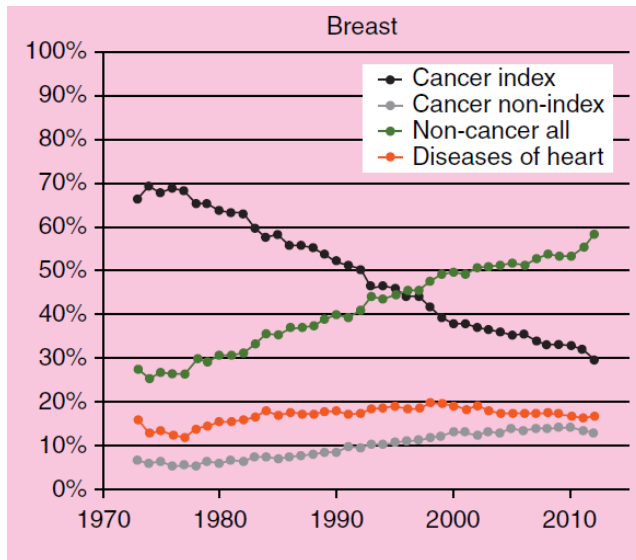
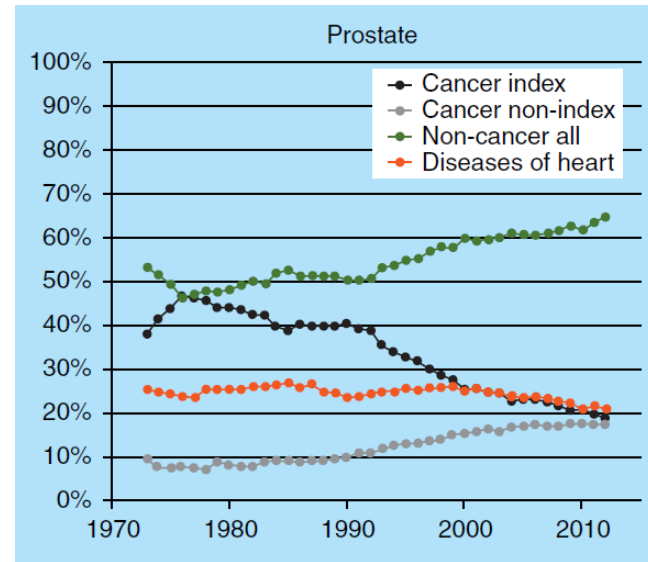
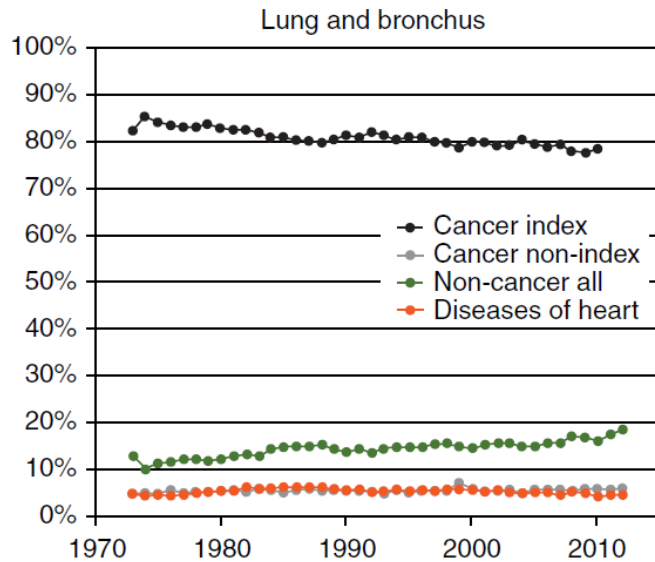
Aging Population of Cancer Survivors



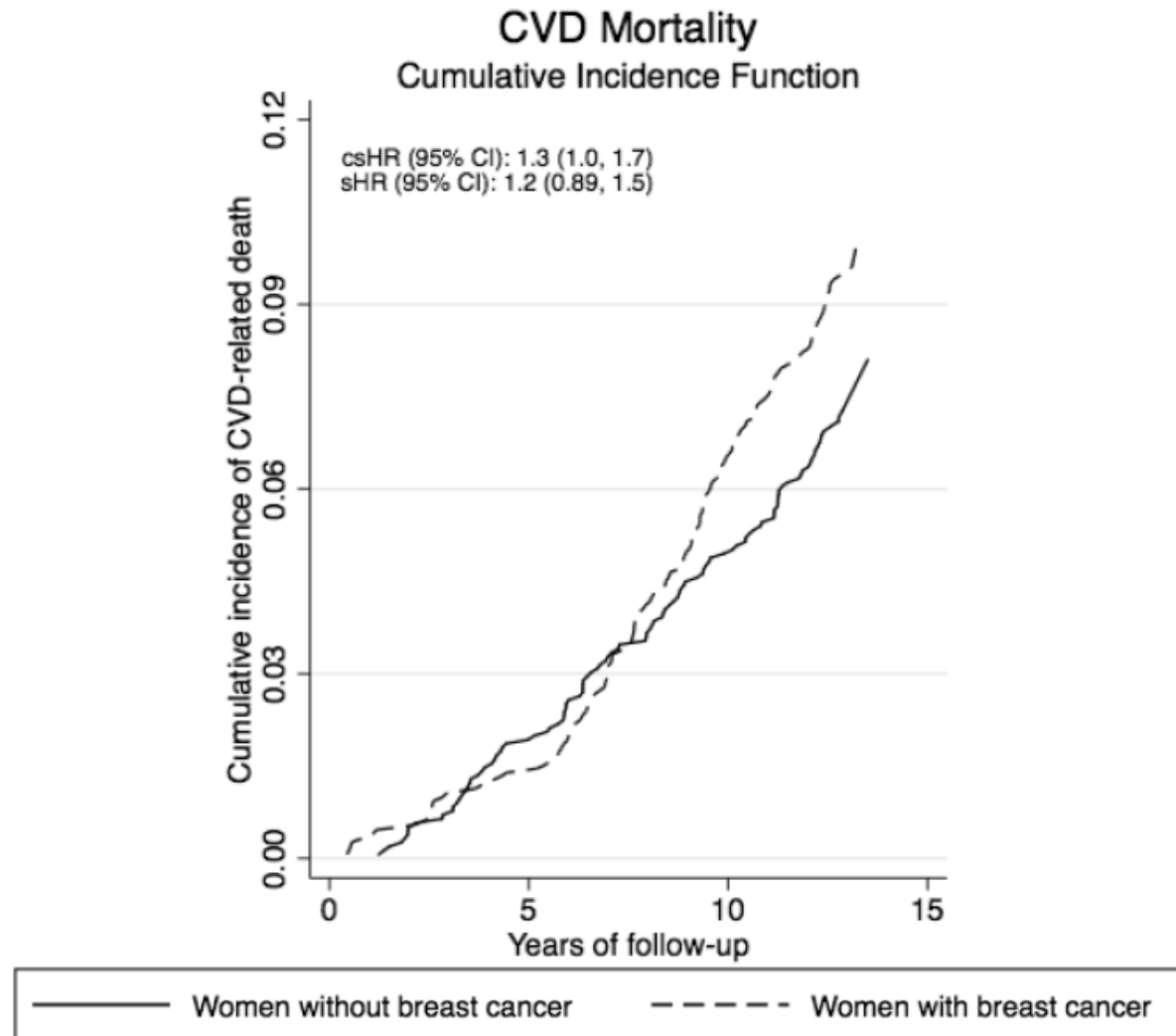
Causes of death in cancer patients



Causes of death in cancer patients

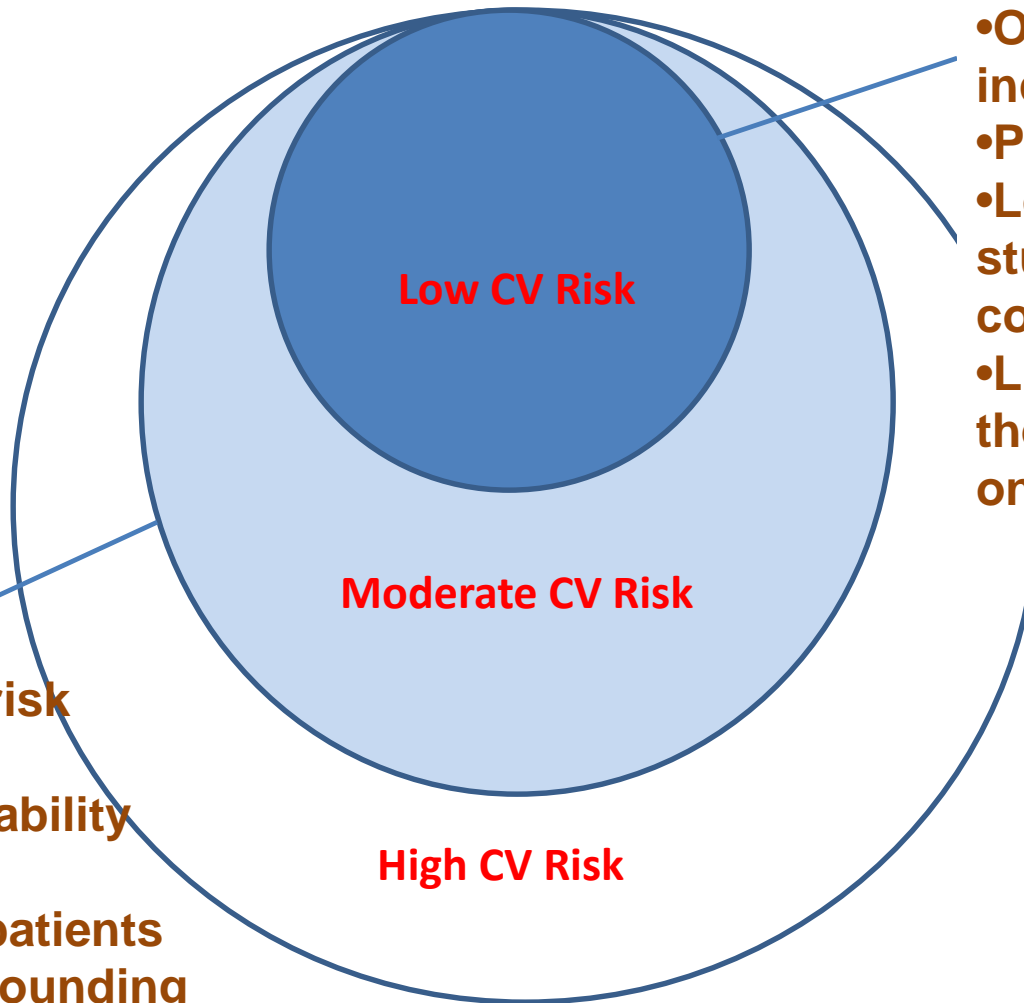


CVD Mortality in Breast CA Survivors



An increase in CVD-related death among breast cancer survivors was evident at 7 years, compared to women without breast cancer.

Considerations for CV risk eligibility in oncology clinical trials



Eligible Patient Population

Narrow Eligibility

- Only low CV risk included
- Poor generalizability
- Longer accrual time, study duration, and cost
- Limited insight into the effects of CV risk on cancer outcomes.

Broad Eligibility

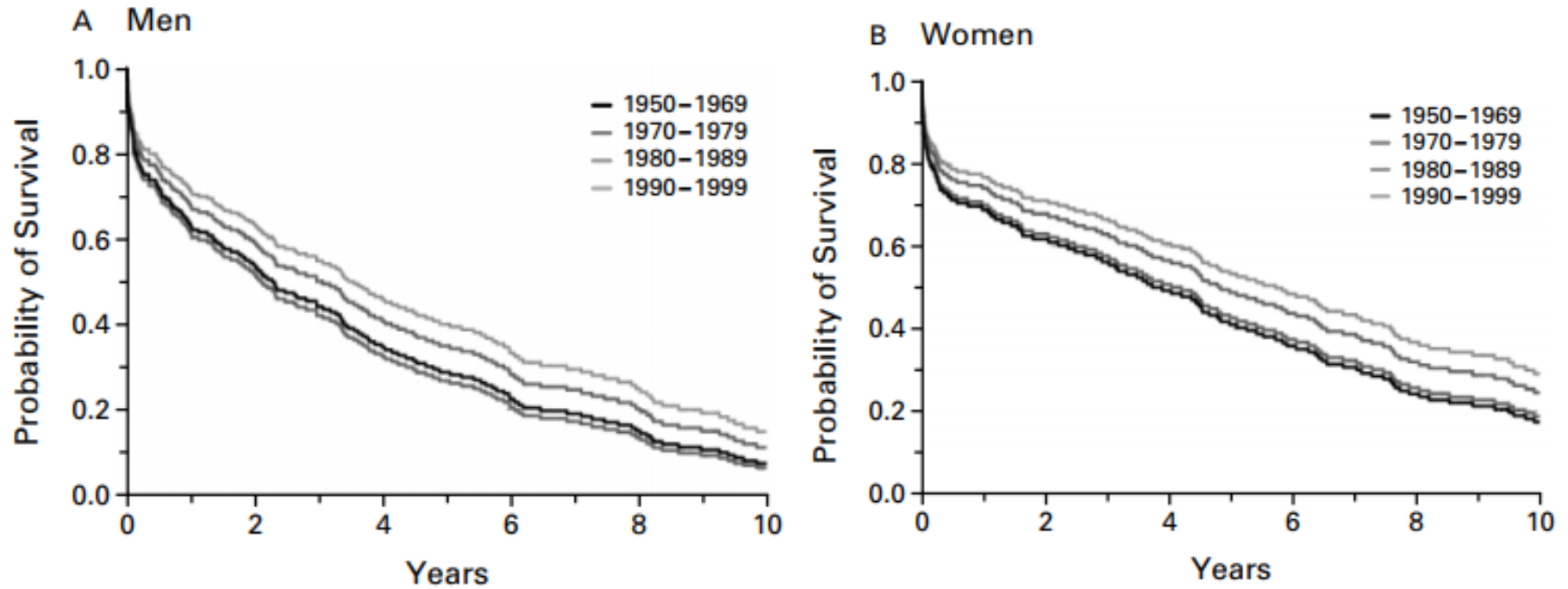
- Only highest CV risk excluded
- Greater generalizability of study results
- Easier to recruit patients
- Potential CV confounding

CVD contraindication for participation in oncology clinical trials

Pre-existing cardiovascular disease may translate to significant short-term risk of CV-related morbidity and mortality, potentially confounding results of cancer trials:

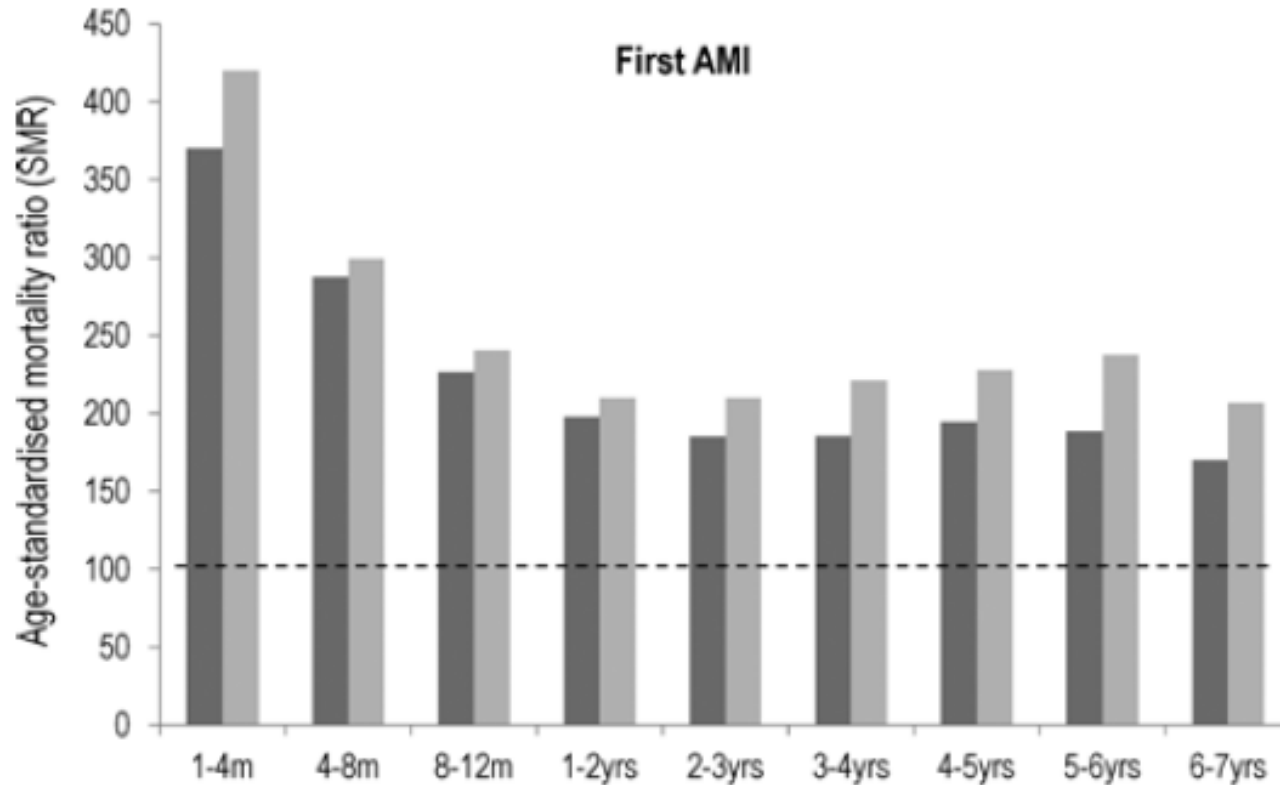
- Acute myocardial infarction
- Heart failure
- CVA
- Severe valvular heart disease (i.e. severe symptomatic aortic stenosis or mitral regurgitation)

Mortality after HF - Framingham Heart Study



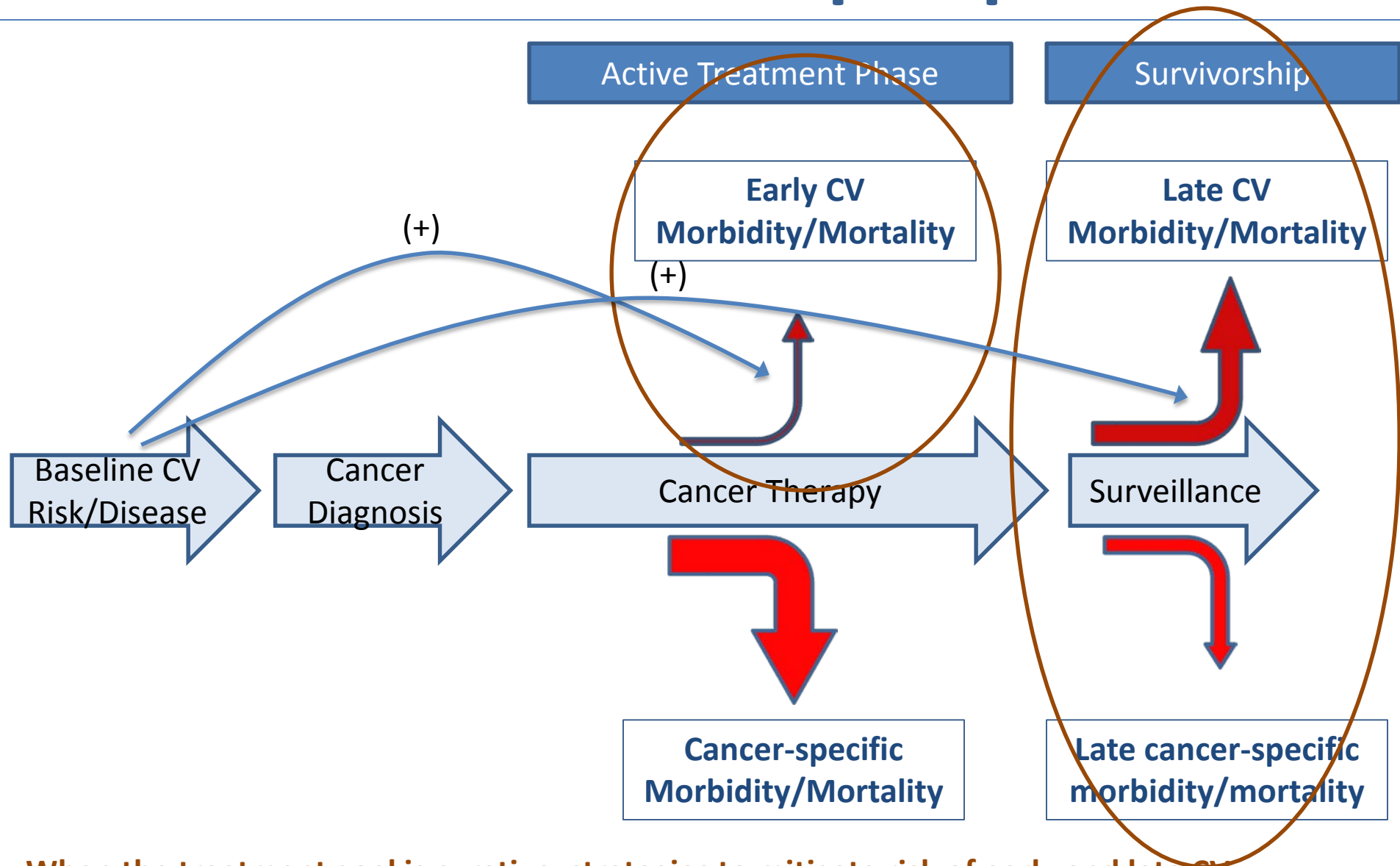
The 1-year mortality rate after HF diagnosis was 28% in men and 24% in women.

Mortality after Acute MI



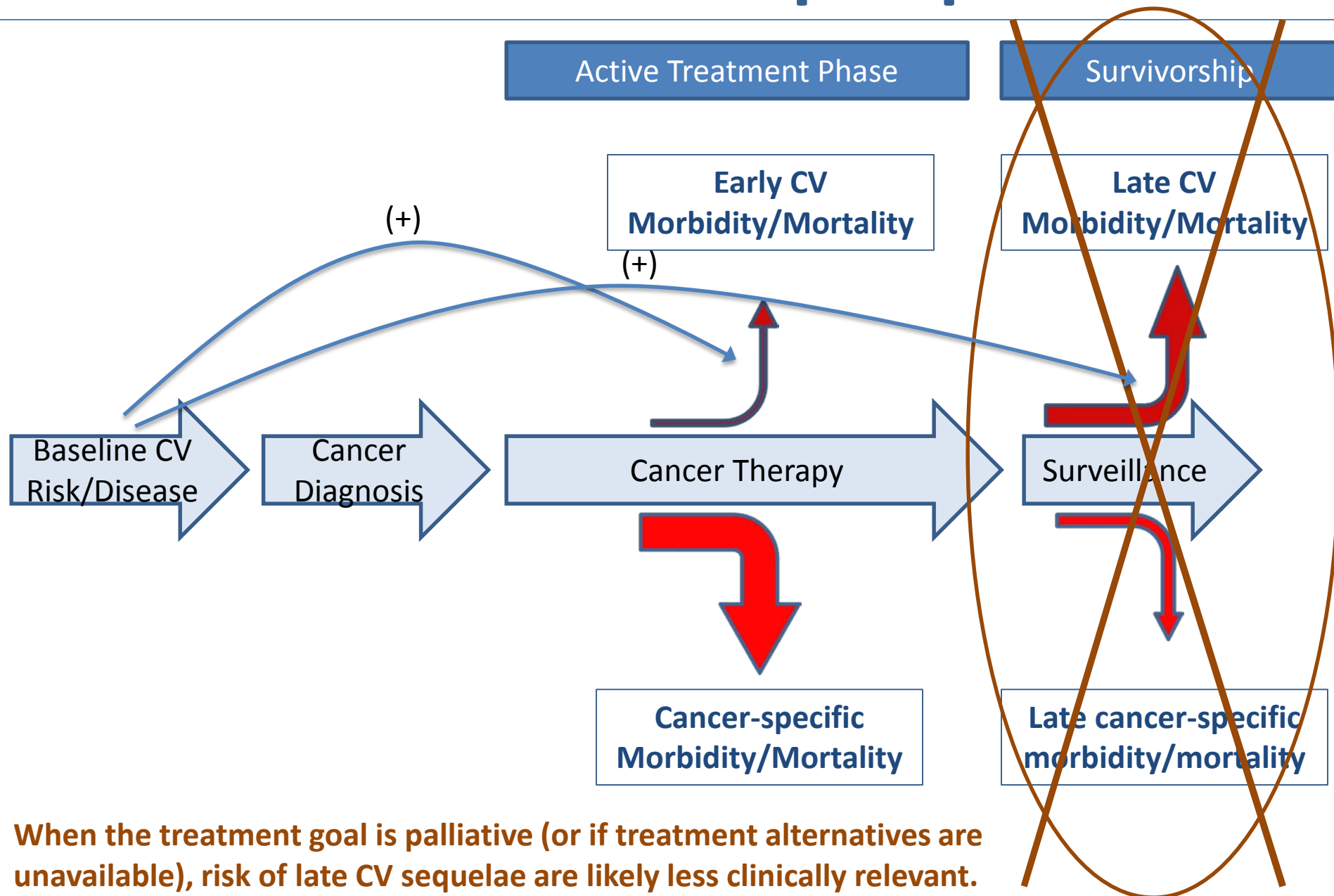
Standardized mortality ratios of acute MI survivors compared to the general population peak at 4 months, but plateau after 1-3 years.

Cardiovascular risk in perspective



When the treatment goal is curative, strategies to mitigate risk of early and late CV sequelae may be important, or consider alternative/safer treatment options.

Cardiovascular risk in perspective



CV and Cancer Outcomes – A Balancing Act

CV Considerations

- Pre-existing CV risk factors or disease
- Potential for CV toxicity
 - Early
 - Late (survivorship)
- Clinical significance of CV toxicity
- Availability of CV treatment options

Cancer Considerations

- Improved cancer-specific morbidity and mortality
- Goals of care: curative versus palliative
- Risk of undertreatment (due to fear of CV risk)
- Presence/absence of alternative treatment options

Approach to CV-specific exclusion criteria

- Appropriate to exclude major CV disease
- When possible, exclusion of “significant” CV risk should be based on known mechanism of CV injury, i.e.
 - Uncontrolled hypertension for VEGF inhibitors
 - Low EF for anti-HER2 rx, proteasome inhibitors
 - Symptomatic PAD/CAD for Bcr-Abl TKIs
- CV exclusion criteria should be well-defined
- CV endpoint data should be collected methodically and in a standardized fashion.

CV Exclusion Criteria: NSABP B-31

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

N9831). Patients were ineligible if they had angina pectoris requiring antianginal medication, arrhythmia requiring medication, a severe conduction abnormality, clinically significant valvular disease, cardiomegaly on chest radiography, left ventricular hypertrophy on echocardiography (trial B-31 only), poorly controlled hypertension, clinically significant pericardial effusion (trial N9831 only), or a history of myocardial infarction, congestive heart failure, or cardiomyopathy.

CV Exclusion Criteria: ENESTnD

- Impaired cardiac function including any one of the following:
 - LVEF < 45% or below the institutional lower limit of the normal range (whichever is higher) as determined by locally read echocardiogram.
 - Inability to determine the QT interval on ECG.
 - Complete left bundle branch block.
 - Use of a ventricular-paced pacemaker.
 - Congenital long QT syndrome or a known family history of long QT syndrome.
 - History of or presence of clinically significant ventricular or atrial tachyarrhythmias.
 - Clinically significant resting bradycardia (< 50 beats per minute).
 - QTc > 450 msec on the average of three serial baseline ECG (using the QTcF formula) as determined by central reading. If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTc.
 - History of clinically documented myocardial infarction.
 - History of unstable angina (during the last 12 months).
 - Other clinically significant heart disease (e.g. congestive heart failure or uncontrolled hypertension).

Conclusions

- Given improvements in cancer outcomes, non-cancer related morbidity and mortality (cardiovascular-specific) are increasingly relevant.
- CV risk factors are common in cancer patients, and clinical trials should strive to be generalizable to a real-world population.
- Goals of cancer care (curative vs. palliative) and presence/absence of alternative treatment options are important factors that affect tolerance for CV toxicity.
- When necessary, exclusion of CV risk/disease should be based on underlying mechanisms of CV injury.

Thank You

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