Minimization, permuted blocks and simple randomization

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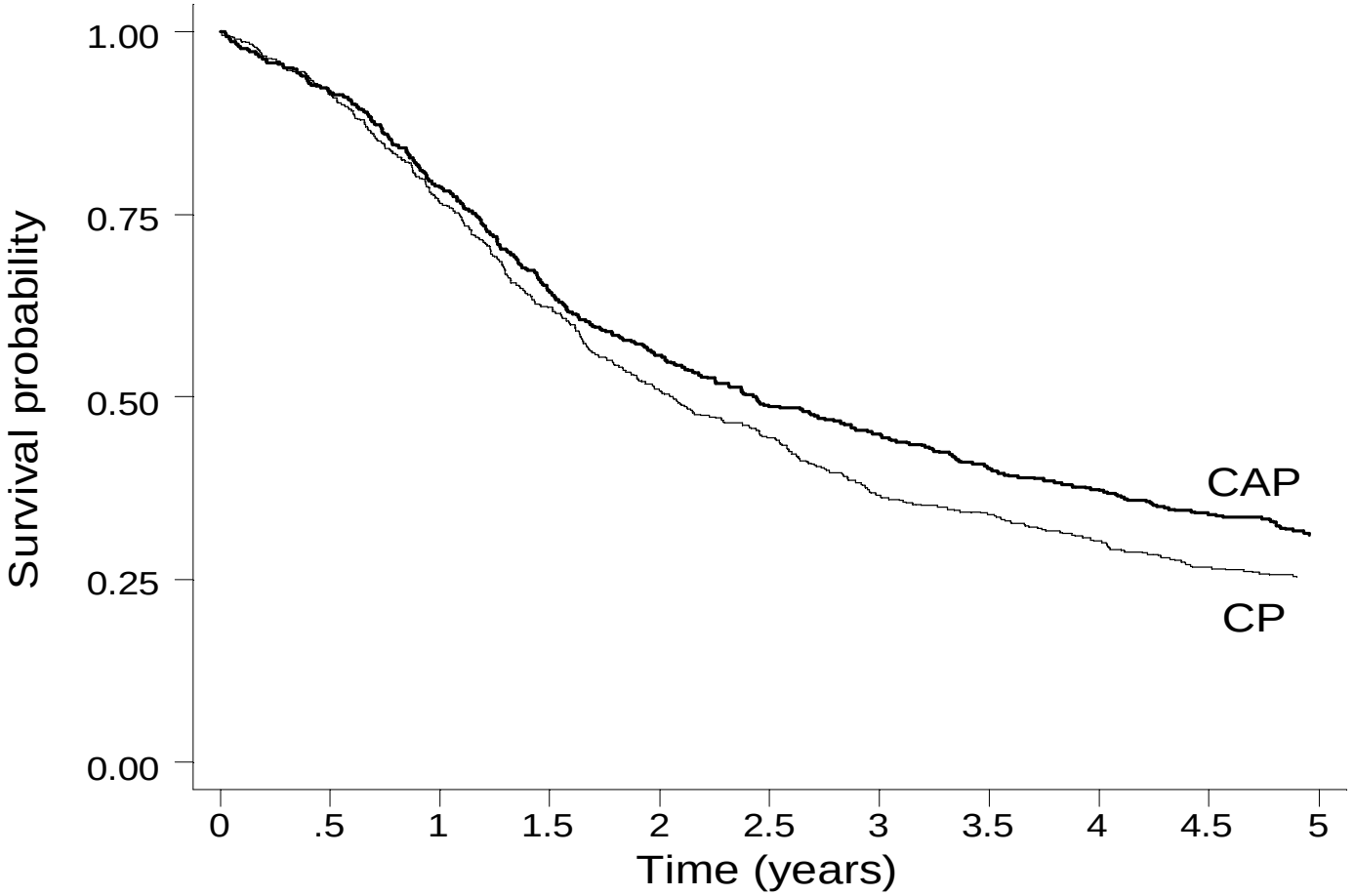
In randomized clinical trials, the treatment allocation method should…

- minimize the type I error
- minimize the type II error
- balance all known and unknown prognostic factors among treatment groups (avoid accidental bias)
- minimize the predictability of treatment assignments (avoid selection bias)
- be simple and foolproof (avoid other biases)

Simulations in advanced ovarian cancer



Simulations – data generation

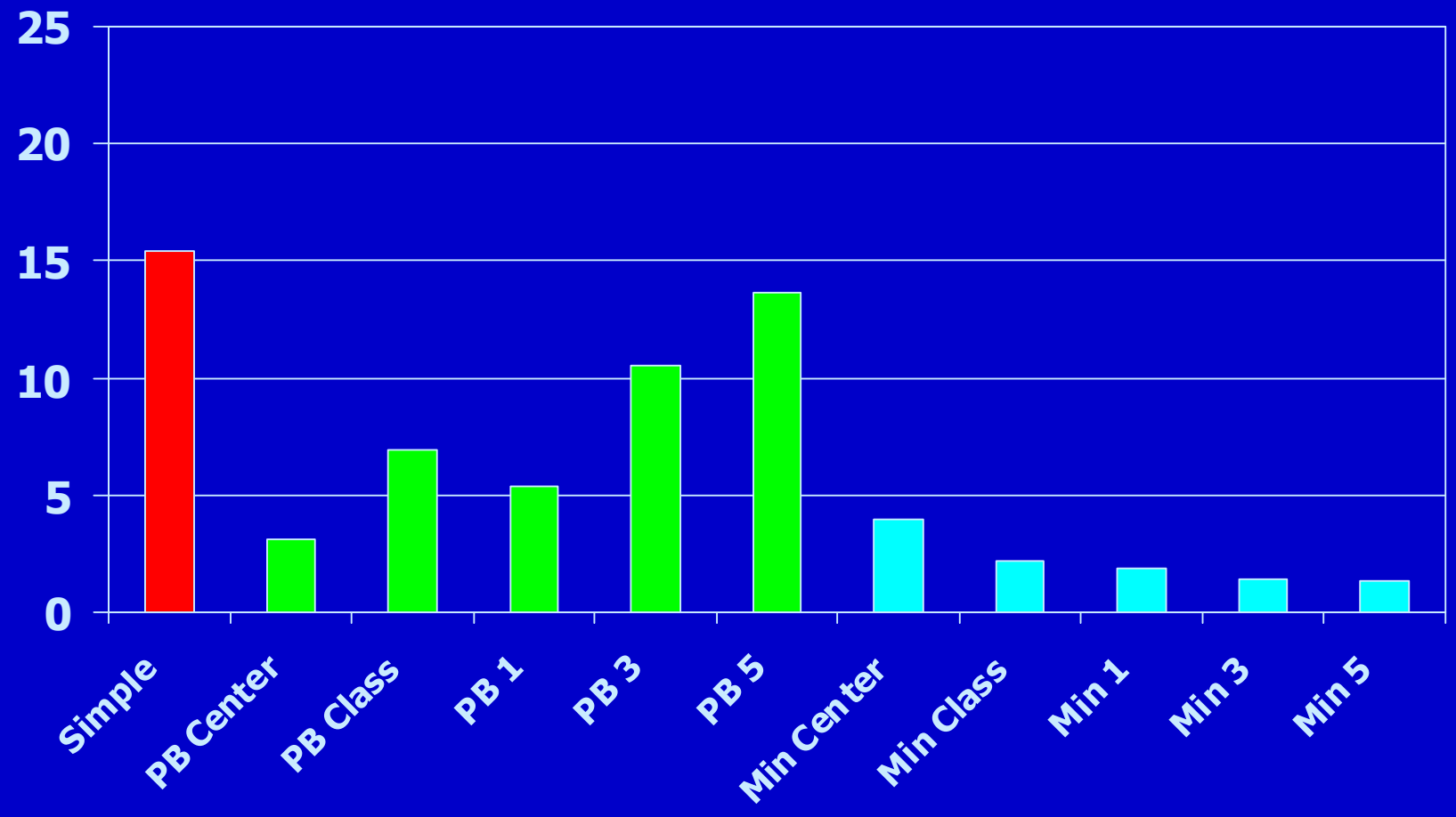
- Patients: sampled at random (N=400), with replacement, from meta-analysis dataset
- Center: sampled at random from skewed distribution
- Time of entry: sampled at random from uniform distribution over accrual period
- Treatment: allocated using various methods (next slide)
- Survival time: unchanged under control, prolonged under treatment, with HR = λ_T/λ_C = 0.8

Simulations - allocation techniques

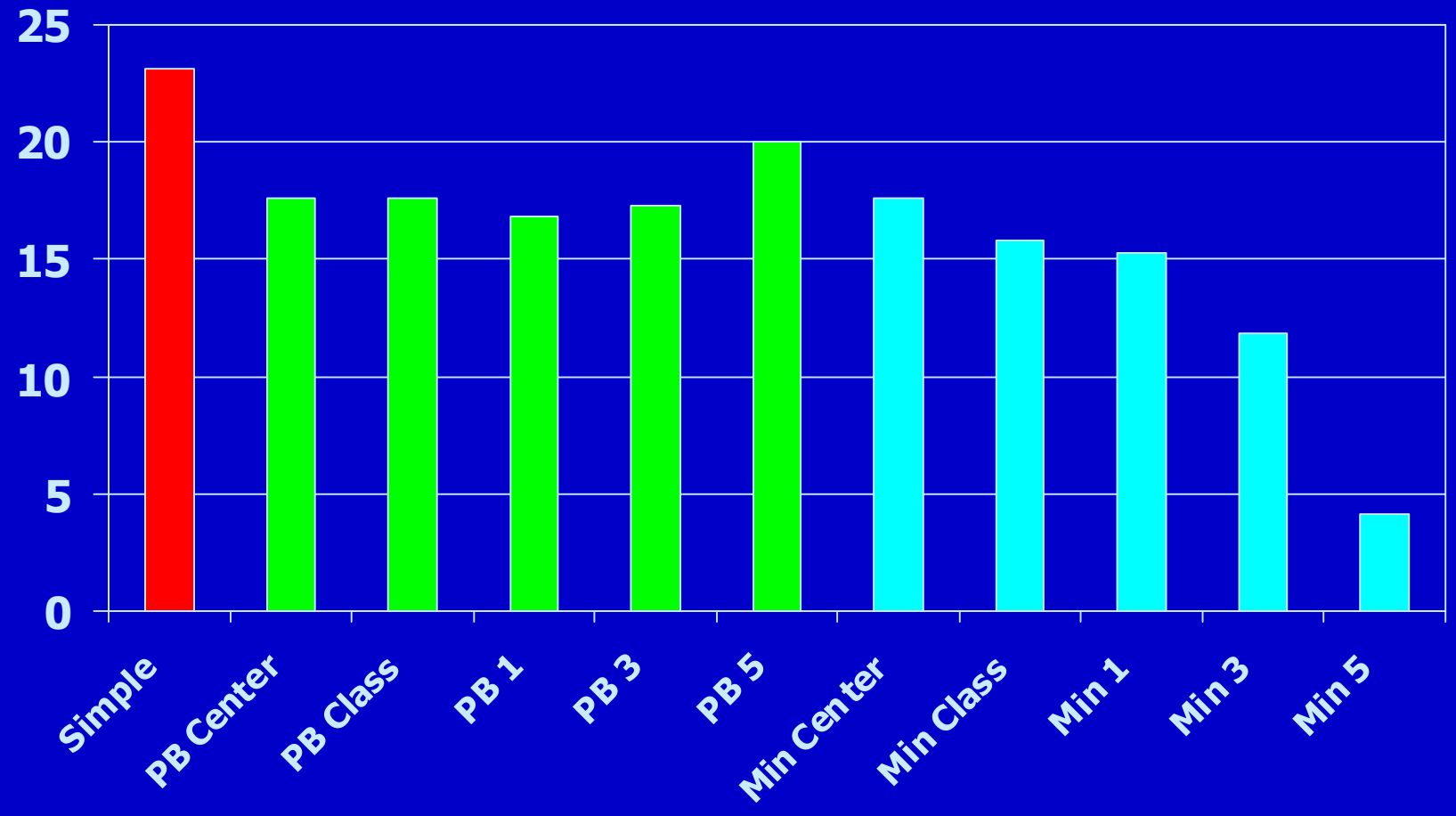
- Simple randomization
- Permuted blocks within strata defined by center
  - only
  - and prognostic class
  - and 1 factor (residual disease)
  - and 3 factors (same + performance status + age)
  - and 5 factors (same + histologic grade + FIGO stage)
- Minimization
  - (as permuted blocks)

Balance

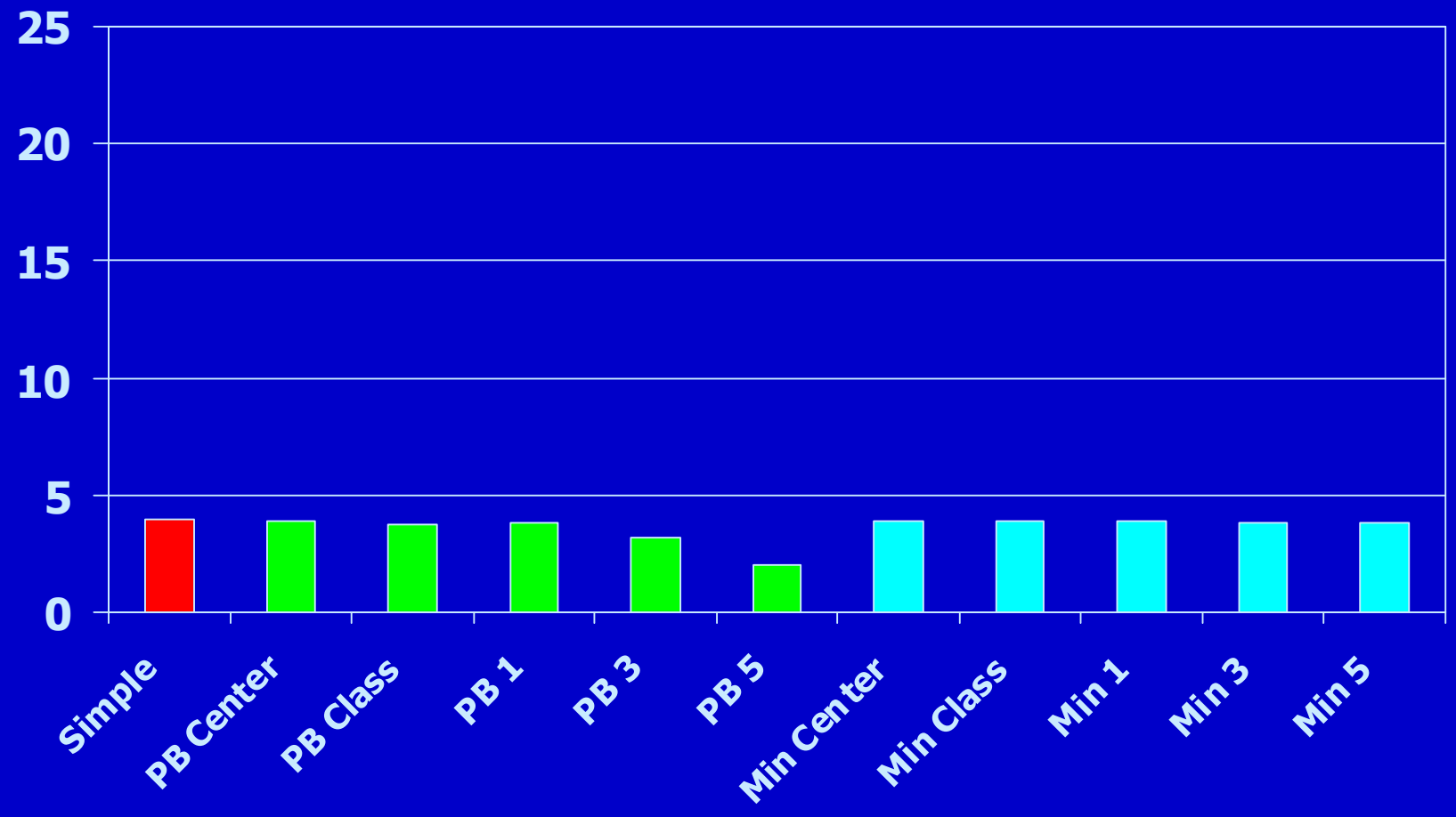
Simulations – mean overall imbalances



Simulations – mean imbalances in factor levels



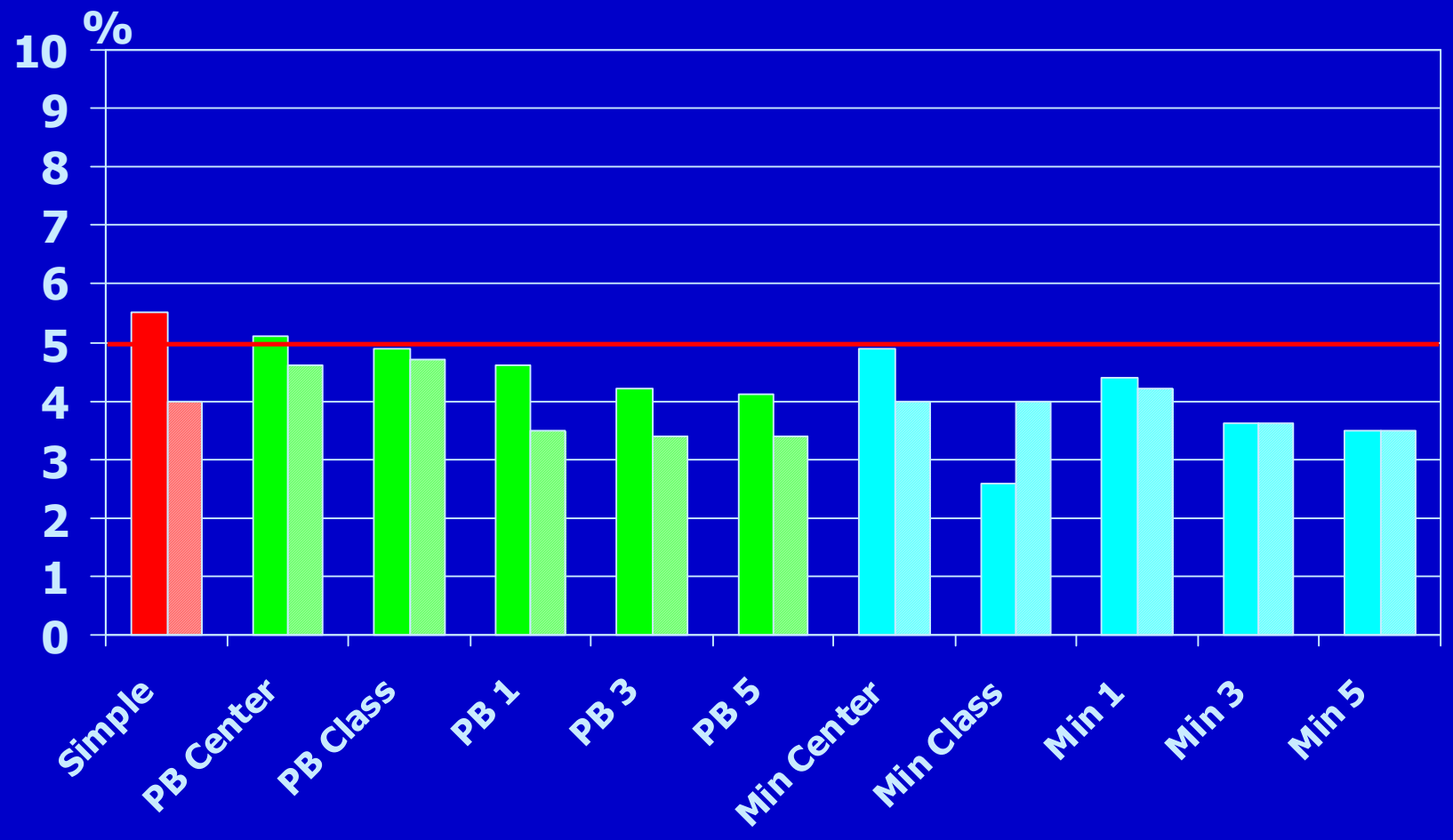
Simulations – mean imbalances in strata



Size and power

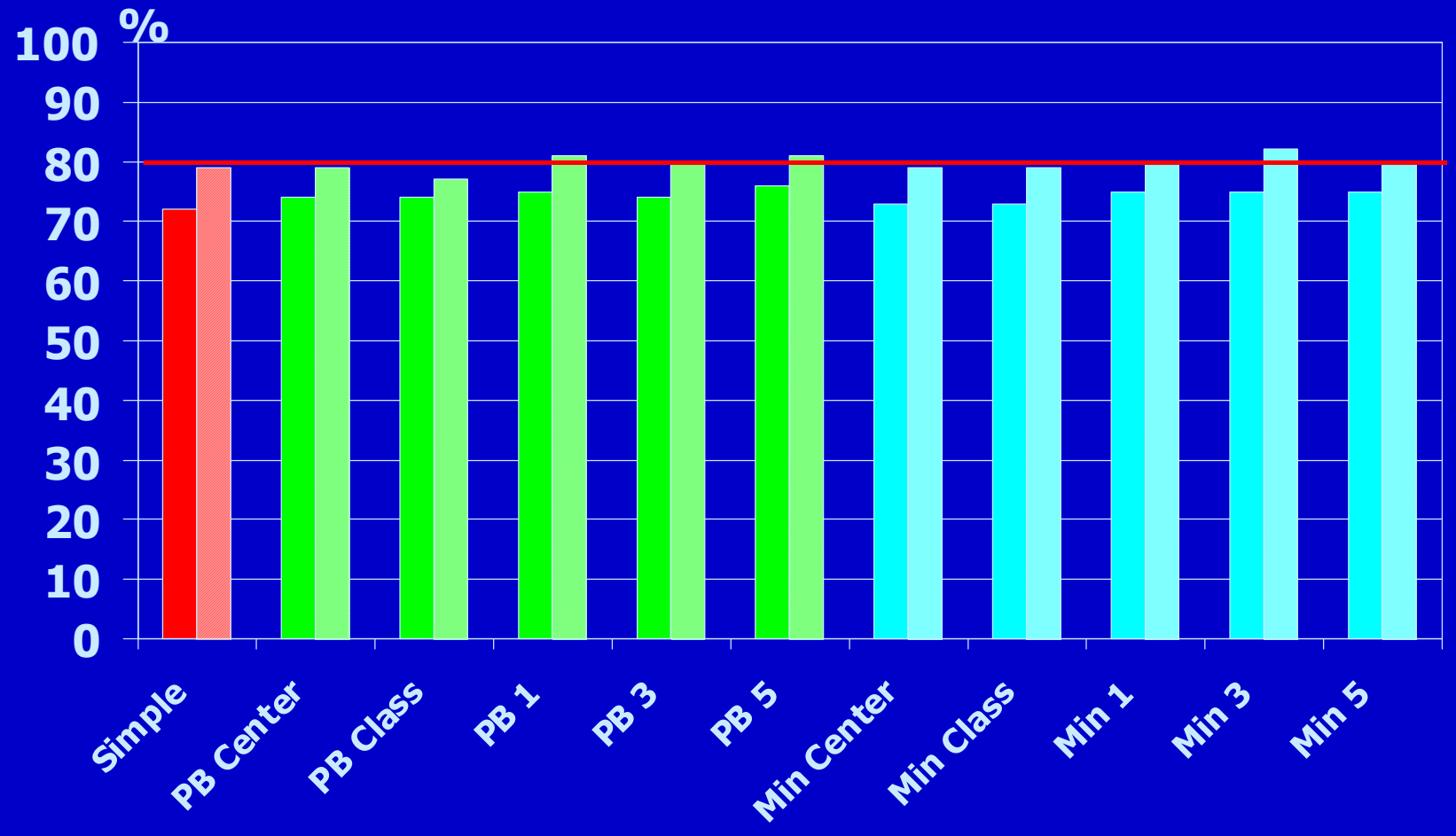
Simulations – size of logrank test

(dashed = stratified for 5 factors)



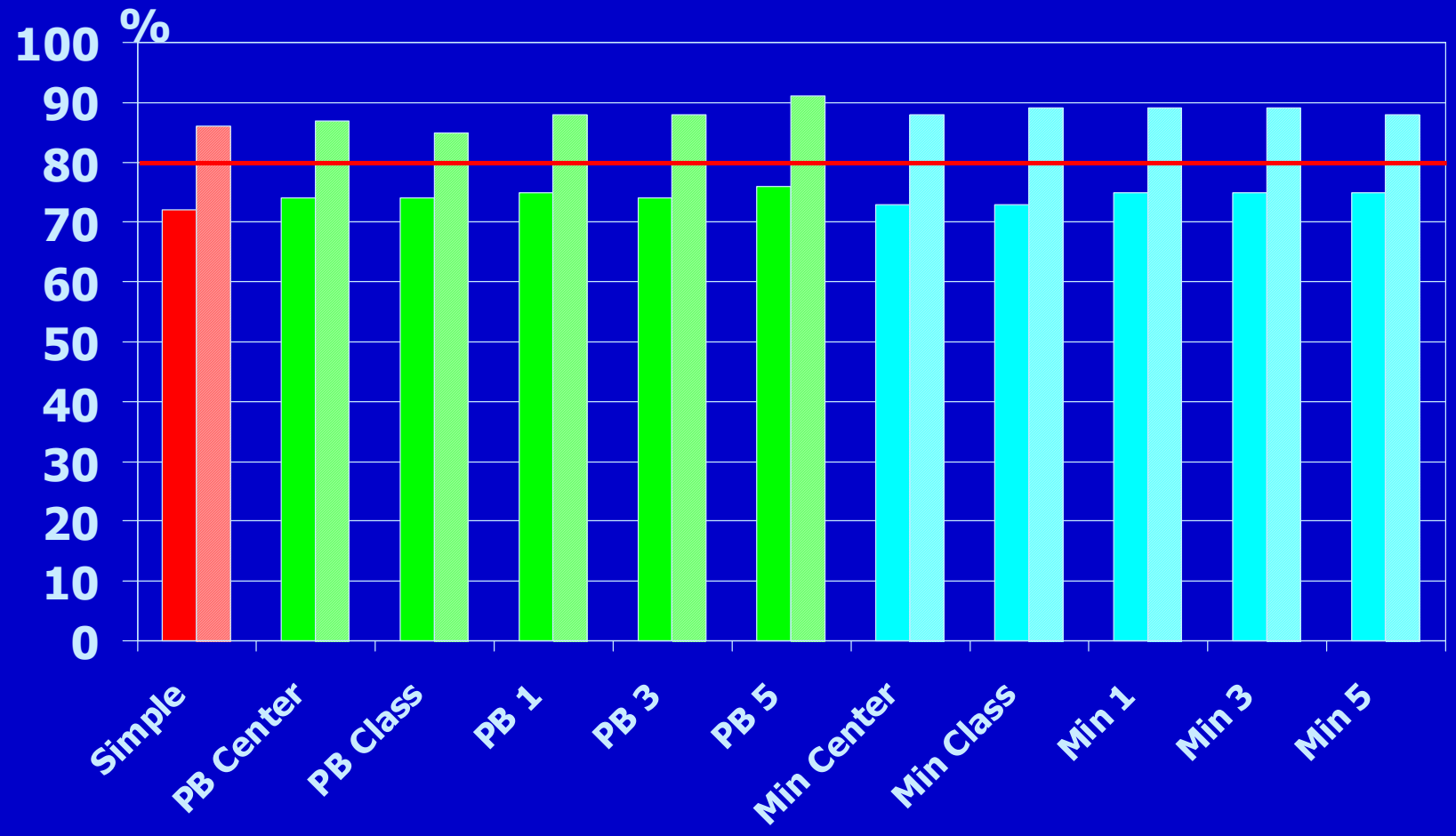
Simulations – power of logrank test

(dashed = stratified for 1 factor)



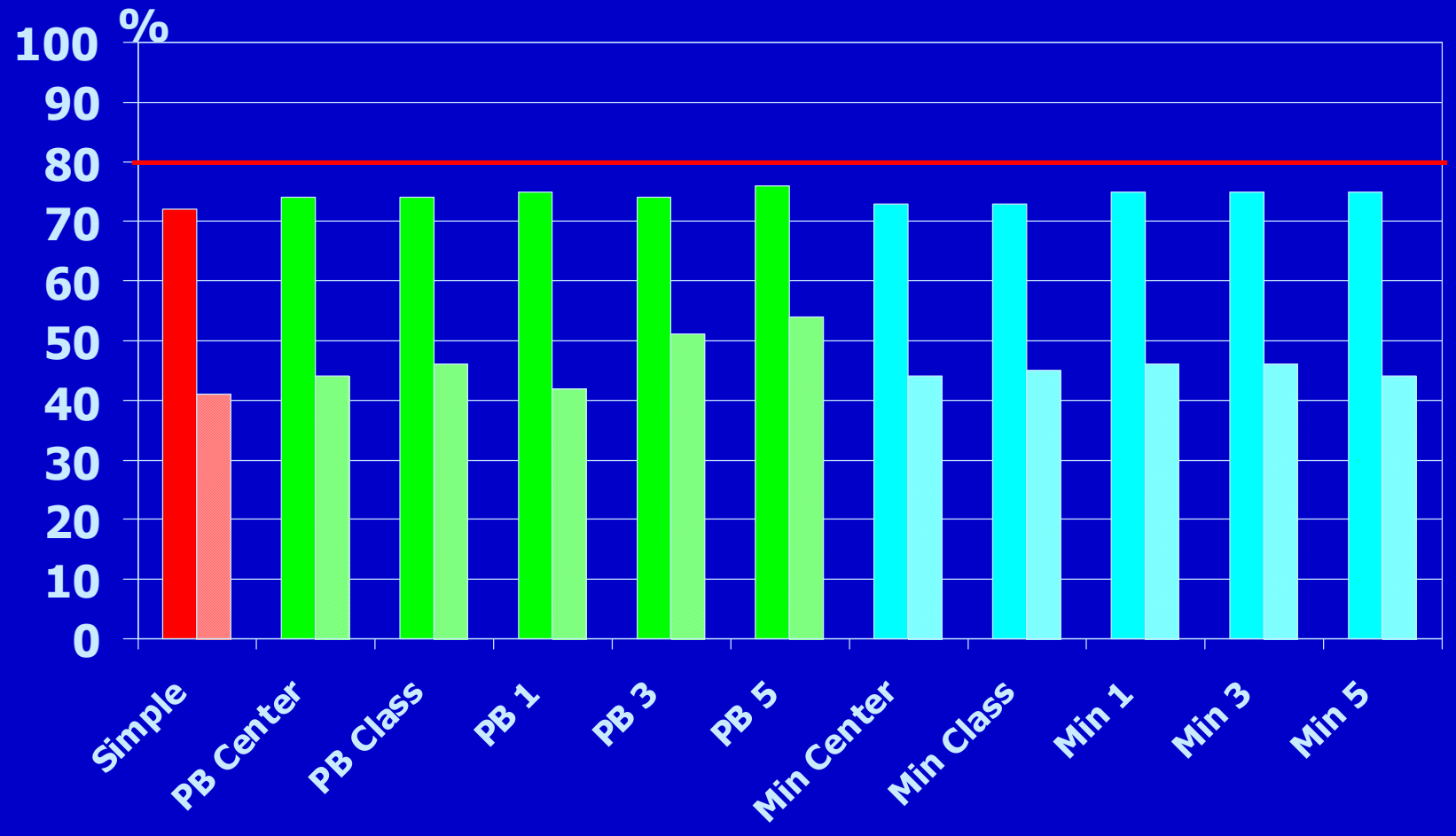
Simulations – power of logrank test

(dashed = stratified for 5 factors)



Simulations – power of logrank test

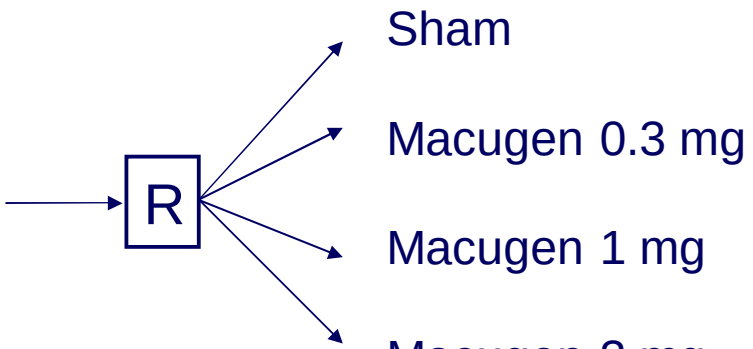
(dashed = stratified for center and all factors)



Simulations in age-related macular degeneration (AMD)

Minimization for

- Type of lesion
- Prior PDT
- Center



Other important baseline factors

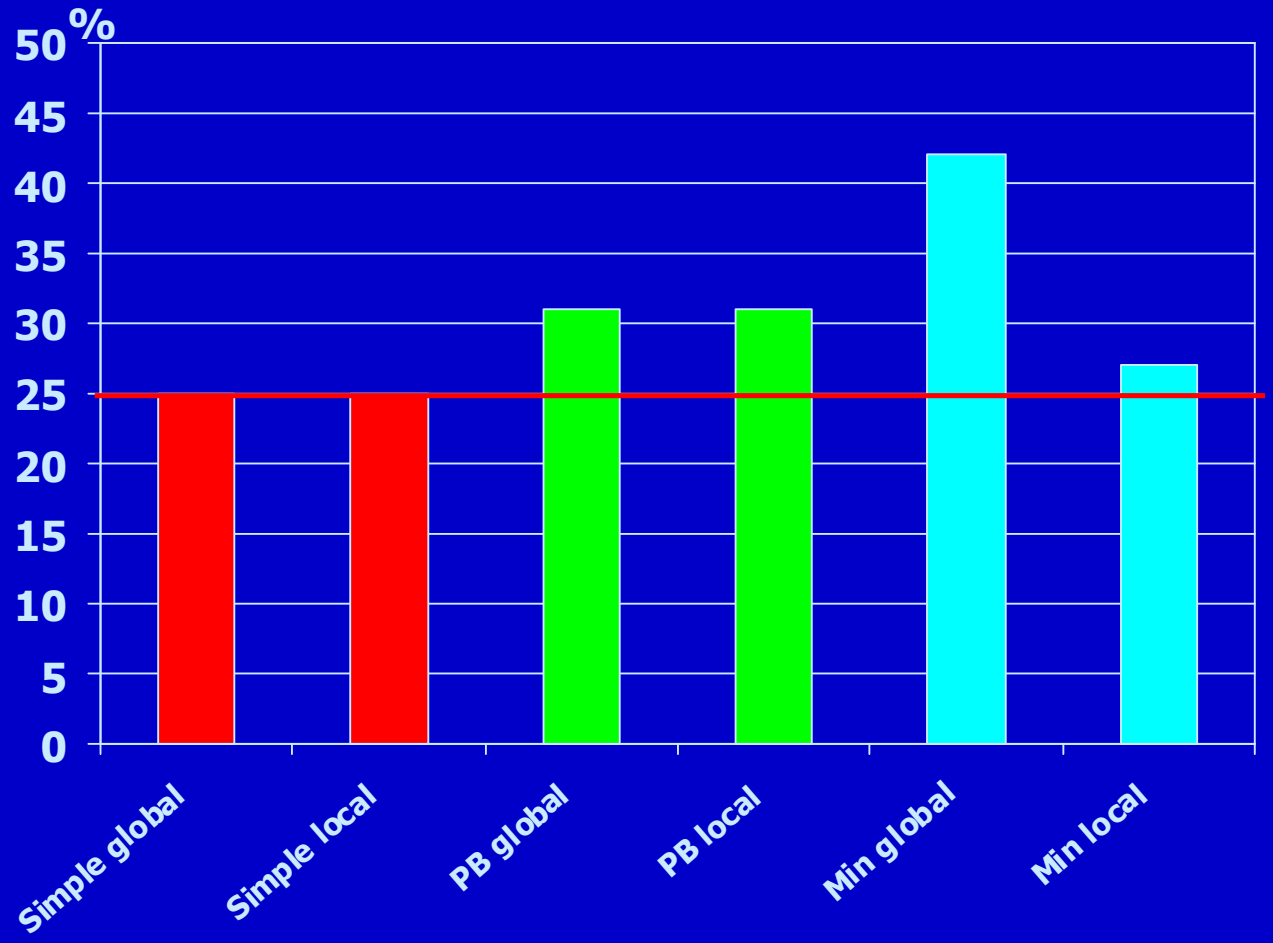
- *Size of lesion*
- *Vision*
- *Gender*

Simulations - allocation techniques

- Simple randomization
- Permuted blocks within strata defined by
  - Type of lesion
  - Prior PDT
- Minimization on
  - Type of lesion
  - Prior PDT
  - Center

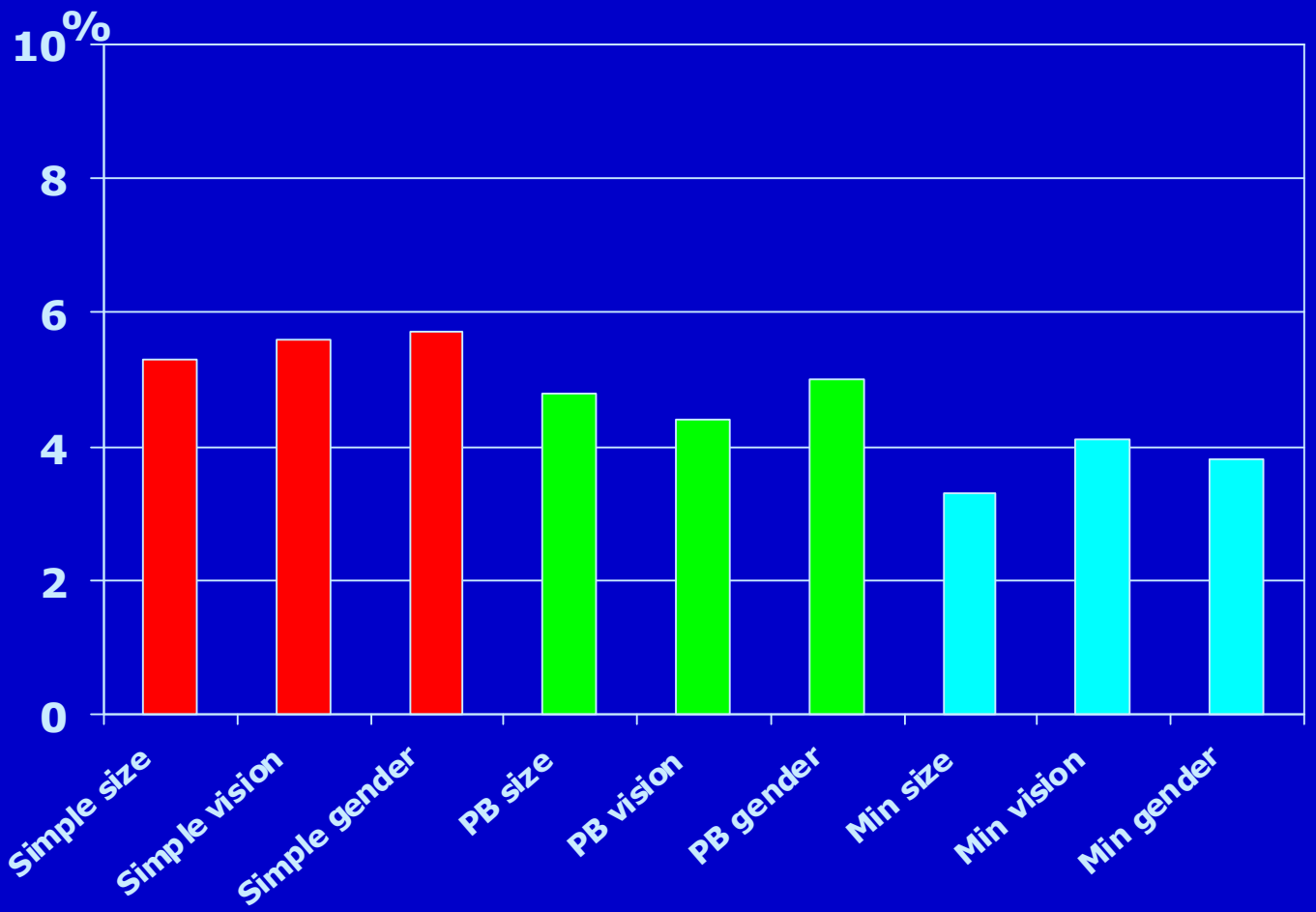
Predictability

Simulations – correctly guessed treatment allocations



Accidental bias

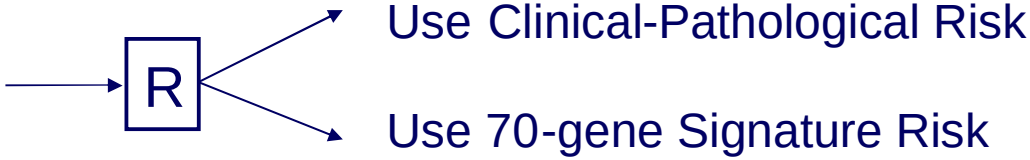
Simulations – imbalances in baseline prognostic factors



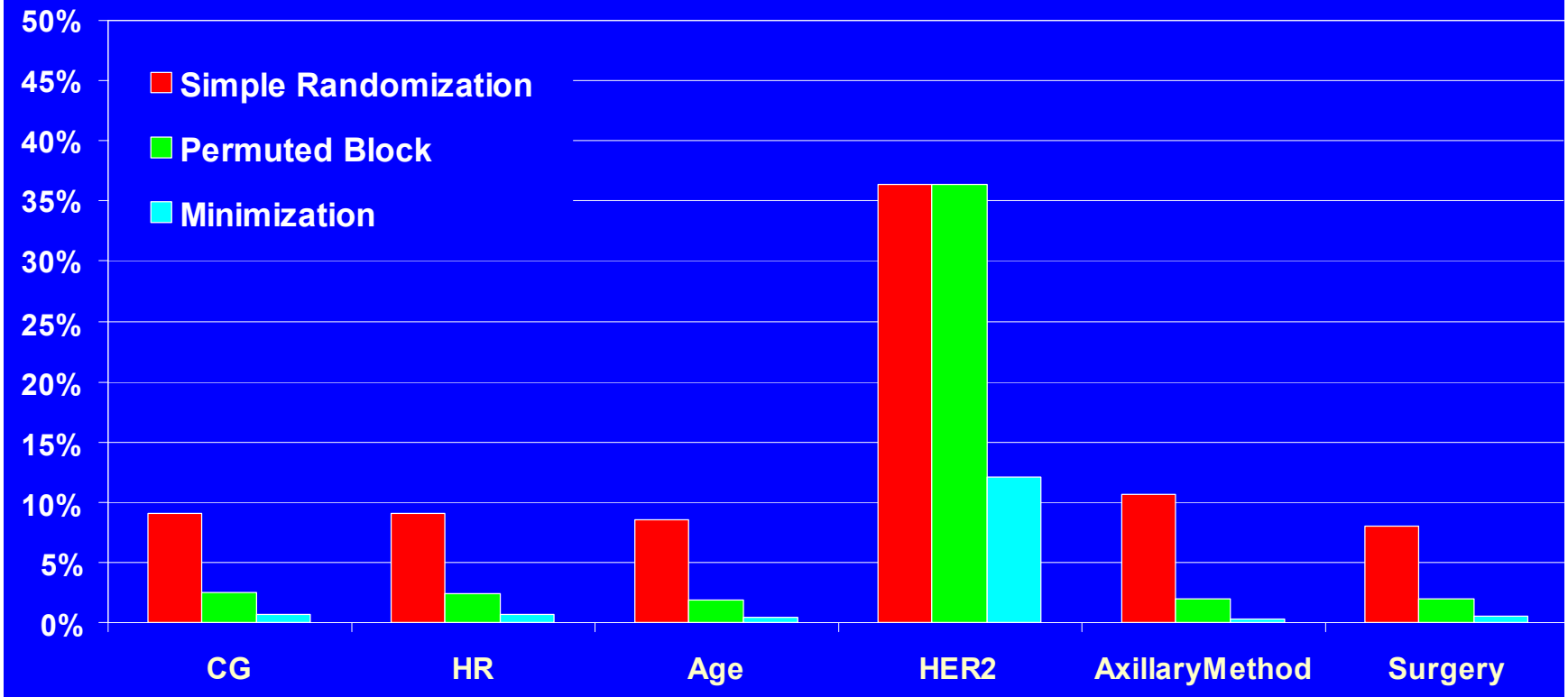
Simulations in **M**icro-array **I**n **N**ode negative **D**isease may **A**void **C**hemo**T**herapy (**MINDACT**)

Minimization for

- CG Risk
- HR Status
- Age
- Her2
- Axillary Method
- Surgery
- Center



Simulations – worst case scenario for baseline covariate imbalances



Conclusions – desirable characteristics

- Balance: minimization best, especially for large numbers of factors
- Size: slight gains with PB or minimization
  (or with stratified analyses)
- Power: negligible gains
  (more gain with stratified analyses)
- Predictability: quite limited if guesses based on local knowledge
- Accidental bias: slight gains with PB or minimization
- Simplicity: simple randomization best

Conclusions – minimization can be recommended…

- to ensure balance over a large number of factors
- regardless of the distribution of patients in the factor levels
- in trials of large or small size
- with center as a minimization factor in double-blind trials
- without center as a minimization factor in open-label trials

Acknowledgment

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(Cytel, Inc.) for the simulations in
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