Use of nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and risk of myocardial infarction in HIV-infected patients enrolled in the SMART study

SMART/INSIGHT and D:A:D Study Groups

Late breaker session, track B
International AIDS Conference,
Mexico City, 7th August 2008

Background

- D:A:D Study (Lancet, April 2008)
  - Abacavir (ABC) associated with excess risk of myocardial infarction
    - Present for current use (not not cumulative or past)
      - Suggesting that abacavir may increase the chance that existing atherosclerosis converts to cardiovascular disease (CVD)
    - Robust after adjustment for CV risk factors = channelling bias for known CV risk factors is less likely

XVII IAC, Mexico, 2008, Abstract THAB0305

Aims and objectives

- To establish whether this finding can be reproduced in an other data set where utilization of various NRTIs* differed from that in D:A:D
- To explore plausible biological mechanisms

*: NRTI=nucleos(t)ide reverse transcriptase inhibitor

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 30, 2006 VOL. 355 NO. 22

CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group*

CD4+ cell count >350 cells/mm^3

n = 2752

Continuous Strategy: Virologic Suppression (VS)

n = 2720

Intermittent Strategy: Drug Conservation (DC)

Clinical outcome: All patients in VS group (n=2752)

Biomarkers: levels of 6 markers of inflammation or coagulation at study entry among patients on NRTI when enrolling (n=791)

Considerations in design of analyses (I)

- Use of NRTI's*:
  - Abacavir (but not didanosine)
    - "ABC (no ddI)"
  - Didanosine (with abacavir or with other NRTIs)
    - "ddI (w/wo ABC)"
  - NRTIs other than ABC and ddI
    - "Other NRTIs"

*: NRTI=nucleos(t)ide reverse transcriptase inhibitor

XVII IAC, Mexico, 2008, Abstract THAB0305

Patient characteristics according to use of NRTIs at study entry (I)

	ABC (not ddI)	ddI (w/wo ABC)	Other NRTI's	Total
N	1019	643	2882	4544
Age (median, IQR)	45 (39-51)	44 (38-49)	44 (38-50)	44 (38-50)
% female	23	23	28	27
%HIV-RNA≤400 cop./mL	82	78	84	83
CD4 (median, IQR), c/µL	639 (495-836)	596 (475-794)	630 (486-814)	630 (487-819)
% prior CV disease	4	5	3	4
% current smokers	38	41	39	39
% ischemic abnorm.[1]	36	35	36	36
% diabetes	7	6	7	7

[1]Q-wave, ST depression, T-wave inversion, any bundle branch block or QTI>112%

XVII IAC, Mexico, 2008, Abstract THAB0305

Patient characteristics according to use of NRTIs at study entry (II)

	ABC (no ddI)	ddI (w/wo ABC)	Other NRTI's	Total
N	1019	643	2882	4544
% BP lowering drugs	21	20	18	19
% lipid lowering drugs	21	21	15	18
Total/HDL ratio (median, IQR)	4.6 (3.6-5.9)	4.7 (3.6-5.9)	4.6 (3.6-5.9)	4.6 (3.6-5.9)
%past/current ABC use	100	28	7	31
% NRTI only	39	6	4	12
% using tenofovir	17	25	22	21
% $\geq$ 5 CV risk factors	18	17	14	15

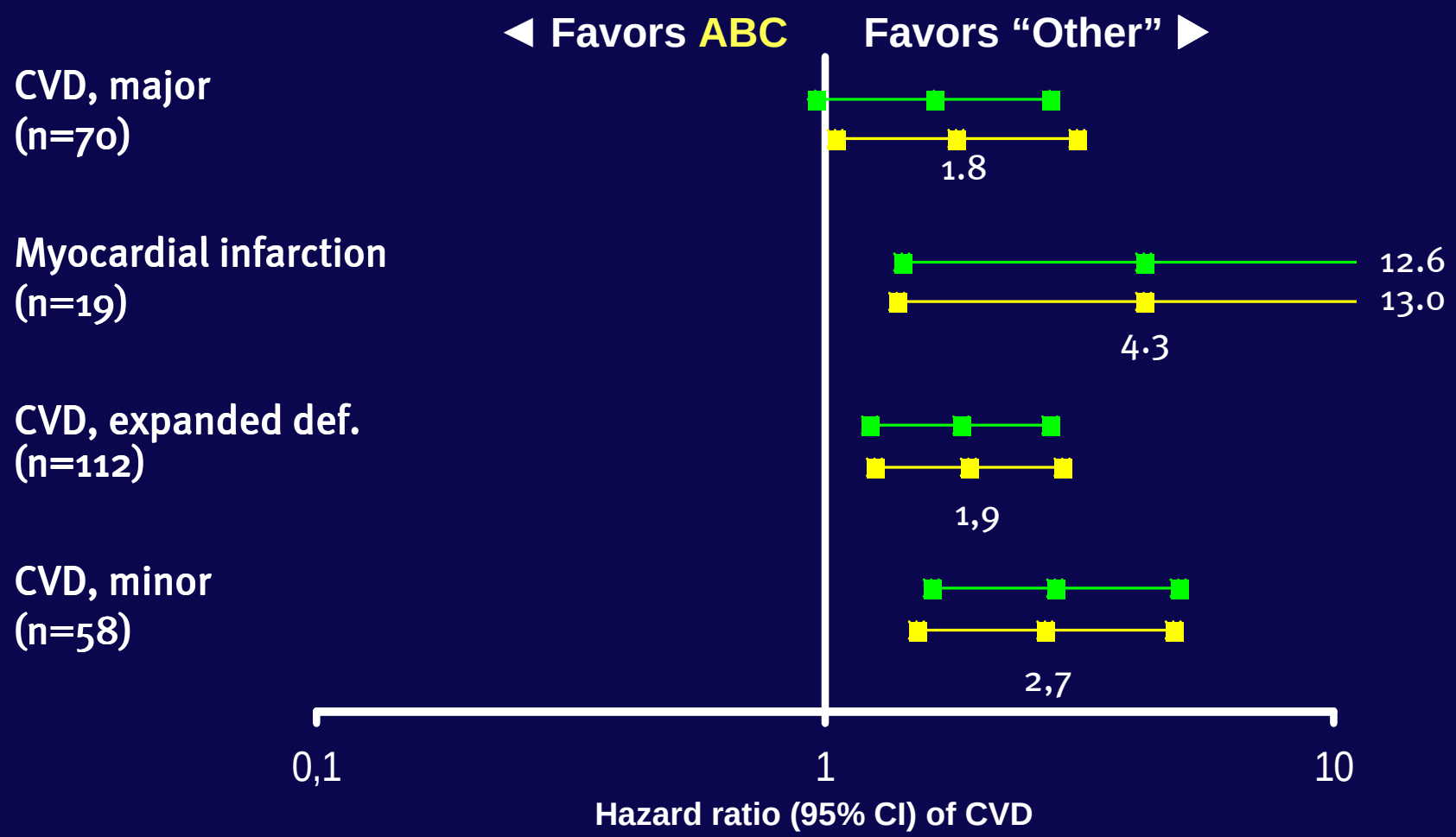
XVII IAC, Mexico, 2008, Abstract THAB0305

Considerations in design of analyses(II)

- CVD events*
  - CVD, major
    - Clinical and silent MI, stroke, surgery for coronary artery disease (CAD), and CVD death
      - —Clinical MI as considered in D:A:D
  - CVD, major, expanded version
    - Major CVD plus peripheral vascular disease, Congestive heart failure (CHF), drug treatment for CAD, and unwitnessed deaths.
  - CVD, minor
    - CHF, peripheral vascular disease or CAD requiring drug treatment

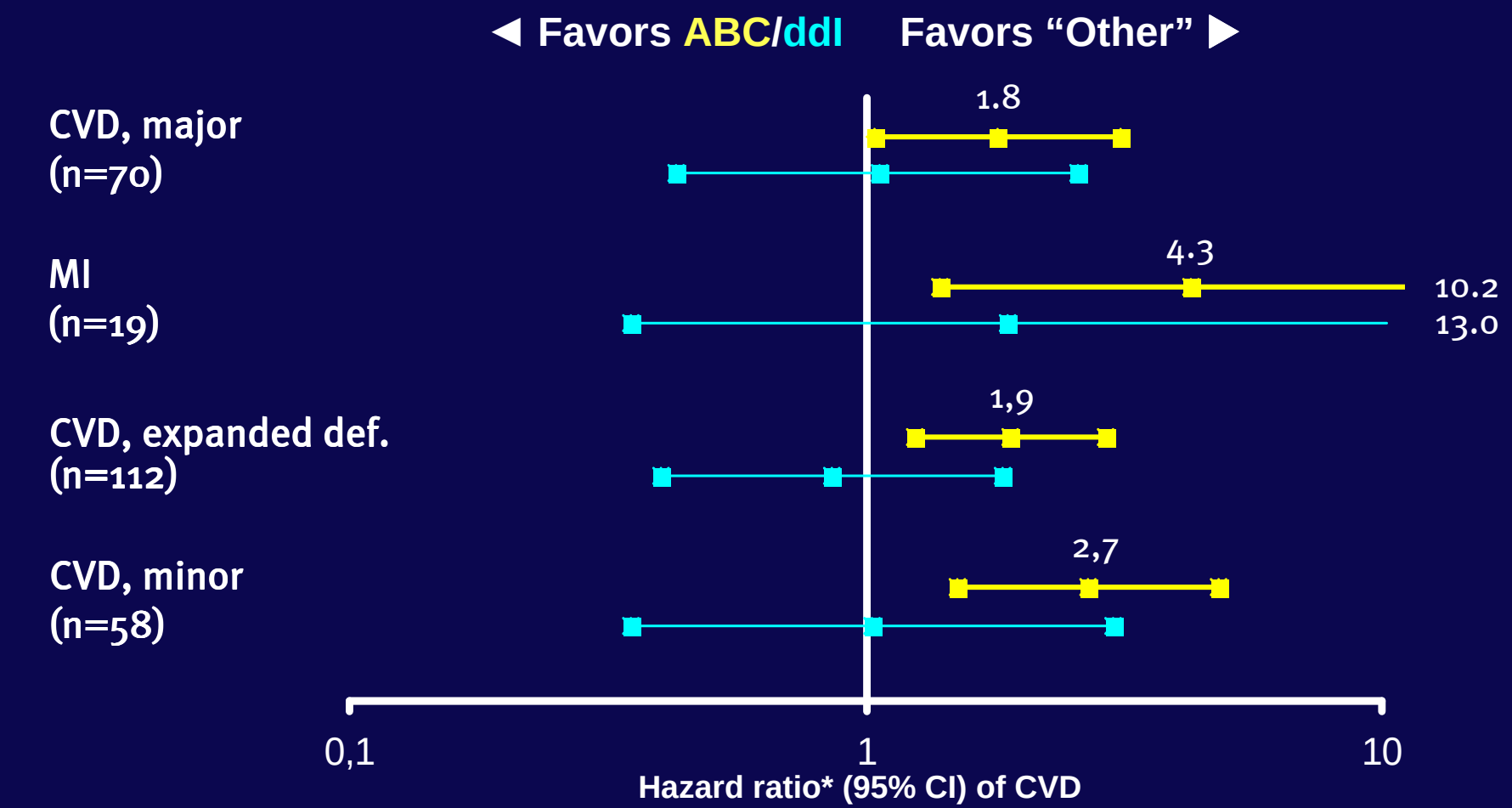
*: Pre-specified (SMART Study Group, NEJM 2006; Phillips *et al*, AVT, 2008)
All events adjudicated by Endpoint Review Committee

Hazard ratios for four types of CVD while receiving "ABC (no ddI)" versus using "Other NRTIs"



XVII IAC, Mexico, 2008, Abstract THAB0305

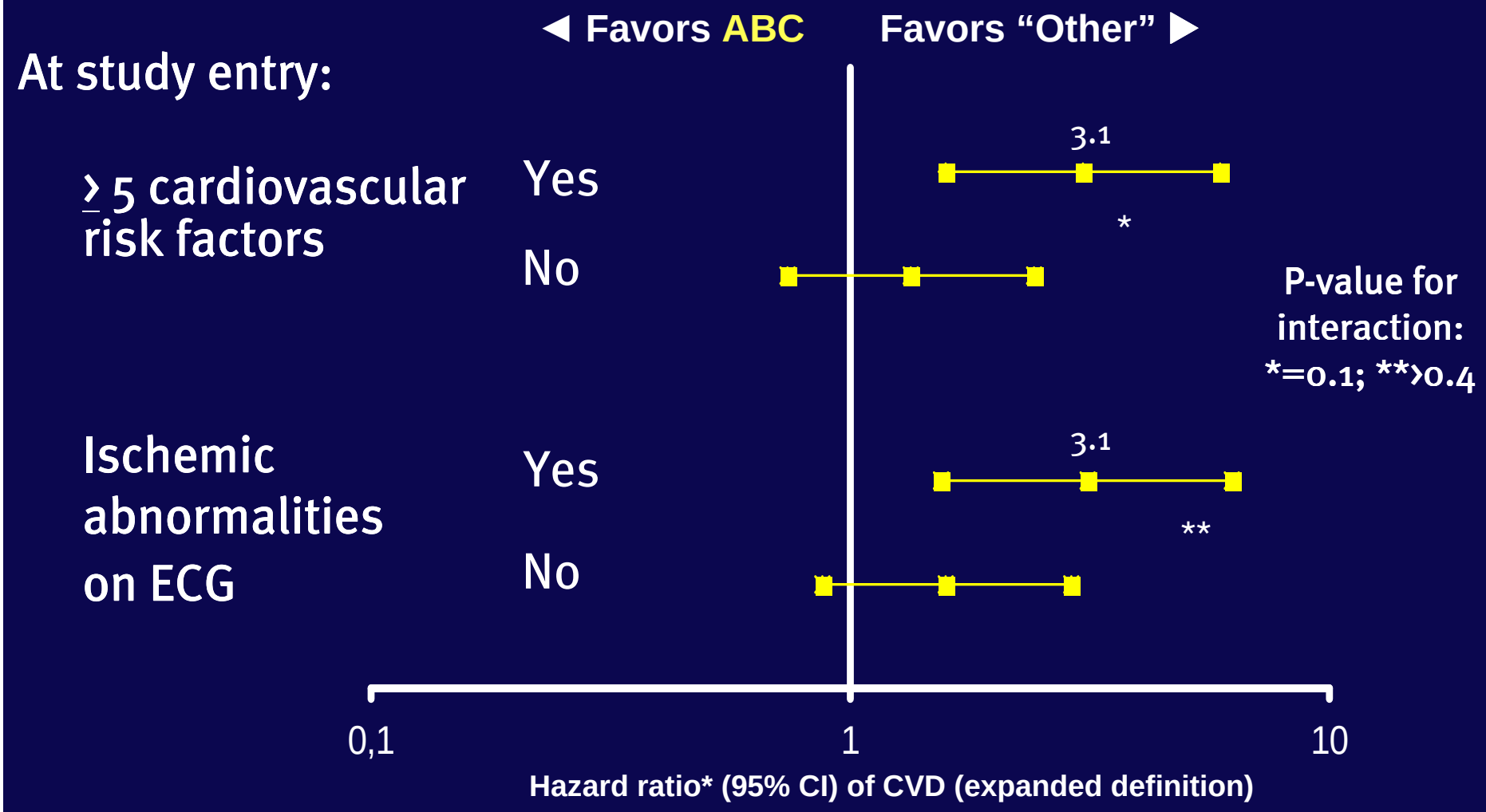
Comparison of hazard ratios* for ”ABC (no ddI)” and for ”ddI (w/wo ABC)” versus ”Other NRTIs”



*: Adjusted for CV risk factors

XVII IAC, Mexico, 2008, Abstract THAB0305

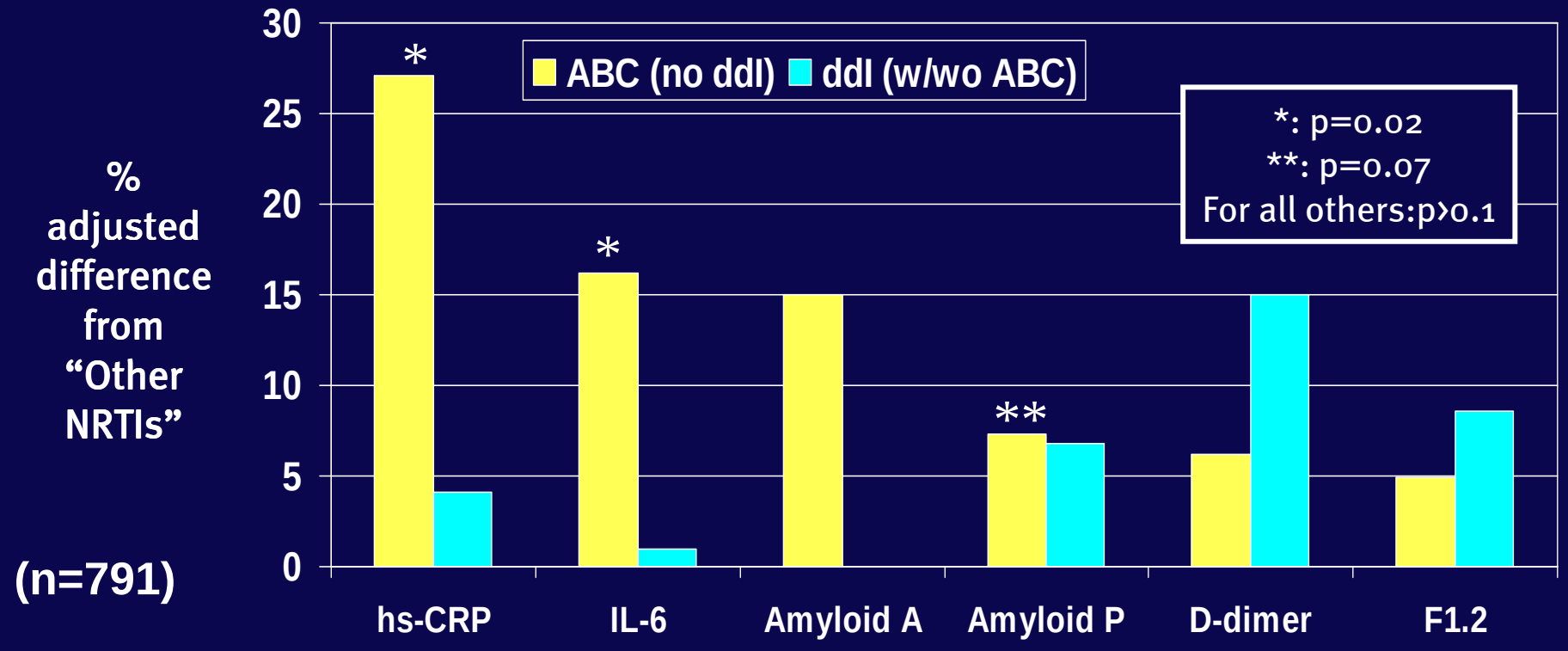
Hazards ratios* for using ”ABC (no ddI)” versus using ”Other NRTIs” according to CV risk status at study entry



*: Adjusted for CV risk factors

XVII IAC, Mexico, 2008, Abstract THAB0305

Adjusted mean differences in biomarker levels at study entry for using "ABC (no ddI)" or "ddI (w/wo ABC)" versus using "Other NRTIs"



Median (IQR) levels in "Others NRTIs"	hs-CRP	IL-6	Amyloid A	Amyloid P	D-dimer	F1.2
	2.3 (1.0-5.3) (µg/mL)	2.2 (1.4-3.7) (pg/mL)	3.6 (1.9-6.8) (mg/mL)	65 (51-86) (µg/L)	0.3 (0.2-0.5) (µg/mL)	0.4 (0.3-0.5) (nmol/L)

XVII IAC, Mexico, 2008, Abstract THAB0305

Limitations

- Possibility of channeling effect; i.e. patients at an *a priori* excess underlying risk of CVD may have been preferentially placed on abacavir
  - CV risk factor profile fairly comparable between groups
  - Adjustment for known and quantifiable CV risk factors failed to affect the association !
  - Definitive solution: randomised controlled trial
- Possibility that patients on abacavir had elevated hsCRP and IL-6 for reasons other than use of abacavir
  - Prospective follow-up
    - preferably in randomised controlled trial setting
- Reduced power for some endpoints
- Overlap in patient populations
  - Analyses of sites not participants in D:A:D - ›90% of endpoints – consistent results

XVII IAC, Mexico, 2008, Abstract THAB0305

Summary

- Consistent with D:A:D, current use of abacavir, during follow-up in SMART
  - associated with an excess risk of CVD
- Abacavir use at study entry
  - associated with increased levels of IL-6 and hs-CRP

Proposed mechanisms of action for how abacavir may increase CVD risk

- The drug causes an increased propensity for subclinical atherosclerosis to cause CVD
  - Data not consistent with abacavir affecting atherosclerosis
- The increased propensity maybe caused by proinflammatory properties of the drug
  - IL-6 and hs-CRP surrogates of ongoing inflammatory reactions in coronary arterial wall leading to instability of existing plaques

XVII IAC, Mexico, 2008, Abstract THAB0305

Conclusions

- Abacavir associated with excess CVD risk in two observational studies
- The drug
  - *does not* appear to affect the underlying atherosclerotic process *per se*
  - *m*ay cause coronary artheritis ➡ instability of plaques
- This adverse effect appears to be only clinically relevant to consider among patients with elevated underlying CV risk

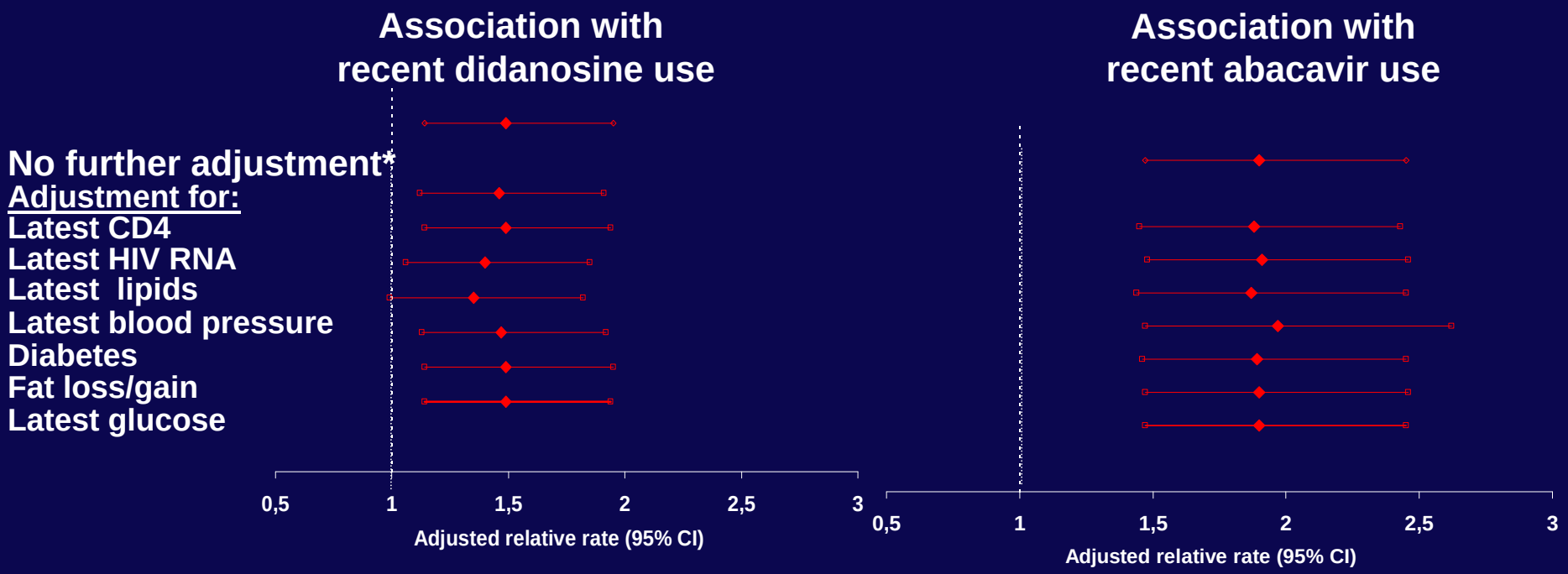
Manuscript: *AIDS* (in press, fast track)
Date of publication: 2nd September 2008

Acknowledgements

- Other members of writing committee: Jacqueline Neuhaus, Abdel Babiker, David Cooper, Daniel Duprez, Wafaa El-Sadr, Sean Emery, Fred Gordin, Justyna Kowalska, Andrew Phillips, Ronald J Prineas, Peter Reiss, Caroline Sabin, Russell Tracy, Rainer Weber, Birgit Grund & James D Neaton
- *SMART study group & INSIGHT* executive committee
- *D:A:D Study Group including Steering Committee*
- Financial support for SMART was provided by: NIAID, NIH grants U01AI068641, U01AI042170 and U01AI46362
- SMART Clinical Trials.gov identifier: NCT00027352

Back-up slides

Association with didanosine and abacavir use and risk of MI:
Additional adjustment for factors that may be influenced by cART



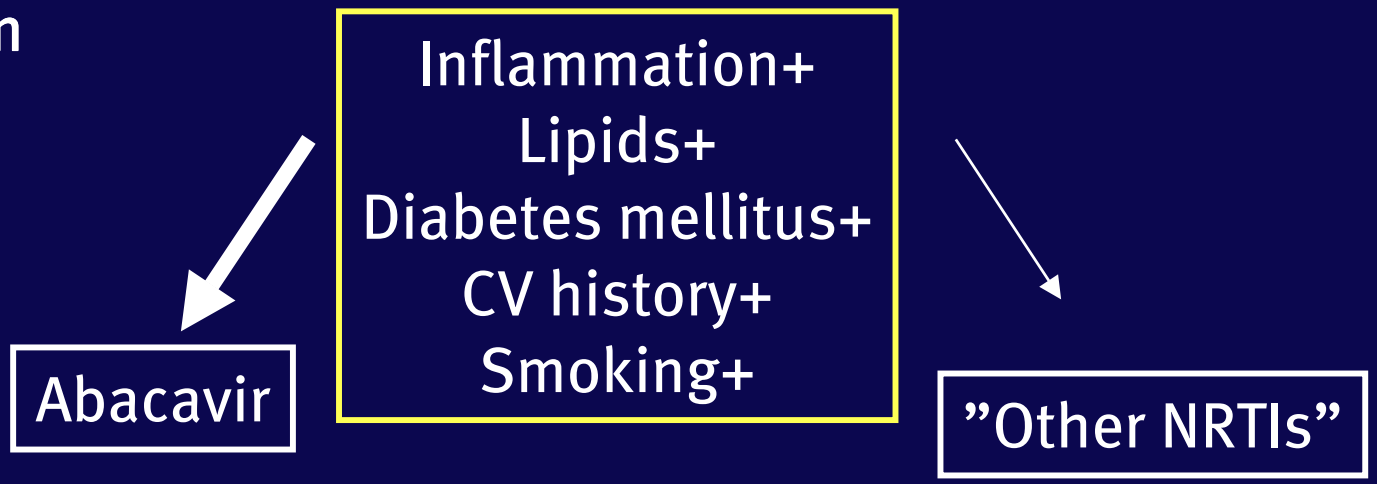
*: Adjusted for demographic factors, calendar year, cohort, CV risk factors that are unlikely to be modified strongly by cART use and cumulative exposure to other antiretroviral drugs

D:A:D Study Group, Lancet 2008

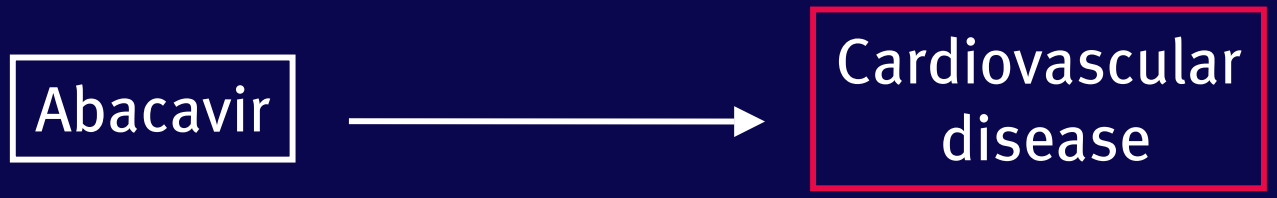
XVII IAC, Mexico, 2008, Abstract THAB0305

Channelling and how to assess this bias statistically

Selection



Testing for association:

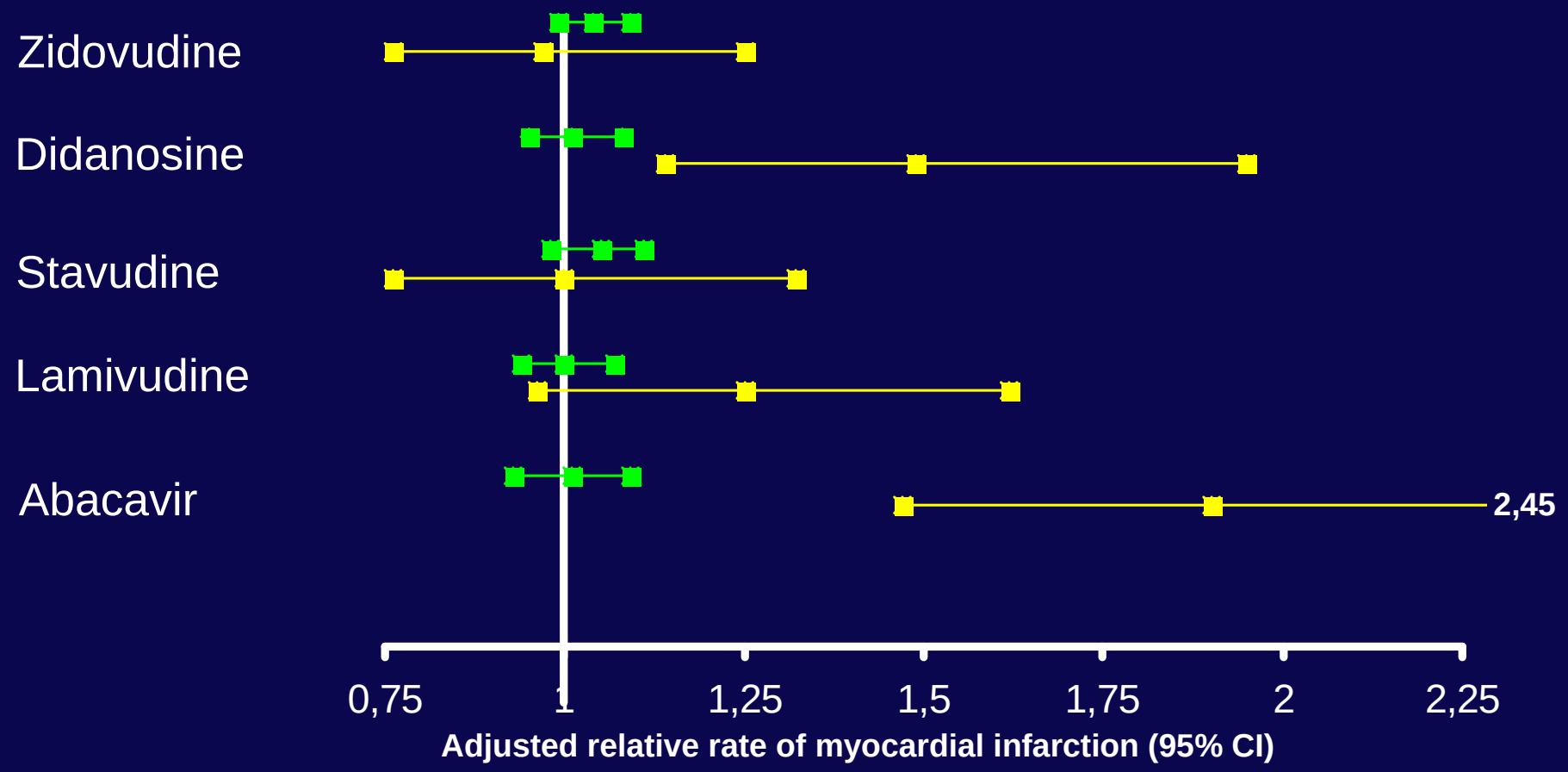


If channelling bias explains association between ABC and CVD, adjustment for shown CV factors would tend to remove the association

XVII IAC, Mexico, 2008, Abstract THAB0305

Relationship with specific drugs

cumulative and recent use



D:A:D Study Group, Lancet 2008

XVII IAC, Mexico, 2008, Abstract THAB0305