

# Predicted Risk of Coronary Heart Disease (CHD) with Tipranavir Exposure Compared to Conventional PI in the RESIST Trial

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## BACKGROUND

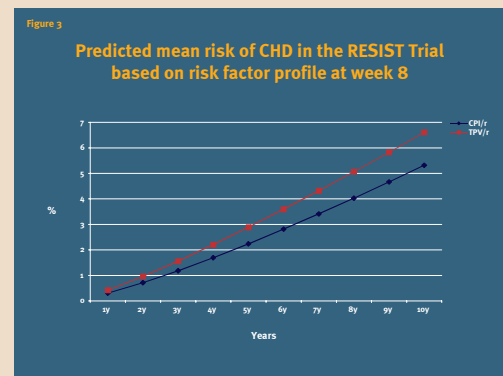
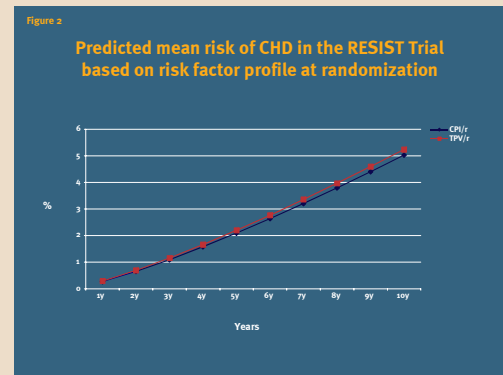
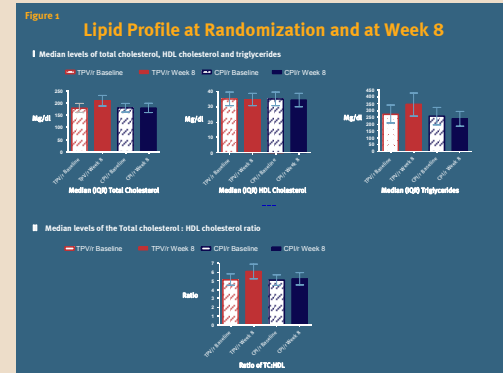
- The use of Tipranavir (TPV/r) is indicated in treatment-experienced patients
  - In two pivotal, phase III clinical trials — RESIST-1 and RESIST-2 — treatment-experienced patients with substantial resistance to existing PIs were randomized to receive an optimized background regimen with either ritonavir-boosted tipranavir (TPV/r) or another conventional ritonavir-boosted PI (CPI/r)
  - TPV/r showed superior treatment responses compared to CPI/r<sup>1</sup>
- Elevation of lipid levels have been observed more frequently after use of TPV/r (500mg/200mg BID) than after use of other low dose ritonavir boosted PIs
- Based on data collected in the RESIST trials, we estimated the potential added risk for coronary heart disease (CHD) associated with TPV/r use compared to CPI/r

## METHODS

- In treatment experienced patients, mean 5 and 10-year CHD risk was modelled according to metabolic factors observed at baseline and after 8 weeks of starting medication in the RESIST trials
  - Primary emphasis was made to the observations at week 8, as most patients remained adherent to randomized drug assignment at this study visit
- The CHD risk estimates were calculated using the Framingham risk equation, a parametric statistical model controlling for multiple cardiovascular risk factors<sup>2</sup>
  - There are data to suggest that the incremental CHD risk associated with metabolic changes induced by PIs occurs without any substantial delay<sup>3</sup>, and that
  - The Framingham score fairly reliably predicted the risk of myocardial infarction in HIV-infected individuals<sup>4</sup>
- The following measured covariates were introduced in to the Framingham prediction model:
  - Age
  - Sex
  - Diabetes
  - Prior cardiovascular disease
  - The ratio of serum Total Cholesterol: HDL Cholesterol (TC:HDL)
- While the following co-variables were unavailable:
  - Blood pressure
  - Smoking
- Therefore, in the primary analyses (A) the prevalence of smoking and the average blood pressure are imputed and takes the average values observed in the D:A:D study<sup>3</sup>:
  - Mean systolic blood pressure 120 mmHg, and smoking prevalence 45%
  - Different average values were considered in sensitivity analyses in men for the following scenarios:
    - Systolic blood pressure 120 mmHg, smoking prevalence 100%
    - Systolic blood pressure 130 mmHg, smoking prevalence 45%
    - Systolic blood pressure 130 mmHg, smoking prevalence 100%
    - Systolic blood pressure 140 mmHg, smoking prevalence 45%
    - Systolic blood pressure 140 mmHg, smoking prevalence 100%
    - Systolic blood pressure 120 mmHg, smoking prevalence 45%, diabetes prevalence 100%
    - Systolic blood pressure 140 mmHg, smoking prevalence 100%, diabetes prevalence 100%, age 60
- The numbers needed to treat to harm one person (NNTH) treated with TPV/r over and above the number of patients experiencing a CHD event on CPI/r were calculated from the absolute CHD risk difference between the study arms:
  - NNTH = 1/absolute risk difference

## RESULTS

- In the RESIST trials, 746 and 737 individuals were randomized to TPV/r and CPI/r, respectively [Table 1]
  - Week 8 data were available for 630 (TPV/r) and 613 (CPI/r) individuals
- Over the first 8 weeks of exposure, changes in lipid levels were observed [Figure 1, I and II]
  - The TC:HDL ratio increased from 5.1(4.1-6.3) to 6.0 (4.7-7.6) in the TPV/r arm, while from 5.0 (4.1-6.2) to 5.2 (4.1-6.5) in the CPI/r arm (p-value for difference between arms at week 8: <0.0001) [Figure 1, II]



## RESULTS (continued)

- The predicted risk of CHD over a 10-year period is illustrated in Figures 2-3:
  - Figure 2 shows the predicted risk of CHD based on baseline parameters, and illustrates that – at baseline – this predicted risk is quite similar for both arms
  - However, at 8 weeks of exposure the modelled CHD risk differ [Figure 3]
- The predicted average risk of CHD over a 5-year period in the primary analysis (A) is 2.88% overall in the TPV/r arm versus 2.24% in the CPI/r arm [Figure 3], for a NNTH estimate of 155 (1/0.0288-0.0224)
  - That is, to observe one additional CHD event over a 5-year period over and above what would be expected after treatment with CPI/r, 155 patients would need to be treated with TPV/r
- However, the absolute risks vary greatly by gender:
  - 3.15% for men, and 1.49% for women in the TPV/r arm versus 2.38% and 1.08% in the CPI/r arm, and thus NNTH is considerably lower for men (131) than women (245)
- On top of the predictions from the primary analysis, Figures 4 and 5 also includes the sensitivity analyses (B-H) for 5-year predicted CHD risk and NNTH in men
- Among the selected scenarios, the highest absolute risk and thus the lowest estimate of NNTH (41) are observed in the analysis to the right [Figures 4 and 5, scenario H], illustrating the risk in diabetic men aged 60 who smokes and have hypertension

## CONCLUSIONS

- In two large pivotal clinical trial studies conducted in highly treatment experienced patients, TPV/r demonstrated superior treatment response to standard of care PI containing regimens<sup>1</sup>
- A difference in lipid parameters is observed in the RESIST studies by week 8, which translates in to an increased predicted risk of CHD in the TPV/r arm compared to the CPI/r arm
  - However, in absolute terms, the incremental risk of CHD is modest and should be balanced against the beneficial effects of treatment in preventing progression to AIDS:
  - The differences in predicted absolute risks between the TPV/r and CPI/r arms results in estimated NNTH in the range of 80-150 for the men in the study over a 5-year period, and considerably higher NNTH (i.e. lower absolute risks) for the women in the study
- In certain subgroups of patients that present at baseline with well-known cardiovascular disease risk factors, and thus a higher a priori risk of CHD, the estimated NNTH is lower
- In aggregate, these findings suggest that in failure patients requiring a boosted PI regimen, the potential added harm on risk of CHD induced by TPV/r versus CPI/r is present but limited in absolute terms in most patients
- However, there are groups of patients in whom the absolute risk of CHD over a 5-year period is as high as 15% irrespective of study arm
- Thus, prudent evaluation of underlying cardiovascular disease risk factors - and consequently absolute risk of CHD - is important to assure appropriate risk assessment and patient management

## COMMENTS

- The estimates of CHD risk presented here need to be interpreted with care:
  - Risk estimates were based on the application of a conventional CHD risk equation (the Framingham score), designed for use in the US general population<sup>2</sup>
  - Although validated in HIV-infected individuals<sup>4</sup>, a more accurate prediction model may be required for this population
  - Further, the underlying assumption for the present analyses is that the lipid levels observed in week 8 remains stable throughout the ensuing prediction period

## References

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Table 1 Baseline Characteristics in the RESIST trials

	TPV/r	CPI/r
No. of subjects	746	737
Baseline date	Aug 2003 (June-Sep)	Aug 2003 (June-Sep)
Median (IQR)		
Age (years)	43(38-49)	42(38-48)
Baseline		
BMI (kg/m <sup>2</sup> )	23.2 (21.1-25.5)	23.0 (21.2-25.2)
Log HIV-RNA	4.8 (4.35-2)	4.8 (4.25-3)
CD4 count (cells-per µL)	358 (66-385)	366 (53-380)
%		
Female	15.7	11.7
Prior CVD	1.5	1.9
Diabetes	4.4	4.2
Region		
Europe	40.6	40.7
North America	41.7	41.9
South America	17.7	17.4

Figure 4 Predicted mean 5-year risk of CHD according to study drug and risk profile

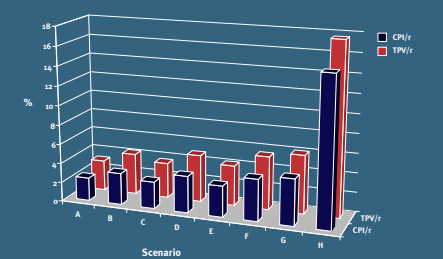


Figure 5 Predicted NNTH for 5-year CHD risk – TPV/r versus CPI/r

