The evidence for race-based therapeutics and the BiDil trials

BiDil is the commercial name given to the fixed-dose combination of 37.5mg hydralazine hydrochloride (an antihypertensive) and 20 mg isosorbide dinitrate (a vasodilator). Each of these drugs is available in generic form and is used to treat congestive heart failure. In the first of two studies of the efficacy of BiDil, volunteers with congestive heart failure were recruited at 11 Veterans Administration centers as part of the Vasodilator Heart Failure Trial (V-HeFT 1). Comparing mortality in the two arms, the investigators observed a trend toward lower mortality with BiDil as compared to placebo (two year cumulative mortality rates of 25.6% and 34.3% respectively; P = 0.093 by the log-rank test). In a subsequent study (V-HeFT 2), the investigators found that BiDil was less effective than enalapril, a recently approved angiotensin converting enzyme inhibitor (two-year cumulative mortality rates of 25% versus 8%, respectively; P = 0.02).

In 1999, the study investigators published a post-hoc analysis of the two V-HeFT trials comparing the mortality in the combination therapy arm against both placebo and active control arms by race. The comparisons for black patients are shown below. The investigators concluded that the evidence suggested that both BiDil and enalapril were effective relative to placebo in black patients.

Trial		Black patients		
V-HeFT1		HI(BiDil)	Placebo	P value (log rank test)
	Patients enrolled	49	79	
	Patients with outcome (%)	15(30.6)	35(44.3)	0.04
V-HeFT2		BiDil	Enalapril (active control)	P value (log rank test)
	Patients enrolled	106	106	
	Patients with outcome (%)	39(36.8)	36(34.0)	Not significant

Based on these findings, the investigators initiated the A-HeFT trial comparing BiDil to placebo in African-American patients. This trial was terminated early because of significantly greater mortality in the placebo arm. The table below summarizes the results from the A-HeFT Trial.

Trial		Black patients		
A-HeFT		BiDil	Placebo	P value (log rank test)
	Patients enrolled	518	532	
	Patients with outcome (%)	32(6.2)	54(10.2)	0.02(stopped early)

Shortly thereafter, the FDA approved BiDil for exclusively African-Americans patients. To date, there has been no clear evidence of a genetic basis for the apparent differential effectiveness of BiDil in white and black patients.

Discussion question 1:

Are you convinced by the evidence that BiDil is effective for African American patients?

Discussion question 2:
Given that many clinical trials predominantly enroll white patients, yet their results are applied to all races, what are your thoughts about the FDA approving BiDil only for African American patients?

Optional discussion question 3:

For students with more experience in hypothesis testing, consider the data for white patients enrolled in the two trials, shown below.

Are you convinced that there is a different effect of BiDil in white and black patients?

		White patients			
Trial		HI (BiDil)	Placebo	P value (log rank test)	P value for the difference between black and white response rate
V-HeFT1	Patients enrolled	132	192		
	Patients with outcome	56(42.4)	85(44.3)	Not significant	0.11
		HI(BiDil)	Active control	P value (log rank test)	
V-HeFT2	Patients enrolled	282	292		
	Patients with outcome (%)	112(39.7)	90(30.8)	0.02	0.09

For your answers to these questions, please substantiate your claims with evidence, either as presented in case, references of the case, or your own outside research.

Mandatory question:

In this case, the p values of the log-rank test are presented. The log-rank test is used for which kind of data?

a. Continuous endpoints
b. Binary endpoints
c. Time-to-event endpoints

References:

V-HEFT Trial paper :
http://www.ncbi.nlm.nih.gov/pubmed/?term=10.1056%2FNEJM198606123142404

Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, et al. (1986) Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 314: 1547–1552. doi:10.1056/NEJM198606123142404.

V-HEFT 2 Trial paper :
http://www.ncbi.nlm.nih.gov/pubmed/?term=10.1056%2FNEJM199108013250502

Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, et al. (1991) A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 325: 303–310. doi:10.1056/NEJM199108013250502.

Subgroup analysis paper : http://www.ncbi.nlm.nih.gov/pubmed/?term=10496190

Carson P, Ziesche S, Johnson G, Cohn JN (1999) Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail 5: 178–187.

Clinical Trial of Only African American subjects for DiBil:
http://www.ncbi.nlm.nih.gov/pubmed/?term=10.1056%2FNEJMoa042934

Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, et al. (2004) Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 351: 2049–2057. doi:10.1056/NEJMoa042934.

Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials:
http://www.nejm.org/doi/full/10.1056/NEJMsr077003