Challenge and Yield of Enrolling Racially and Ethnically Diverse Patient Populations in Low Event Rate Clinical Trials

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Background and Purpose—We report patient enrollment and retention by race and ethnicity in the CREST (Carotid Revascularization Endarterectomy Versus Stent Trial) and assess potential effect modification by race/ethnicity. In addition, we discuss the challenge of detecting differences in study outcomes when subgroups are small and the event rate is low.

Methods—We compared 2502 patients by race, ethnicity, baseline characteristics, and primary outcome (any periprocedural stroke, death, or myocardial infarction and subsequent ipsilateral stroke up to 10 years).

Results—Two hundred forty (9.7%) patients were minority by race (6.1%) or ethnicity (3.6%); 109 patients (4.4%) were black, 32 (1.3%) Asian, 2332 (93.4%) white, 11 (0.4%) other, and 18 (0.7%) unknown. Ninety (3.6%) were Hispanic, 2377 (95%) non-Hispanic, and 35 (1.4%) unknown. The rate of the primary end point for all patients was 10.9%±0.9% at 10 years and did not differ by race or ethnicity (P_{inter}>0.24).

Conclusions—The proportion of minorities recruited to CREST was below their representation in the general population, and retention of minority patients was lower than for whites. Primary outcomes did not differ by race or ethnicity. However, in CREST (like other studies), the lack of evidence of a racial/ethnic difference in the treatment effect should be interpreted with caution because of low statistical power to detect such a difference.

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Studies have described racial or ethnic disparities in stroke incidence, mortality, treatments provided, and outcomes.[1–14] Overall, stroke mortality among blacks is ≈1.4× higher than for their white counterparts, with stroke mortality 2.0× to 3.0× higher between the ages of 45 and 64 years.[15] In contrast, stroke mortality in Hispanics, Asians, and Native Americans is lower than for whites.[15] The higher stroke mortality in blacks seems to be attributable to an elevated risk of stroke incidence that mirrors the pattern of elevated mortality in blacks, with black–white differences in stroke case-fatality contributing little.[16] Although stroke mortality among Hispanics is lower than their white counterparts, the Northern Manhattan Study estimated stroke incidence to be twice that of whites,[14] and the Brain Attack Surveillance in Corpus Christi study estimated an incidence ratio of 2.00 for ages 45 to 59 years, 1.57 for ages 60 to 74 years, and 1.13 for ages >75 years.[17]

Previous in-hospital database studies have shown that blacks and Hispanics have poorer outcomes after carotid endarterectomy.[18,19] For carotid artery stenting, the CARE Registry (The Carotid Artery Revascularization Registry) showed that the risk of perioperative stroke did not differ by race for carotid artery stenting although the risk for stroke or major adverse cardiac or cerebrovascular events was significantly higher in blacks for carotid endarterectomy.[20]

Despite the National Institutes of Health Revitalization Act of 1993 requiring clinical trials to be "designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women

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or members of minority groups, as the case may be, differently than other subjects in the trial,"[21] minorities have been under-represented in stroke clinical trials,[5,22] as well as in trials for other diseases.[23–25] Efforts to meet these requirements have generally focused on ensuring a minority inclusion proportional to population representation, with less attention on the statistical ability to detect a differential treatment effect (as suggested by the law).

The CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) is a multicenter randomized National Institutes of Health–funded clinical trial in patients with symptomatic and asymptomatic carotid disease.[26] The risk of the composite primary end point of stroke, myocardial infarction, or death during a 30-day periprocedural period and subsequent ipsilateral stroke (up to 10 years) did not differ for carotid artery stenting and carotid endarterectomy patients with asymptomatic and symptomatic carotid artery stenosis.[27,28]

In this report, we describe CREST's racially and ethnically diverse population, differences in enrollment and treatment outcomes, and investigate the ability to generate treatment guidelines for minorities based on our clinical trial results.

Methods

The CREST protocol was approved by the institutional/ethics review boards at all participating sites, and each participant provided written informed consent in English, Spanish, or French. The study design, primary, and long-term results have been previously published.[26–28] For site selection, a guideline for clinical center participation included having a referral population of ≥4% minorities in the context of a trial enrollment goal of 12% for minorities.

Race and ethnicity were determined by self-report, using the 5 categories for race in the National Institutes of Health Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (American Indian or Alaska Native; Asian; black; Native Hawaiian or Other Pacific Islander; and white) and the 2 categories for ethnicity (Hispanic or Latino, and Not Hispanic or Latino).[29] A total of 2502 patients were randomized from 2000 to 2008 and followed through April 2014.[30] The adjudication of suspected outcome events was blinded to treatment assignment, and the primary analysis was by intention-to-treat.

Herein, we assess racial and ethnic differences in the baseline characteristics and primary outcome (any periprocedural stroke, death, or myocardial infarction and subsequent ipsilateral stroke up to 10 years). Symptomatic participants were defined as having had a transient ischemic attack, amaurosis fugax, or nondisabling stroke in the arterial distribution ipsilateral to the study carotid artery within 180 days of randomization. Asymptomatic patients were defined as having no transient ischemic attack or stroke ipsilateral to the study carotid artery within 180 days of randomization.

Standard survival techniques were used including Kaplan–Meier survival and proportional hazards models. The potential for effect modification by race/ethnicity was assessed by a treatment-by-race/ethnicity term in the proportional hazards models after adjusting for age, sex, symptomatic status, and treatment.

The data, methods, and materials used to conduct the research will be made available as an National Institutes of Health–archived data set to any researcher for purposes of reproducing the results or replicating the procedure.

Results

Two hundred forty (9.7%) patients were minority by race or ethnicity (Table 1), with 109 (4.4%) patients black, 32 (1.3%) Asian, 2332 (93.4%) white, 11 (0.4%) other, and 18 (0.7%) unknown; 90 (3.6%) were Hispanic, 2377 (95%) non-Hispanic, and 35 (1.4%) unknown. For comparison, the 2010 Census of the Population estimates the US population above age 45 years (reflecting ages in CREST) to be 11.0% black, 4.5% Asian, 0.9% American Indian, and 83.6% white; and 9.4% were Hispanic and 90.6% were non-Hispanic.[31]

Table 1. Distribution of Enrolled Participants by Race and Ethnicity*

Minority (Non-White or Hispanic)†	n (%)
Racial category	240 (9.7%)
Black	109 (4.4)
Native Hawaiian or Pacific Islander	3 (0.1)
Asian	32 (1.3)
American Indian or Alaska Native	8 (0.3)
White	2332 (93.2)
Unknown‡	18 (0.7)
Ethnicity	
Hispanic	90 (3.6)
Non-Hispanic	2377 (95.0)
Unknown§	35 (1.4)

*A total of 2469 subjects had race and ethnicity information available to categorize subject by minority status.

†As 2 subjects were Hispanic and non-white (American Indian or Alaska Native; Native Hawaiian or Pacific Islander), the numbers for non-white and Hispanic do not add to the minority total.

‡Of the 18 missing information on race, 10 were Hispanic so categorized as minority.

§Of the 35 missing information on ethnicity, 6 were non-white so categorized as minority.

Compared with whites in CREST, non-whites were younger (mean age 67±8.9 versus 69±8.8 years; P=0.004), more often female (44% versus 34%; P=0.01), symptomatic (63% versus 52%; P=0.01), and diabetic (51% versus 29%; P<0.0001) but less often dyslipidemic (76% versus 85%; P=0.004), current or past smokers (19% versus 27%; P=0.04), or had a history of cardiovascular disease (34% versus 46%; P=0.007; Table 2). Hispanics were more often diabetic than non-Hispanics (48% versus 30%; P=0.0002; Table 3).

As shown in Table 4, the 10-year rate for the primary end point did not differ between whites (11.1%±0.96%) and for non-whites (8.3%±2.3%; P_{inter}>0.75; Figure 1) or between Hispanics (15.1%±5.7%) and for non-Hispanics (10.8%±9.3%; P_{inter}>0.24; Figure 2).

Discussion

Enrollment of minority patients in CREST (9.7%) was marginally less than the study goal of 12% and also less than the representation of minorities in the general population (16.4% non-white and 9.4% Hispanic). It is tempting to attribute the low recruitment of minorities in the study to the well-documented challenges of minority recruitment to clinical trials[23]; however, it is also possible that the underlying carotid disease may differ between racial/ethnic groups. For example in the Middlesex County Ischemic Stroke Study, 70%+ carotid stenosis was present in 30% of whites compared with 18% of

Table 2. Baseline Characteristics of Minorities (Aggregate) Versus Whites*

Variable	Non-White (n=152)	White (n=2332)	*P* Value
Baseline characteristics			
Age, y, mean (SD)	67.0±8.9	69.2±8.8	0.004
Female, %	44.1	34.4	0.01
Symptomatic, n (%)	62.5	51.9	0.01
Assigned to CAS, %	53.3	50.3	0.77
Assigned treatment received within 30 d of randomization	84.2	91.3	0.003
Left carotid artery treated, %	47.4	51.6	0.31
Risk factors			
Diabetes mellitus	51.3	29.0	<0.0001
Dyslipidemia	76.3	85.1	0.004
Hypertension	90.1	85.7	0.12
Smoking	19.2	26.8	0.04
History of cardiovascular disease or CABG	34.3	45.7	0.007

CABG indicates coronary artery bypass graft; and CAS, carotid artery stenting.
*n=18 with unknown race are excluded from this table.

blacks and 25% of Hispanics.[32] There could also be racial differences in the referral pattern where, even conditional on the presence of treatable carotid disease, whites are more likely to be referred for revascularization than their non-white counterparts (odds ratio=3.03; *P*=0.015).[33] In risk-adjusted analyses, Martin et al[34] found that black patients were less likely to receive diagnostic carotid imaging than whites but less likely

Table 3. Baseline Characteristics by Ethnicity

Variable	Hispanic or Latino (n=90)	Not Hispanic or Latino (n=2377)	*P* Value
Age, y, mean (SD)	68.0±9.5	69.0±8.8	0.29
Female, %	27.8	35.0	0.16
Symptomatic, n (%)	53.3	52.6	0.90
Severe stenosis (≥70%)	87.8	86.2	0.28
Assigned to CAS, %	47.8	50.5	0.79
Assigned treatment received within 30 d of randomization	90.0	91.0	0.74
Left carotid artery treated, %	55.6	51.0	0.40
Risk factors			
Diabetes mellitus	48.3	29.6	0.0002
Dyslipidemia	82.0	84.4	0.55
Hypertension	92.1	85.7	0.08
Smoking	20.5	26.5	0.21
History of cardiovascular disease or CABG	50.6	44.9	0.30

CABG indicates coronary artery bypass graft; and CAS, carotid artery stenting.
*n=35 with unknown ethnicity are excluded from this table

Table 4. Primary End Point at 10 Years by Race and Ethnicity in CREST

Primary End Point at 10 y	No. of Events (Rate±SE)	HR* (95% CI)	*P* Value	Race/Ethnicity by Treatment* $P_{interaction}$
Race†				
White	192 (11.1±0.96)	0.97 (0.54, 1.75)	0.92	0.75
Non-white	12 (8.3±2.3)	Reference		
Ethnicity‡				
Non-Hispanic	193 (10.8±0.93)	0.72 (0.37, 1.40)	0.33	0.24
Hispanic	9 (15.1±5.7)	Reference		

CI indicates confidence interval; CREST, Carotid Revascularization Endarterectomy Versus Stent Trial; and HR, hazard ratio.
*Adjusted for age, sex, symptomatic status, and treatment.
†n=18 with missing race are excluded from these analyses.
‡n=35 with missing ethnicity are excluded from these analyses.

to have moderate or severe stenosis. Finally, among those admitted to Veteran's Hospitals (where access to care should not be an issue) for stroke or transient ischemic attack, blacks were less likely than whites to have an imaging study of their carotid arteries (67% versus 79%; *P*=0.001), and among those imaged, there was a higher degree of carotid stenosis in whites (≈40% with 50%+ carotid stenosis) than blacks (≈20% with 50%+ carotid stenosis).[35] As such, it is possible that a portion of under-representation of minorities could be attributable to a lower prevalence of high-grade carotid stenosis in blacks and to a lower likelihood that they would have been referred to the CREST sites that tend to be tertiary treatment centers.

The challenges and barriers in enrollment of minority subjects in trials are well described.[24,25] A contributing factor toward lower minority enrollment in CREST could have been the smaller percentage of physicians, nurses, and coordinators at the clinical sites that were black, Asian, or Hispanic. In addition, as reported in the literature, the lower income levels of minorities create barriers such as loss of worktime and costs of travel which make it more difficult to attend clinic visits.[4,24,36–38]

We failed to detect a difference in treatment efficacy by either race or ethnicity. We have shown that periprocedural

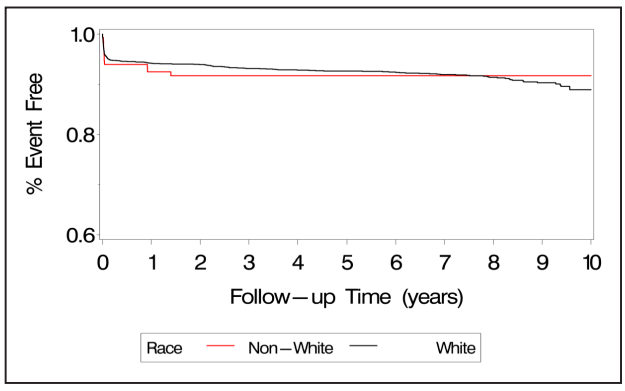

Figure 1. Primary end point through 10 years by race. *X* axis: follow-up time (y). *Y* axis: % event free. Race (non-white):race (white).

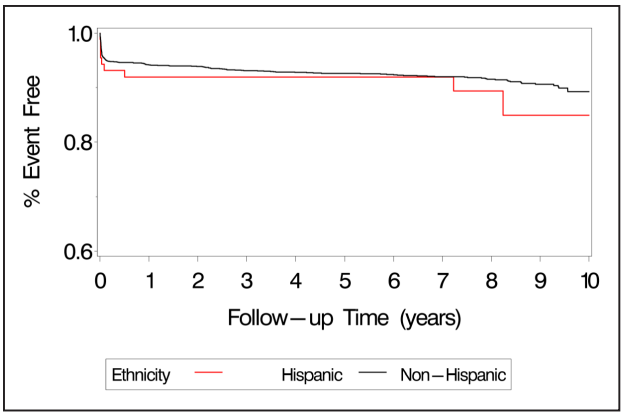

Figure 2. Primary end point through 10 years by ethnicity. *X* axis: follow-up time (y). *Y* axis: % event free. Ethnicity (Hispanic): ethnicity (non-Hispanic).

risk increases with age[39] and is higher for symptomatic compared with asymptomatic patients.[27] As such, one potential explanation for not detecting a racial/ethnic difference is that, in truth, a difference did not exist, potentially because the younger age (lower risk) of minorities was offset by the higher proportion of minorities that were symptomatic (higher risk). However, perhaps a more likely contributor is the lack of statistical power to detect a racial/ethnic difference in outcomes in a single study. CREST (like most other trials) is designed to provide statistical power to detect an overall treatment effect. As described above, the natural interest in identifying subgroups (including racial/ethnic subgroups) with a differential treatment effect is the underlying reason why the primary report of a trial almost always includes a forest plot to show effects in subgroups. Key to the identification of subgroups at differential risk is the test for effect modification (ie, interaction) between the subgroup and treatment. In general, the sample size to detect these interactions is at least 4× larger than the same size to detect a similar main effect.[40,41] As such, when a study is designed to detect the main effect, the sample size is at most only one fourth the size to reliably detect interactions. Furthermore, the power to detect these interactions is also a function of the prevalence of the risk factor in the study, with the maximum power for risk factors that are 50% prevalent. As such, we restricted the a priori secondary aims of CREST attempting to detect differential treatment effects to variables that divide the study population into approximately equal subgroups, specifically age (which we can dichotomize at the median), sex, and symptomatic status. It is specifically because we anticipated that minority status would create subgroups of ≈90% white and 10% minority (a split that would be associated with low power) that we chose not to include race as one of the a priori factors where we were assessing the potential for effect modification. This implies not only that this assessment is post hoc but also we acknowledge that the inability to detect a difference by race was expected.

However, the challenge to detect treatment differences by race and ethnicity is not only an issue for CREST but also for practically all other clinical trials, raising the question of whether the implied goals of the 1993 Revitalization Act (to assess if "variables being studied in the trial affect … members of minority groups … differently than other subjects in the trial") are being addressed. Fortunately, although individual studies are relatively unlikely to adequately address this question, the potential for pooling data from multiple studies does allow the opportunity to more powerfully address the potential for a differential treatment effect in subgroups. The ability to address the potential of an effect modification in subgroups is one of the major reasons why the CREST investigators have contributed data and have joined the Carotid Stenosis Trialists Collaboration, an effort pooling the data from CREST and other European revascularization trials.[42–46] The Carotid Stenosis Trialists Collaboration has already published the subgroup analysis assessing differential treatment effects between subgroups defined by age,[47] obesity,[48] and by the time between symptoms and revascularization,[49] with analysis by treatment differences by sex underway. However, there are numerous challenges to assessing racial/ethnic differences in such an international collaboration, including (1) that the vast majority of black participants in the pooled data are in CREST, so there is little gain in power through pooling, (2) that Hispanic participants in the United States may differ from European populations with a Spanish heritage, and (3) that any factor where the majority of a subgroup is from a single study would confound the subgroup membership with the study, making estimated differences difficult to interpret. Pooling data of domestic studies with similar patient populations might allow for a differential analysis in subgroups.

We agree with Yancey et al[25] that prevention and treatment trials, which may have greater difficulty recruiting, should be specifically designed to target ≥1 minority groups to be able to analyze outcomes for these populations. In addition to designing trials with power to assess a targeted population, future studies might add, as a goal, the inclusion of a larger percentage of minority lead-investigators and staff located in population centers with greater diversity.[25]

Conclusions

The proportion of minority participation in CREST was suboptimal at 9.7%. Primary outcomes did not differ by minority or ethnic status. However, as for practically all trials, the ability to detect racial/ethnic differences in a single study is woefully underpowered, implying that great caution should be taken in the interpretation of the lack of a detected racial/ethnic difference. Future trials can be designed for specifically targeted populations and to pool data to detect these differences.

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Disclosures

None.

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Challenge and Yield of Enrolling Racially and Ethnically Diverse Patient Populations in Low Event Rate Clinical Trials

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