DOES RACE PREDICT SHORT-TERM MORTALITY AFTER CAROTID SURGERY? THE RESULTS OF A META-ANALYSIS

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Although African Americans are more likely to have an ischemic stroke and suffer a greater burden of stroke-related mortality and disability, they are less likely to have carotid surgery treatment than whites, even after accounting for clinical characteristics and ability to pay. Not surprisingly, little is known about their short- and long-term outcomes, including death, after undergoing carotid endarterectomy (CEA). The purpose of this study was to systematically review the published literature to clarify what role race has with respect to perioperative mortality risk following CEA.

A search of MEDLINE (1966-May 2000), Scientific Citations (1945-May 2000), and the Cochrane Collaboration Stroke Group databases was performed to identify studies that related to African American-white differences for CEA mortality. Three studies met the specified eligibility criteria that allowed for the inclusion of 224,554 subjects (5,569 African Americans and 218,985 whites). Each showed some indication of increasing perioperative mortality risk for African Americans, but the findings were only significant for the studies of Hsia and colleagues (odds ratio (OR), 1.365; 95% confidence interval (CI), 1.164–1.600) and Huber and coworkers[28] (OR, 2.247; 95% CI, 1.367–3.695) but not for the study of Estes and colleagues (OR, 1.429; 95% CI, 0.827–2.469). After pooling the data, using a fixed-effects model, the OR was 1.429 (95% CI, 1.235–1.654). There was no evidence of significant heterogeneity between the studies and the random-effects model gave comparable results.

African Americans, as compared to whites, appear to have a greater likelihood of short-term death following carotid surgery by more than 40%. This excess risk is possibly related to coexisting illness, which needs to be carefully weighed when considering a patient for CEA. Prospective studies are needed to further clarify these observed differences. (*J Natl Med Assoc.* 2002;94:25–30.)

Key words: carotid endarterectomy ♦ carotid stenosis ♦ hospital mortality

As a surgical procedure aimed at reducing the degree of narrowing or stenosis of the carotid artery due to atherosclerosis and thereby decreasing the risk for subsequent stroke, carotid endarterectomy (CEA) is an important part of secondary prevention for selected patients.[1] Since its development in the 1950s,[2,3] it has become one of the most common, and certainly one of the most studied, surgical procedures performed to date.[4] Several randomized clinical trials (RCTs) have demonstrated its efficacy over standard medical management for patients with severe stenosis who are symptomatic[5,6] and also for patients who are asymptomatic.[7,8] Despite these

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proven benefits, there are known risks associated with CEA that include cardiovascular and cerebrovascular complications as well as death.[9] Interestingly, the literature available in this area is somewhat limited, which may reflect the rather low incidence rate of serious adverse events that have been observed, especially for perioperative death (ranging between 0.5 to 3.2% for different studies),[10] making it difficult to identify important risk factors. Most of these reports, in any case, have been based upon a relatively narrow patient population. Indeed, the overwhelming majority of subjects participating in trials tend to be male, younger than 70 years of age, and white.[5,6,7,8]

Regarding race, research has shown that African Americans, after accounting for clinical characteristics and ability to pay, are less likely to receive CEA[11,12], even though they are more likely to have an ischemic stroke[13] and suffer a greater burden of stroke-related mortality and disability.[14,15] On the other hand, transient ischemic attacks and carotid stenosis, which are indications for CEA, are reportedly less prevalent among African Americans.[16,17] It should be kept in mind, however, that additional evidence indicates that whites are more likely to be examined by a neurologist and receive diagnostic procedures that would determine their degree of stenosis and later appropriateness for CEA.[11,12] Given these circumstances, it is not surprising that relatively little is known specifically about the impact of race upon the short- and long-term outcomes following CEA. In this context, the recently conducted RCTs notably did not shed much light on this issue. Overall, less than 5% of these subjects were nonwhite, and sufficient data for outcome events among African Americans were lacking. In the absence of pertinent subgroup analysis, it is not clear how generalizeable the results are from these studies.[18]

Accordingly, the author sought to clarify what role race has with respect to perioperative mortality risk following CEA by systematically reviewing the published literature. Specifically, a meta-analysis was performed to assess whether or not African Americans have, compared to whites, a greater likelihood of death within 30 days after undergoing carotid surgery.

METHODS

For the present systematic review, an electronic search of MEDLINE (OVID) from 1 January 1966 to 1 May 2000 was performed using the following terms: 1) "carotid$" and 2) "endarterectom$" and 3) "death$" or "mortal$" and 4) "black$" or "african$" or "race$" or "racial$" or "ethnic$." A similar strategy was followed using the Scientific Citations (The Web of Science, Institute for Scientific Information) from 1945 to 1 May 2000. Additionally, the Cochrane Collaboration Stroke Group Database[19] was searched. Moreover, the reference lists of relevant retrieved articles were also examined.

To be included in this review, articles had to fulfill the following criteria: 1) they had to be a prospective or retrospective study; 2) they had to report the total numbers of African American and white subjects participating in the study separately; 3) they had to report the total number of deaths or relevant odds/risk ratio (with confidence interval (CI)) for African Americans and whites occurring within 30 days of having CEA performed; and 4) for African Americans and whites, at least 10 deaths for each group had to be reported. The latter requirement was chosen to avoid the problem of weighting small studies inappropriately as discussed previously by Petitti.[20]

In estimating risk, the odds ratio (OR) was calculated for a fixed-effects model using the method of CIs as described by Prentice and Thomas[21] and Greenland.[22] Between-study heterogeneity was evaluated by using the Breslow-Day test of homogeneity.[23] For sensitivity analysis, a random-effects model was also applied according to the method of DerSimonian and Laird.[24] In assessing the potential for publication bias, a funnel plot[25] was constructed with the included studies of this current review.

RESULTS

A total of three investigations fulfilled the eligibility requirements.[26,27,28] The studies of Hsia and colleagues[26] and Estes and coworkers,[27] both used information from the Medicare claims database. In the latter study, a 20% random sample of those who underwent CEA was drawn for the years 1988 to 1990. These subjects were then prospectively followed through 1992. With the former study, the authors considered all subjects listed in the database for the years 1985 to 1989. However, due to the overlapping study years (i.e., 1988 to 1989), a potential for dependency between the two study populations existed. To minimize this possibility, for the study of Hsia, data were used only for the period

Table 1. Summary of Meta-Analysis Comparing Perioperative Mortality Risk for Blacks Versus Whites with Odds Ratios and 95% Confidence Intervals

Study (Publication Year)	Total Blacks	Total Whites	Odds Ratio	95% Confidence Interval
1. Hsia et al.[26] (1992)	4,201	158,857	1.365	1.164–1.600
2. Estes et al.[27] (1998)	538	21,627	1.429	0.827–2.469
3. Huber et al.[28] (1998)	830	38,501	2.247	1.367–3.695
Overall fixed-effects model (studies 1,2,3)			1.429	1.235–1.654
Overall random-effects model (studies 1,2,3)			1.540	1.158–2.049
P-value for heterogeneity test: 0.1733				
Overall fixed-effects model (studies 1,2)			1.367	1.176–1.595
Overall random-effects model (studies 1,2)			1.367	1.176–1.595
P-value for heterogeneity test: 0.9875				
Overall fixed-effects model (studies 1,3)			1.429	1,229–1.663
Overall random-effects model (studies 1,3)			1.653	1.027–2.658
P-value for heterogeneity test: 0.1733				
Overall fixed-effects model (studies 2,3)			1.830	1.267–2.645
Overall random-effects model (studies 2,3)			1.819	1.168–2.832
P-value for heterogeneity test: 0.4866				

1985 to 1987. Hence, the three investigations included in the present analysis were based upon a total of 224,554 subjects (5,569 African Americans and 218,985 whites; Table 1).

Among other details of the selected studies, all used the International Classification of Diseases Ninth Revision code of 38.12 to identify those undergoing the procedure of CEA. Formally, none of these studies directly addressed indications for surgery (e.g., symptomatic vs. asymptomatic carotid stenosis). However, in the investigation by Estes and colleagues[27], the subjects were required to have a simultaneous diagnosis of precerebral stenosis or occlusion (code 433). Furthermore, this was the only study to present adjusted odds ratios for outcome events. In considering exclusion criteria, Estes removed from their analysis those less than 66 years of age, those having a CEA in both 1987 and 1988, those not residing in one of the 50 states or the District of Columbia, those reporting a race other than African American or white, and those having missing information for the date of death, number of training residents at the hospital, or the number of beds in the hospital. For this population, about 12% were 80+ years old and 43% were female. In the investigation by Hsia, exclusions were not explicitly stated. Generally, those less than 65 years of age constituted about 6% of this population, those 80+ years of age represented about 13%, and females were about 44%.

Regarding the work of Huber et al.,[28] this study was retrospective in design and drew its population from nonfederal Florida hospital discharge records using the Agency for Health Care Administration database for the federal fiscal years 1992 to 1996. In defining outcome events, perioperative mortality was considered only for those events that occurred during admission as documented in the discharge status record. However, it was stated that the 30-day mortality rate would not likely differ from the in-hospital rate since the majority of complications and deaths following CEA occur during the same hospital stay.[29] As far as exclusions, those considered another race besides white or African American did not form part of the analysis that was reported. For this population, roughly 18% were less than 65 years old, 4% were 84+ years old, and 42% were female.

Overall, each study showed some indication of increasing perioperative mortality risk following CEA for African Americans, although the findings were significant only for the studies of Hsia and colleagues[26] (OR, 1.365; 95% CI, 1.164–1.600) and Huber and colleagues[28] (OR, 2.247; 95% CI, 1.367–3.695) and not for the study of Estes and colleagues[27] (OR, 1.429; 95% CI, 0.827–2.469). When the fixed-effects model was applied, the summary OR was 1.429 (95% CI, 1.235–1.654), indicating a significantly higher risk of death for African Americans as compared to whites. Furthermore, there

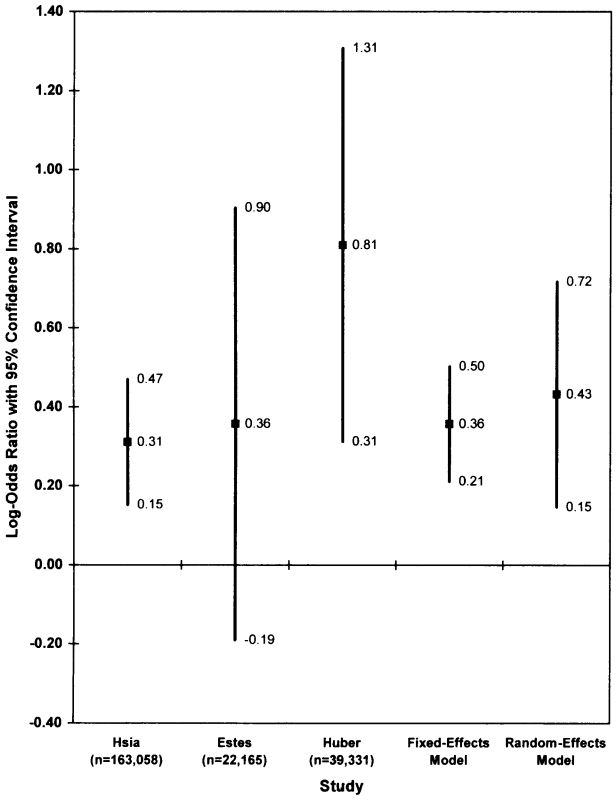

Figure 1. African Americans vs. whites perioperative mortality risk following carotid endarterectomy

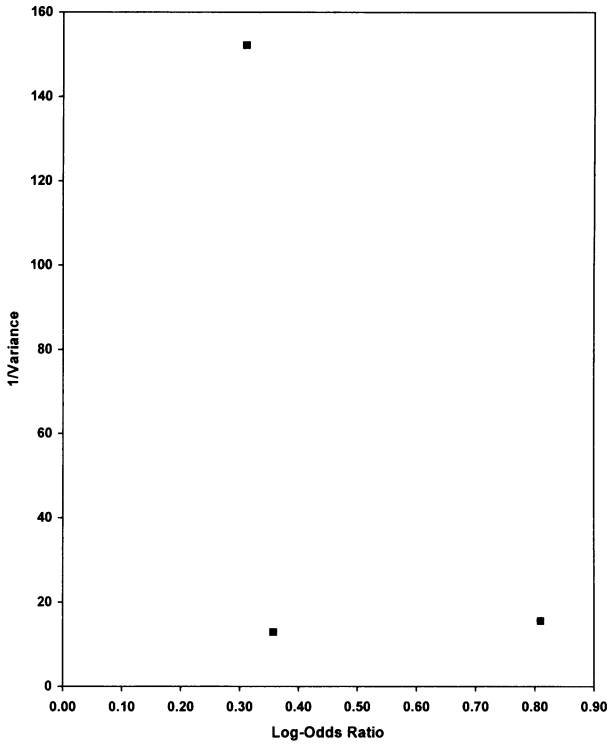

Figure 2. Funnel plot of studies comparing perioperative morality risk between African Americans vs. whites following carotid endarterectomy

was no evidence of significant heterogeneity between the three studies ($p = 0.1733$). This was supported by the results of the random-effects model that demonstrated a summary OR of 1.540 (95% CI, 1.158–2.049), which is comparable to the results from the fixed-effects model. These findings are summarized in Table 1 and Fig. 1. Similarly, sensitivity analyses carried out for the two-way combinations of studies were also consistent with the above conclusion (Table 1).

Considering the possibility of publication bias, visual inspection of the funnel pot (Fig. 2) seems to hint at some asymmetry in the lower-left corner of the graph, which would be consistent with a publication bias favoring positive findings. However, the graph is only based upon three points and, therefore, it is difficult to characterize any pattern with confidence.[30] Furthermore, in discussing a direct statistical analog to the funnel plot, Begg and Mazumdar[31] observed that in many configurations with lower power, the chance of bias in the estimate of summary effect size is also low.

DISCUSSION

To the author's knowledge, this is the first systematic review of the impact of race upon the perioperative mortality risk following carotid surgery. The principal findings of this analysis were that all three studies[26,27,28] examined suggested that African Americans had a greater likelihood of death compared to whites, although the results were significant for only two investigations,[26,28] which represented about 90% of the included study subjects. However, when the data were pooled, the odds for death after CEA were significantly increased for African Americans by over 40%. Furthermore, there was no evidence of any appreciable differences between the studies.

In the one study of Estes et al.[27] that individually could not demonstrate a significant effect for race, it should be noted that the reported OR was derived from a logistic regression model that adjusted for a number of variables including age, sex, and comorbidity. On the one hand, this provides some control for potential confounding factors that was not addressed in the studies by Hsia et al.[26] and Huber et

al.[28] On the other hand, if the number of endpoints for a particular subgroup is rather limited, spreading this subgroup further by fitting an increasing number of parameters may lead to greater variability and wider CIs.[32] In this study, unadjusted results were not provided nor were individual counts of death by race given. Therefore, it was not possible to assess directly what impact the inclusion of other covariates had upon the effect of race.

In trying to explain why African Americans have a greater likelihood of death immediately following CEA, there is at least one plausible reason: underlying risk. As implied by the data of Estes and colleagues[27] and Huber and colleagues[28], coexisting illness may be more prevalent in this subgroup of patients, which could alter their risk profile. For example, it is well recognized that diabetes, certain stroke subtypes, and hypertension are more prevalent among African Americans as compared to whites.[33,34] Interestingly, Estes reported a protective effect for hypertension but explained this as relating to undercoding since persons with multiple chronic illnesses are likely to have more serious conditions coded in their chart.[35] Furthermore, Rigdon[36] reported that among African American females, acute perioperative hypertension, but not chronic coexisting hypertension, was correlated with CEA complications.

Other patient characteristics that may be relevant to these racial differences include: indications for surgery, such as symptomatic vs. asymptomatic carotid stenosis; underlying severity of illness that prompted treatment, for example, the degree and location of stenosis[37,38]; aversion to surgery, which could relate to a delay in seeking treatment[39]; and pathophysiological differences, as suggested by some newly implicated genes associated with carotid stenosis.[40] Additional factors may involve the perioperative management of patients, skills and techniques of the surgeon, and the institutional setting.[36,41,42] By and large, there is a paucity of data available so it is not possible to draw any firm conclusions. Consequently, there is a tremendous need for prospective research to examine these areas further. In the interim, clinicians, particularly surgeons, need to carefully weigh the limited benefits of CEA against the known risk factor profile of patients, especially for those who are African American.

When considering the limitations of this analysis, one major weakness relates to the study designs of the investigations examined. Indeed, one school of thought posits that it is highly problematic to perform meta-analysis on observational studies precisely because of the potential for bias and confounding, especially with retrospective studies.[43,44] However, as Thorton and Lee[45] point out, many epidemiologic studies are observational and, therefore, excluding them may not only seriously bias the results of a meta-analysis but may even preclude a meta-analysis from being done at all. In the case of short-term mortality risk for African Americans, the fairly recent RCTs[5,6,7,8] for CEA were not designed to assess whether or not there were important differences in outcomes between the overall study population and specific subgroups. Consequently, in searching for the "best evidence" regarding the issue of race, one must consider nonexperimental studies, including those relying on administrative databases, despite the inherent weaknesses of their design. As far as other relevant limitations, the possibility of publication bias can not be excluded as mentioned before. Hence, the results reported here are unlikely to be definitive.

In conclusion, the results of this meta-analysis suggest that African Americans, as compared to whites, have a greater likelihood of short-term death following carotid surgery by more than 40%. This excess risk is possibly related to coexisting illness, which needs to be carefully weighed when considering a patient for CEA. Prospective studies that include significant numbers of African Americans are needed to further clarify what underlying risk factors are most important in determining short- as well as long-term outcomes.

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