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# Complement polymorphisms and cognitive dysfunction after carotid endarterectomy

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## Abstract

**Object—**The role of genetic polymorphisms in the neurological outcome of patients after carotid endarterectomy (CEA) remains unclear. There are single nucleotide polymorphisms (SNPs) that predispose patients to postoperative cognitive dysfunction (CD). We aim to assess the predictability of three complement cascade-related SNPs for CD in patients having CEAs.

**Methods—**In 252 patients undergoing CEA, genotyping was performed for the following polymorphisms: *complement component 5 (C5)* rs17611, *mannose-binding lectin 2 (MBL2)* rs7096206, and *complement factor H (CFH)* rs1061170. Differences among genotypes were analyzed via the chi-square test. Patients were evaluated with a neuropsychometric battery for CD 1 day and 1 month after CEA. A multiple logistic regression model was created. All variables with univariate $p < 0.20$ were included in the final model.

**Results—**The *C5* genotypes A/G (OR 0.26, 95% CI 0.11–0.60, $p = 0.002$) and G/G (OR 0.22, 95% CI 0.09–0.52, $p < 0.001$) were significantly associated with lower odds of exhibiting CD at 1 day after CEA compared with A/A. The *CFH* genotypes C/T (OR 3.37, 95% CI 1.69–6.92, $p < 0.001$) and C/C (OR 3.67, 95% CI 1.30–10.06, $p = 0.012$) were significantly associated with higher odds of exhibiting CD at 1 day after CEA compared with T/T. Statin use was also significantly associated with lower odds of exhibiting CD at 1 day after CEA (OR 0.43, 95% CI 0.22–0.84, $p = 0.01$). No SNPs were significantly associated with CD at 1 month after CEA.

**Conclusions—**The presence of a deleterious allele in the *C5* and *CFH* SNPs may predispose patients to exhibit CD after CEA. This finding supports previous data demonstrating that the complement cascade system may play an important role in the development of CD. These findings warrant further investigation.



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**Disclosure**

None of the authors have conflicts of interest to disclose.

Author contributions to the study and manuscript preparation include the following. Conception and design: Heyer, Connolly. Acquisition of data: Heyer, Malone, Mergeche. Analysis and interpretation of data: Heyer, Kellner, Malone, Bruce, Mergeche, Connolly. Drafting the article: Heyer, Kellner, Mergeche. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Heyer. Statistical analysis: Heyer, Bruce. Administrative/technical/material support: Mergeche, Ward. Study supervision: Heyer, Connolly.

### Keywords

carotid endarterectomy; complement; vascular disorders; single nucleotide polymorphism; neuropsychometric; cognitive dysfunction

Although carotid endarterectomy is considered a safe procedure, with a stroke rate of 1%–2%, accumulating evidence indicates that subtle postoperative cognitive dysfunction (CD) occurs in 9%–28% of cases.[16,25] The etiology of CD is likely multifactorial, resulting from focal ischemia during clamp time, post-recanalization hyperperfusion, microemboli, and individual genetic factors.[13] These potential mechanisms have been investigated in more detail through radiographic correlation, serum marker quantification, atherosclerotic plaque analysis, and genetic studies.

Single-nucleotide polymorphism analyses and genome-wide association studies have identified multiple candidate genes for involvement in the pathophysiology of ischemic stroke. SNPs associated with elevated inflammation increase the incidence of CD following both carotid artery and cardiac surgery. Less-active forms of complement component 3, a protein that decreases the activity of the complement system, correlate with increased CD 1 day after surgery. In addition, less-active forms of complement factor H (CFH), an inhibitor of the common complement pathway, are also associated with increased CD 1 day following CEA.[11]

Polymorphisms in the complement components C5 and MBL2 have recently been implicated in the risk of ischemic stroke and cardiovascular disease.[29] In a larger cohort study, we aim to confirm these prior genetic findings and further delineate the role of the complement cascade by analyzing the *C5, CFH*, and *MBL2* SNPs of the complement cascade and evaluating their utility in the prediction of CD after CEA.

## Methods

### Patients

We performed a nested cohort study of 252 patients prospectively recruited in this IRB-approved study. Written informed consent was obtained from all patients. This subgroup consists of individuals who consented to genetic testing while enrolled in a larger study investigating the relationship between stroke risk factors and CD. All patients were genotyped for the *C5, CFH*, and *MBL2* polymorphisms. A second group of 155 age- and education-matched patients undergoing lumbar laminectomy or microdiscectomy were contemporaneously recruited to serve as a postoperative reference group for neuropsychometric testing. All patients were native English speakers with no history of drug abuse, Axis I psychiatric disorders, or previous ipsilateral CEA.

### Surgery and Anesthesia

Eligible patients were scheduled for elective CEA for high-grade carotid artery stenosis. All patients received general anesthesia with standard hemodynamic and temperature monitoring, as previously described.[16] No patient received blood transfusion. The surgical technique, anesthetic management, and indications for CEA have remained constant at our institution, as previously described.[16,25]

### Genotyping

DNA was extracted from buffy coats of whole blood samples and amplified by PCR. PCR was performed with an Eppendorf Mastercycler Gradient thermal cycler. Primers were

identified for *C5* rs17611, *CFH* rs1061170, and *MBL2* promoter rs7096206. PCR products were treated with QIAquick PCR purification kits (Qiagen). Sequencing was performed using the respective primers in conjunction with BigDye Termination v3.1 cycle sequencing kits (Applied Biosystems). Analysis was performed using an Applied Biosystems 3730xl capillary instrument. Finally, SNPs of interest were determined using Chromas 2.01 software (Digital River).

### Neuropsychometric Testing

A reference group was used to account for trauma of surgery, effects of general anesthesia, and practice effect associated with repeated neuropsychometric testing, as previously described.[16,25] Patients were examined with a previously described battery of neuropsychometric tests preoperatively and postoperatively at 1 day and 1 month after CEA. The neuropsychometric battery evaluates a variety of cognitive domains—verbal memory, visuospatial organization, motor function, and executive action.

A variety of factors affect the risk of CD in patients after CEA, but only age greater than 75,[25] statin use,[15] and diabetes mellitus[25] have been previously shown to significantly and independently affect the risk of CD. Other factors that might also affect the risk, but have not been shown to independently affect the risk, of CD were evaluated as well. These included years of education, body mass index, history of smoking, hypertension, extensive peripheral vascular disease, symptomatic history of stroke or transient ischemic attack, and duration of cross-clamping of the carotid artery.

### Statistical Analysis

Allele and genotype frequencies were compared with values predicted by Hardy-Weinberg equilibrium using a chi-square test. Each patient's neuropsychometric performance was calculated, as described previously.[9,16,26] The tests were grouped by cognitive domain and patients were considered to have CD based on 2 criteria to account for both focal and global/hemispheric deficits: 1) scoring at least 2 SD worse than the reference group in 2 or more cognitive domains or 2) scoring at least 1.5 SD worse than the reference group in all 4 cognitive domains.

Statistical analysis was performed using R environment for statistical computing (R Development Core Team, 2008). For univariate analyses, the Student t-test, the Wilcoxon rank-sum test, the Fisher exact test, the Pearson chi-square test, and simple logistic regression were used where appropriate. The alpha level was adjusted for multiple hypotheses using the Benjamini and Hochberg method to control for the false discovery rate.[1] Multiple logistic regression models were constructed to identify independent predictors of CD at 1 day and 1 month after CEA. All factors with $p < 0.20$ in a simple univariate logistic regression were entered into the final models for 1 day and 1 month after CEA. To control for population stratification and confounding, any variables significantly associated with differences in any of the SNP genotypes were included in the model as well. Model fit and calibration were confirmed with the likelihood ratio test, Hosmer-Lemeshow goodness-of-fit test, and receiver operating characteristic analysis. In the event of missing values for predictor variables, the sample mean was imputed. Significance was set at $p \leq 0.05$.

## Results

### Patients

Baseline patient characteristics and hospital course variables did not differ between genotypes for the *C5* and *CFH* alleles (Tables 1 and 2). In the *MBL2* allele, however, the G/

G genotype group differed from the other 2 genotype groups in age (mean age in the G/G group 68.9 ± 5.3 years with 5.0% of patients older than 75 years of age vs 70.4 ± 9.2 years with 29.8% older than 75) and statin use (50.0% in the G/G group vs 75.2% in the combined C/C and G/C group) (Table 3).

### Incidence of CD by Genotype

Each SNP had one genotype with an incidence of CD 1 day postoperatively that differed significantly from the other 2 genotypes (Fig. 1). Patients with the G/G *MBL2* genotype had a 45.0% incidence of CD, as opposed to 17.2% in the patients with the C/G genotype ($p = 0.015$, $\alpha=0.017$) and 19.1% in those with the C/C genotype ($p = 0.018$, $\alpha = 0.033$). Similarly, 40.4% of the patients with the *C5* genotype A/A had CD 1 day after CEA as compared with 18.5% of those with the A/G genotype ($p = 0.004$, $\alpha = 0.033$) and 14.4% of those with the G/G genotype ($p < 0.001$, $\alpha = 0.017$). The incidence of CD among patients with the T/T *CFH* genotype was 13.5%, which was significantly lower than that of patients with the C/T (27.6%, $p = 0.006$, $\alpha = 0.017$) or C/C (33.3%, $p = 0.020$, $\alpha = 0.033$) genotypes. There were no significant differences in the incidence of CD at 1 month after CEA among the genotypes for *CFH, C5*, or *MBL2*.

### Multiple Logistic Regression Models

Variables associated with CD at $p < 0.20$ in univariate regression included years of education, statin use, and the *CFH, C5*, and *MBL2* SNPs. Age greater than 75 years and statin use were both significantly associated with the *MBL2* SNP genotype.

The final logistic regression model for 1 day after CEA included years of education, statin use, age greater than 75 years, and the *CFH, C5*, and *MBL2* SNPs (Table 4). The A/G and G/G genotypes for *C5* were both associated with significantly decreased odds of CD compared with the A/A genotype (OR 0.26, 95% CI 0.11–0.60, $p = 0.002$ and OR 0.22, 95% CI 0.09–0.52, $p < 0.001$, respectively). The C/T and C/C CFH genotypes were associated with significantly increased odds of CD compared with the T/T genotype (OR 3.37, 95% CI 1.69–6.92, $p < 0.001$ and OR 3.56, 95% CI 1.30–10.06, $p = 0.012$, respectively). Statin use was also associated with decreased odds of CD (OR 0.43, 95% CI 0.22–0.84, $p = 0.014$). The final logistic regression model for 1 month after CEA included years of age greater than 75 years, years of education, statin use, hypertension, and the *C5* SNP. None of the included variables were significantly associated with CD at 1 month after CEA.

## Discussion

Postoperative CD is a well-documented neurological phenomenon that occurs after a variety of vascular and nonvascular procedures, including cardiac bypass surgery,[18,34] CEA,[14,23] carotid stenting,[9,35] carotid angioplasty, [32] diagnostic coronary angiography,[19] and noncardiac surgery.[26] The pathophysiology, incidence, and time course of CD vary depending on the specific surgery in question. Cognitive dysfunction associated with noncardiac surgery occurs in 25% of patients at 1 week postoperatively and 10% at 3 months and is associated with increasing age, duration of anesthesia, low education level, a second operation, postoperative infections, and respiratory complications.[26] The incidence of CD following CEA has been reported to be 25% at 1 day after the procedure and 9% at 1 month, while more long-term reports of results at 1–5 years after treatment range from no change to improvement.[5] Risk factors for CD following CEA include age greater than 75 years and diabetes,[25,35] whereas statin use is associated with less CD.[15]

Cognitive dysfunction after CEA is thought to be, in part, due to a systemic surgery-induced inflammatory response that damages multiple organ systems, including the brain, through

neuroinflammation mediated by cytokines including interleukin-1 and tumor necrosis factor-α.[33] Cognitive dysfunction following CEA is also considered secondary to general anesthesia, transient hypotension, microemboli, and hyperperfusion following revascularization.

Multiple markers related to cardiovascular disease and inflammation have been associated with CD following CEA. Markers examined by our group that have been shown to correlate with CD include S100β,[3] monocyte chemoattractant protein 1 (MCP-1),[20] induced nitric oxide synthase (iNOS),[36] APOE-E4,[17] and matrix metalloproteinase 9 (MMP9).[10] We have also identified specific SNPs that have correlated with CD. The presence of at least one *APOE*-E4 allele has been associated with increased risk of CD at 1 month after CEA. A SNP in the promoter region of the *iNOS* gene leading to increased function also correlated with less CD at 1 month. This mechanism may be related to cerebral preconditioning, permitting neurons and/or glia to withstand a temporary period of nonlethal ischemia.

Polymorphisms associated with the complement system were first implicated in CD by Gigante et al.,[11] when they found that an activating SNP on *C3a* and a deactivating SNP on the complement inhibitor gene *CFH* were independently associated with CD 1 day following CEA. Other studies have been performed examining the role of complement genetics in acute cerebrovascular disease. In 135 stroke patients, an *MBL2*-activating SNP correlated positively with increased MBL2 levels and worse outcome at 3 months following ischemic stroke.[2] In addition, Mocco et al.[24] found that C3a and C5a are acutely elevated in the peripheral blood of acute stroke patients. Levels of C3 and C3a are elevated in cryptogenic and large-vessel–disease stroke,[30] and a recent SNP study examining 16 SNPs at the *C3* locus in 844 patients with ischemic stroke compared with 668 healthy community-based controls found a positive association with the SNPs rs2277984 and rs3745565 (OR 1.20, 95% CI 1.02–1.41, p = 0.02 and OR 0.73, 95% CI 0.59–0.92, p = 0.006, respectively). [27]

In this study, we found that SNPs associated with multiple complement cascade components are associated with CD at 1 day, but not 1 month, after CEA. The less-active G allele of the *C5* SNP rs17611 was found to decrease the likelihood of CD if at least one G allele was present. The homozygous A/A allele has been associated with elevated C5a serum concentration levels. Consistent with the findings in our study, increased C5a levels and the 2416AA *C5a* genotype have recently been associated with increased risk of cardiovascular disease[29] and ischemic stroke.[12] The C5a molecule is inflammatory and directly simulates adhesion molecule production and the generation of chemokines by endothelial cells, thereby promotion proinflammatory mechanisms on many cellular levels.[4]

CFH is a negative regulator of the alternative pathway of complement. The *CFH* Y402H polymorphism has been well studied in macular degeneration, with the C allele conferring increased risk.[7] This allele has been correlated with increased complement activation and increased mortality after intracerebral hemorrhage, and it has been previously correlated with CD in a smaller population of patients treated with CEA.[11] Here we have confirmed our earlier findings in this larger patient population. Recent basic science work has shown that the protective *CFH* allele protein product directly binds oxidized phospholipids, thereby decreasing systemic oxidative stress.[28] More work is necessary to explore this proposed mechanism in CD.

In experimental stroke, the complement system is partially activated through the lectin pathway. MBL is a C-type collectin homologous to C1q that can activate the complement cascade through the lectin pathway. The SNP studied here is a polymorphism, with replacement of G by C in the promoter region of the *MBL2* gene on chromosome 10 that leads to an X to Y amino acid change resulting in a low expression of MBL2 and reduced

serum concentration in the range of a 25%–50% decrease per deleterious allele.[21] Deficient MBL leads to a deficiency of immune defense and increased risk of various infections. [8,22] Although the univariate analysis suggested that the *MBL2* GG genotype might correlate with CD, this result was not maintained in the multivariate analysis. We found the *MBL2* C allele correlated with both age greater than 75 and statin use in the univariate analysis. We have previously found statin use to protect against CD following CEA for asymptomatic carotid artery stenosis,[15] and this class of medications is currently under investigation as neuroprotective agents in a number of cerebrovascular conditions.[6,31] Lower age in this group may have also been confounded by statin use, which may have delayed either the development of atherosclerosis or presentation with neurological symptoms.

This study was limited by a number of factors. First, all patients were enrolled at a single institution, and bias may have been introduced by patient selection or institutional standards regarding surgical or anesthetic technique. Second, given the small size of our cohort, additional studies are needed to validate, further characterize, and define the medical relevance of these SNPs. Third, the genetic contribution to CD was significant 1 day after CEA, but was not present 1 month after CEA, limiting the applicability of these results. However, it is reasonable to consider that patients with the high-risk genotypes may demonstrate an exaggerated inflammatory response to the surgical stimulus of CEA and maintain elevated proinflammatory cytokine levels as well as increased complement activation 1 day after surgery. This proinflammatory state likely resolves by the 1-month followup, and therefore, the association is no longer evident.

## Conclusions

The activating *C5* allele and a deactivating *CFH* allele both correlate positively with CD following CEA, whereas an activating *MBL2* allele does not. This study further delineates the complement cascade as a detrimental participant in postoperative CD following carotid artery revascularization.

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## Abbreviations used in this paper

| | |
|---|---|
| **CD** | cognitive dysfunction |
| **CEA** | carotid endarterectomy |
| **CFH** | complement factor H |
| **C5** | complement component 5 |
| **iNOS** | induced nitric oxide synthase |
| **MBL2** | mannose-binding lectin 2 |
| **MCP** | monocyte chemoattractant protein |
| **MMP** | matrix metalloproteinase |

| | |
|---|---|
| **OR** | odds ratio |
| **PCR** | polymerase chain reaction |
| **SNP** | single-nucleotide polymorphism |

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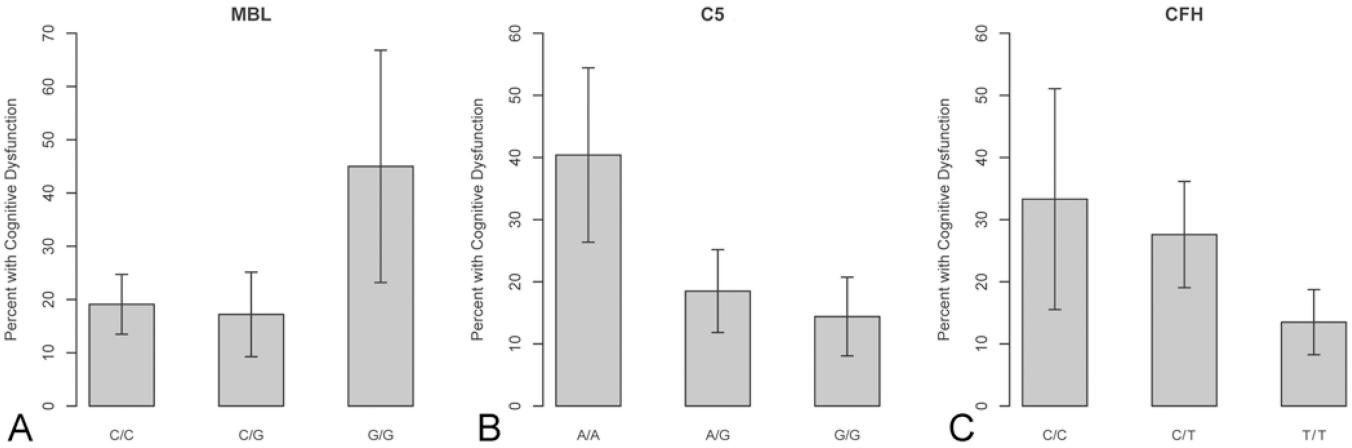


**Fig. 1.**

Graphs showing the results of univariate analysis. The incidence of CD 1 day after CEA differed significantly among the genotypes of each SNP: the G/G *MBL2* genotype had a significantly higher incidence of CD compared to the C/G and C/C genotypes **(A)**, the A/A *C5* genotype had a significantly higher incidence of CD compared to the A/G and G/G genotypes **(B)**, and the T/T *CFH* genotype had a significantly lower incidence of CD compared to the C/T and C/C genotypes **(C)**. *Error bars* are standard error.

## TABLE 1

Patient characteristics—*C5* genotypes [*]

| Characteristic | A/A (n = 47) | A/G (n = 130) | G/G (n = 118) |
|---|---|---|---|
| age >75 yrs | 23.4% | 24.6% | 33.9% |
| yrs of education (mean) | 14.4 ± 3.0 | 14.4 ± 3.4 | 14.7 ± 3.1 |
| BMI (mean) | 26.0 ± 4.2 | 27.4 ± 4.6 | 27.4 ± 4.9 |
| history of smoking | 78.7% | 71.5% | 71.2% |
| hypertension | 48.9% | 59.2% | 58.5% |
| statin use | 72.3% | 74.6% | 72.9% |
| diabetes mellitus | 19.1% | 24.6% | 19.5% |
| PVD | 27.7% | 29.2% | 25.4% |
| symptomatic [†] | 51.1% | 50.0% | 39.0% |
| cross-clamp duration in minutes (mean) | 43.8 ± 18.1 | 47.4 ± 16.6 | 45.2 ± 18.8 |
| CD at 1 day after CEA | 40.4% | 18.5% | 14.4% |
| CD at 1 month after CEA | 16.7% | 18.1% | 6.8% |
| white | 87.2% | 90.8% | 92.4% |
| black | 6.4% | 3.8% | 1.7% |
| Hispanic | 2.1% | 1.5% | 1.7% |
| other | 4.3% | 3.8% | 4.2% |

[*] Values represent percentages of patients unless otherwise indicated. Means are given with SDs.

Abbreviations: BMI = body mass index; PVD = peripheral vascular disease.

[†] Due to previous cerebrovascular accident, stroke, or transient ischemic attack.

## TABLE 2

Patient characteristics—*CFH* genotypes*

| Variable | C/C (n = 27) | C/T (n = 105) | T/T (n = 163) |
|---|---|---|---|
| age >75 yrs | 14.8% | 27.6% | 30.7% |
| yrs of education (mean) | 13.9 ± 2.9 | 14.7 ± 3.4 | 14.6 ± 3.2 |
| BMI (mean) | 27.3 ± 4.5 | 27.1 ± 4.8 | 27.3 ± 4.7 |
| history of smoking | 85.2% | 69.5% | 72.4% |
| hypertension | 66.7% | 62.9% | 52.1% |
| statin use | 81.5% | 78.1% | 69.3% |
| diabetes mellitus | 14.8% | 25.7% | 20.2% |
| PVD | 14.8% | 31.4% | 27.0% |
| symptomatic† | 59.3% | 50.5% | 40.5% |
| cross-clamp duration in minutes (mean) | 43.1 ± 15.6 | 48.1 ± 18.3 | 45.1 ± 17.6 |
| CD at 1 day after CEA | 33.3% | 27.6% | 13.5% |
| CD at 1 month after CEA | 20.0% | 14.5% | 11.2% |
| white | 88.9% | 90.5% | 91.4% |
| black | 11.1% | 1.9% | 3.1% |
| Hispanic | 0% | 2.9% | 1.2% |
| other | 0% | 4.8% | 4.3% |

*Values represent percentages of patients unless otherwise indicated. Means are given with SDs.

†Due previous cerebrovascular accident, stroke, or transient ischemic attack.

## TABLE 3

Patient characteristics—*MBL2* genotypes [*]

| Variable | C/C (n = 188) | C/G (n = 87) | G/G (n = 20) |
|---|---|---|---|
| age >75 yrs [†] | 31.4% | 26.4% | 5.0% |
| yrs of education (mean) | 14.7 ± 3.1 | 14.4 ± 3.6 | 13.9 ± 2.0 |
| BMI (mean) | 26.8 ± 4.5 | 27.9 ± 5.1 | 27.8 ± 4.0 |
| history of smoking | 72.9% | 71.3% | 75.0% |
| hypertension | 60.6% | 49.4% | 60.0% |
| statin use [†] | 75.5% | 74.7% | 50.0% |
| diabetes mellitus | 21.8% | 20.7% | 25.0% |
| PVD | 28.7% | 28.7% | 10.0% |
| symptomatic [‡] | 49.5% | 39.1% | 40.0% |
| cross-clamp duration in minutes (mean) | 46.0 ± 18.2 | 45.7 ± 16.6 | 46.6 ± 18.6 |
| CD at 1 day after CEA | 19.1% | 17.2% | 45.0% |
| CD at 1 month after CEA | 12.2% | 15.4% | 16.7% |
| white | 91.5% | 88.5% | 95.0% |
| black | 2.7% | 4.6% | 5.0% |
| Hispanic | 1.6% | 2.3% | 0% |
| other | 4.3% | 4.6% | 0% |

[*] Values represent percentages of patients unless otherwise indicated. Means are given with SDs.

[†] Significant association with SNP genotype ($p < 0.05$).

[‡] Due to previous cerebrovascular accident, stroke, or transient ischemic attack.

## TABLE 4

Univariate and multivariate logistic regression model—CD at 1 day after CEA

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| **Variable** | **OR (95% CI)** | **p Value** | **OR (95% CI)** | **p Value** |
| age >75 yrs | 1.01 (0.53–1.87) | 0.970 | 1.26 (0.62–2.52) | 0.515 |
| yrs of education | 0.92 (0.84–1.01) | 0.097 | 0.93 (0.84–1.03) | 0.191 |
| BMI | 0.99 (0.93–1.05) | 0.821 | | |
| history of smoking | 0.95 (0.51–1.82) | 0.865 | | |
| hypertension | 1.26 (0.71–2.27) | 0.443 | | |
| statin use | 0.49 (0.27–0.90) | 0.021 | 0.43 (0.22–0.84) | 0.014 |
| diabetes mellitus | 1.42 (0.72–2.69) | 0.297 | | |
| PVD | 1.06 (0.55–1.96) | 0.865 | | |
| symptomatic * | 1.35 (0.76–2.38) | 0.305 | | |
| cross-clamp duration | 0.99 (0.97–1.01) | 0.350 | | |
| *MBL2* (ref = G/G) | | | | |
| C/G | 0.25 (0.09–0.73) | 0.010 | 0.58 (0.19–1.86) | 0.354 |
| C/C | 0.29 (0.11–0.77) | 0.011 | 0.60 (0.20–1.79) | 0.347 |
| *C5* (ref = A/A) | | | | |
| A/G | 0.33 (0.16–0.70) | 0.003 | 0.26 (0.11–0.60) | 0.002 |
| G/G | 0.25 (0.11–0.54) | <0.001 | 0.22 (0.09–0.52) | <0.001 |
| *CFH* (ref = T/T) | | | | |
| C/T | 2.45 (1.32–4.59) | 0.005 | 3.37 (1.69–6.92) | <0.001 |
| C/C | 3.20 (1.24–7.92) | 0.013 | 3.67 (1.30–10.06) | 0.012 |

* Due to previous cerebrovascular accident, stroke, or transient ischemic attack.