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Grant Title: CAROTID ARTERY WALL PROPERTIES AS MARKERS OF SUBCLINICAL
ATHEROSCLEROSIS AND RISK OF CEREBROVASCULAR DISEASE IN
HEALTHY POSTMENOPAUSAL WOMEN FROM A MULTI ETHNIC COMMUNITY
OF NORTHERN MANHATTAN

Date of Grant: *July 1, 2001 - June 30, 2004*

FINAL GRANT REPORT

Summary

Dr. Tanja Rundek has completed a three year grant funded by The Goddess Fund Career Development Award in the time period from July 1, 2001 to June 30, 2004. This grant considerably helped develop her career and set a background for novel research in the area of neurosonology and stroke prevention, while also meeting the objectives for scholar career development and promotion of stroke awareness among women. In 2001, when Dr. Rundek started the scholarship, she was a research scientist practically unknown in the field of stroke. With the help of The Goddess Fund Career Development Award she developed a new field of neurosonology research in stroke prevention. *This led to a career promotion in 2002 from a Research Scientist to an Assistant Professor of Neurology, a tenure-track position at Columbia University.*

Furthermore, the research results obtained from The Goddess Fund Career Development Award made it possible for Dr. Rundek to establish an extensive foundation for future research. Tanja Rundek is the recipient of two investigator initiated grants, one supported by Pfizer Inc. (Atorvastatin and Carotid Distensibility) and the other by Sanofi/BMS (Clopidogrel and Aspirin Stroke Study-CASS). Just recently she received funding from the American Institute of Ultrasound in Medicine (AIUM) and the prestigious Gilbert Baum Memorial Grant for promotion of ultrasound in medicine. (N.B., Dr. Gilbert Baum, 1894-1974 an ultrasound pioneer and AIUM past president was the first to report on the application of ultrasound of the eye and established the use of ultrasound in ophthalmology. The Baum family established the fund to



sponsor relevant clinical research using ultrasound outside the field of obstetrics and gynecology.) Dr. Rundek has been the first and only recipient of this grant since its establishment in 1999. The research funded by The Goddess Fund Career Development Award had an imperative role in the application for the Gilbert Baum Memorial Grant as it helped generate the high quality and exciting preliminary clinical ultrasound data.

The Goddess Fund Career Development Award also enabled Dr. Rundek to publish several important research papers in the field of neurosonology and stroke prevention that further substantiated her research and provided her with international recognition.

Detailed Activities

During the active time of The Goddess Fund Career Development Award, Dr. Tanja Rundek completed and promoted the following activities in chronological order:

1. Organized the Research Neurosonology Laboratory at the Stroke Division of Neurology Department at Columbia University in order to conduct clinical neurosonology research for stroke prevention, particularly among women.
2. Established and implemented the standardized scanning and reading protocols for carotid intima-media wall thickness (IMT) and carotid distensibility (elasticity) using high resolution B-mode ultrasound imaging of the carotid arteries.
3. Conducted reliability studies of the carotid IMT and distensibility methods.
4. Performed 300 carotid ultrasound tests on women of various ages among the three race-ethnic backgrounds in northern Manhattan. The enrollment of a total sample of 300 women (healthy volunteers) targeted for the purpose of this research grant has been completed.
5. As a part of other large epidemiology studies, over 1,000 scans have been recorded and the measurements of carotid IMT and distensibility have been completed.
6. All stored carotid scans have been reviewed and all measurements were performed. Data were checked for accuracy and consistency and the analyses of the subclinical carotid atherosclerosis parameters are in progress. The analyses include descriptive statistics of the carotid IMT and distensibility among



women by age and race-ethnic background, the association analyses of carotid IMT and distensibility with vascular risk factors, and the estimation of the 3-year risk (hazard ratio) of stroke and other vascular events (heart attack , vascular death). The final analyses of this study will be done after the completion of the 3-year follow up. The final analyses and the preparation of a manuscript are expected to be completed by the end of the year.

7. Dr. Tanja Rundek presented the preliminary results of The Goddess Fund Career Development Award at the following professional and scientific meetings:
 - a) The 26th American Heart Association Stroke meeting in February 2001
 - b) The 9th European Neurosonology Conference in May 2001
 - c) The 27th American Heart Association Stroke meeting in February 2002
 - d) The 54th American Academy of Neurology meeting in April 2002
 - e) The 10th European Neurosonology Conference in May 2002
 - f) The 28th American Heart Association Stroke meeting in February 2003
 - g) The 55th American Academy of Neurology meeting in April 2003
 - h) The International Symposium on Triglycerides, Metabolic Disorders, and Cardiovascular Disease meeting in July 2003
 - i) The American Heart Association meeting in November 2003
 - j) The 29th American Heart Association Stroke meeting in February 2004
 - k) The 56th American Academy of Neurology meeting in April 2004
 - l) The 11th European Neurosonology Conference in May 2004

The Research Results

During the active time period of the Goddess Fund Career Development Award, Dr. Tanja Rundek presented and published the following research results:

1. The first results obtained as the part of this award were on the association between carotid intima-media thickness (IMT) and the three gene polymorphisms (stromyelysin-1, interleukin-6, and hepatic lipase gene) that are involved in cellular matrix, lipid and inflammatory mechanisms of atherosclerosis. These results were presented at the 26th American Heart Association Stroke meeting in February 2001, and published in *Stroke* in 2002 [T. Rundek, at al. *Carotid Intima-Media Thickness is Associated with Allelic Variants of Stromelysin-1, Interleukin-6 and Hepatic Lipase Genes: The Northern Manhat-*



tan Prospective Cohort Study. Stroke 2002, 333(5): 1420-1423.] The IMT reliability results were published in the same paper.

The Reliability Studies

a.) Carotid intima-media thickness (IMT)

In a sample of 88 stroke-free community subjects, a mean absolute difference of carotid IMT between two readers was 0.19 ± 0.36 mm; a variation coefficient 7.5%; a correlation coefficient 0.77, and a percent error 10.6%. Intra-reader mean absolute IMT difference was 0.07 ± 0.04 mm, a variation coefficient 5.4%, a correlation coefficient 0.94, and a percent error 5.6%. These results are similar to those reported by other community studies, such as in ARIC (The Atherosclerosis Risk in Communities Study) or in The Rotterdam Study.

b.) Carotid distensibility

Among 28 subjects, the reliability study of carotid distensibility showed a good reproducibility of the ultrasound measures of the common carotid wall diameters in a community study. The inter-reader reliability correlation coefficient (ICC3,1) for systolic diameter was 0.96 and for diastolic 0.95. Also, a significant association between increased CCA diameters and increased age and men was observed. [Presented at the 9th European Neurosonology Conference in May 2001; *T. Rundek et al, Cerebrovascular Diseases 2001*].

2. In a study of the *gender differences of carotid distensibility* among 180 stroke-free subjects from the Northern Manhattan Prospective Cohort Study, we found that elderly women had significantly smaller carotid artery diameter than men (women 6.70 ± 1.22 mm vs. men 7.31 ± 1.36 mm, $p=0.002$). Among women, white women (6.57 ± 0.99 mm) had reduced carotid diameters in comparison with Black and Hispanic women (6.86 ± 1.22 mm), $p<0.05$. Moreover, we observed increased carotid artery wall stiffness and reduced elasticity in women compared to men (women 9.96 ± 4.41 vs. men 8.64 ± 3.21 , $p=0.058$). This preliminary observation suggests that postmenopausal women have smaller carotid arteries and stiffer walls, which may predispose them to the greater risk of stroke in comparison to men. [Presented at the 27th AHA Stroke meeting in February 2002; *T. Rundek et al, Stroke 2002*].
3. In a study of the *association between maximum carotid plaque thickness (MCPT) and risk of vascular events (ischemic stroke, myocardial infarction or vascular death)* among 1966 stroke-free subjects from the Northern Manhattan Prospective Cohort (mean age 69 ± 10 years; 59% women; 51% His-

panic, 24% African-American, 22% Caucasian), we found that carotid plaque was present in 1141 (58%) of subjects (in 59% of women and 58% of men). The mean MCPT was 1.1 ± 0.9 mm, median 1.0 mm, and the 75th percentile 1.8 mm. After mean follow-up of 3.7 years, vascular events occurred among 121 subjects; 55 had fatal or non-fatal ischemic stroke, 42 fatal or non-fatal myocardial infarction, and 24 died of other vascular causes. MCPT greater than 1.8 mm was a significant predictor of the combined vascular outcome (HR 2.70, 95%CI 1.89-3.86) in univariate well as in multivariate analysis (HR 2.00, 95%CI 1.38-2.92; after adjusting for age, gender, race-ethnicity, medical, lifestyle and socioeconomic factors: hypertension, diabetes, HDL, body mass index, alcohol intake, current smoking, and education). In addition, MCPT > 1.8 mm was associated with an increased risk of ischemic stroke alone in univariate (HR 2.56, 95%CI 1.42-4.39) and multivariate analysis (HR 1.7, 95%CI 0.96-3.00). We concluded that small non-stenotic carotid plaques are associated with a 2 fold increase risk of ischemic stroke, independent of the presence of other vascular risk factors. This suggests that carotid-B-mode ultrasound assessment of maximal plaque thickness may serve as a marker of subclinical atherosclerosis and a useful method to select individuals at high-risk for vascular events. [Presented at the 54th American Academy of Neurology meeting in April 2002; *T. Rundek et al, Neurology 2002*].

4. In a study of the association *between carotid distensibility (CD) and vascular risk factors* among 313 stroke-free subjects from the Northern Manhattan Cohort Study (mean age 68 ± 9 y; 62% women; 52% Caribbean-Hispanic, 24% African-American, 20% Caucasian), we obtained the mean values of the carotid distensibility parameters: STRAIN (the percentage change in diameters) of $7.5 \pm 4.5\%$ (range 1.2-27%), STIFFNESS of 9.30 ± 7.14 (range 2.01-51.64), and DISTENSIBILITY of 0.15 ± 0.09 (range 0.02-0.50). Hypertension was present in 52% of subjects, hypercholesterolemia in 44%, and diabetes in 13%; 19% were current smokers. In the final multivariate regression model (after inclusion of the variables significantly associated with STIFFNESS in the univariate models), increased STIFFNESS was associated with older age ($\beta=0.018$, $p<0.05$) and white race-ethnicity ($\beta=2.553$, $p<0.05$), but not with vascular risk factors. This suggests that carotid distensibility may be a marker of subclinical atherosclerosis independent of other vascular risk factors. Reversal of arterial wall dysfunction may prevent plaque formation, and reduce the risk of stroke or coronary heart disease. We concluded that carotid distensibility may be a useful method in assessing vascular risk and serve as a surrogate endpoint for vascular events in interventional trials. [Presented at the 10th European Neurosonology Conference in May 2002; *T. Rundek et al, Cerebrovascular Diseases 2002*].
5. In an association study *between carotid IMT and the metabolic syndrome*, an emerging combined risk

factor for stroke, heart disease and diabetes, we found a significant association between increased carotid IMT and the metabolic syndrome among women. The recently released Third Report of the National Cholesterol Education Program: Adult Treatment Panel (NCEP ATP III) defines the metabolic syndrome to have 3 or more of the following abnormalities: waist circumference greater than 102 cm in men and 88 cm in women; serum triglycerides level of at least 150 mg/dL; high-density lipoprotein cholesterol level of less than 40 mg/dL in men and 50 mg/dL in women; blood pressure of at least 130/85 mm Hg; or serum glucose level of at least 110 mg/dL. We analyzed 400 subjects from the Northern Manhattan Study (mean age 68 years, 59% women, 52% Hispanics, 25% African American, 22% Caucasian). *Our finding may explain in part the greater risk for stroke and heart disease among postmenopausal women.* This study contributes to the growing knowledge of pre-clinical atherosclerosis in a high-risk population such as women with metabolic syndrome. Therefore, further studies are needed in order to understand the progression from pre-clinical to clinical atherosclerotic disease and gender specific increased risk of stroke and heart disease. [Presented at the International Symposium on Triglycerides, Metabolic Disorders, and Cardiovascular Disease meeting in New York, July 2003; [T.Rundek, at al. *Metabolic Syndrome is Associated with Carotid Arteriosclerosis among Women but not Men: the Northern Manhattan Study Cohort*].

6. In a study *on the correlation between brachial endothelial function and subclinical carotid atherosclerosis* among 612 subjects from the Northern Manhattan cohort, we observed a *significant association between endothelial dysfunction and increased carotid plaque thickness. This effect was independent of other vascular risk factors and was more pronounced among women.* Brachial flow-mediated dilatation, a measure of endothelial function, may be another useful marker for vascular risk assessment and a measure of the effectiveness of interventions to reduce the risk of MI, stroke or vascular death. [Presented at the AHA meeting, Orlando, November 2003; T. Rundek at al. *Brachial endothelial function is associated with subclinical carotid atherosclerosis: The Northern Manhattan Study. Circulation. 2003; Vol. 108:18 (Supp IV): 2402*].
7. In the most recent study on association *between coenzyme Q10 (coQ10) and statin therapy* among 40 men and women with elevated LDL-cholesterol levels who received 80 milligrams oral atorvastatin for thirty days, we found that even brief exposure to the statin drug atorvastatin markedly lowers blood plasma levels of coQ10. Coenzyme Q10 is an antioxidant made in the body whose production declines with age. In addition to its role as an antioxidant, coenzyme Q10 is a component of the mitochondrial respiratory chain and acts as a cell membrane stabilizer. Therefore, anything that reduces coenzyme Q10 levels could have significant adverse effects. After two weeks, and at the study's



conclusion, the participants were examined for changes in liver enzymes, kidney function, and any adverse effects, including muscle pain or weakness. Plasma levels of coenzyme Q10 were measured at the beginning of the study and at 14 and 30 days. Plasma coenzyme Q10 levels in thirty-two participants were reduced by 49 percent. After thirty days, the mean coenzyme Q10 concentration was reduced from 1.26 micrograms per milliliter to 0.62 micrograms per milliliter. This significant decrease of coQ10 could explain the most common adverse effects of statins, particularly muscle pain, exercise intolerance and myoglobinuria. [Published in Archives of Neurology; *T. Rundek at al.* Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke, Arch Neur, 2004:(16):884-92].

Grants Awarded as a Result of The Goddess Fund Career Development Award

The results on carotid distensibility and risk of stroke among women obtained as the part of the Goddess Fund Career Development Award were used to generate new hypotheses and propose new and novel projects. The following grants were highly scored and awarded:

1. *The Short-Term Effect of Atorvastatin on Carotid Artery Wall Elasticity: B-Mode Ultrasound Pilot Study* (an investigator initiated grant funded by Pfizer, Inc; 12/ 2002 – 12/ 2004, Principal Investigator: T. Rundek). This is a clinical trial aimed to reduce arterial stiffness and risk of stroke using atorvastatin, a lipid-lowering drug. The patient enrollment was completed in 2003 while the follow up is still ongoing. The main study results are expected to be ready for the presentation at the AHA meeting at the end of this year.

This clinical trial is an open-label pilot study of the short-term effect, 14 and 30 days, of a single dose of atorvastatin on carotid wall elasticity assessed by repeated B-mode ultrasound imaging. We hypothesized that the positive effect of atorvastatin on the carotid distensibility would be independent of the degree of lipid-lowering effect of atorvastatin, but may be associated with the reduction of inflammatory markers (CRP, IL-6, and TNF). The study group consists of 40 women and men aged 45 years and over who are potential candidates for treatment with a statin on the basis of the Third Report of the National Cholesterol Education Program: Adult Treatment Panel (NCEP ATP III) guidelines, but not yet treated with a statin. Each subject has 3 carotid ultrasound scans performed in the three time points: at baseline, Day 14, and Day 30. The results on the effect of atorvastatin on the coenzyme Q10 have been published recently. Neither severe nor non-severe adverse events have been reported.



2. *Clopidogrel and Aspirin in Reduction of Carotid Thickness and Stiffness after Stroke (CASS) Trial* (an investigator initiated grant funded by Sanofi/BMS; 7/ 2004 – 7/ 2006, Principal Investigator: T. Rundek)
The primary objective of this study is to determine whether clopidogrel (Plavix) is superior to acetylsalicylic acid (ASA) in the reduction of carotid artery IMT and stiffness progression in ischemic stroke patients after 12 months of treatment. Carotid intima-media thickness and stiffness will be assessed by repeated high-resolution B-mode and M-mode ultrasound. This is a randomized, single center, open-label, single blind, high-resolution B/M-mode carotid ultrasound study. A group of 100 patients (50 in each treatment group) over 40 years of age with non-disabling ischemic stroke ≥ 3 months after stroke onset will be randomly assigned to clopidogrel or ASA. The primary endpoint is a reduction from baseline in the carotid IMT progression and stiffness at 12 months. The secondary outcomes include the reduction from baseline in the carotid IMT progression and stiffness at 6 months, and the reduction from baseline of inflammatory markers (CRP, IL-6, and TNF alfa) at 6 and 12 months.

3. *Carotid Artery Distensibility and Risk of Stroke* (funded by the American Institute of Ultrasound in Medicine and the Gilbert Baum Memorial Grant; 12/ 2004 – 12/ 2005, Principal Investigator: T. Rundek).
The objective of this study is to determine whether carotid distensibility is associated with risk of stroke. The specific aims of this study are to determine whether decreased carotid distensibility increases the risk of first stroke (ischemic or hemorrhagic) independent of traditional stroke risk factors and whether the stroke risk associated with carotid distensibility varies among different age, gender, and race-ethnic group. It is a case-control study among 70 stroke patients and controls using repeated ultrasound measurements.

Published Results

Papers

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2. **T. Rundek**, K. Nielsen, S. Phillips, K.C. Johnston, M. Hux, D. Watson; for the GAIN Americas Investigators. Health Care Resource Use After Acute Stroke in the Glycine Antagonist in Neuroprotection (GAIN) Americas Trial. *Stroke* 2004; 35(6):1368-74
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Press Releases and Web Articles

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2. Metabolic syndrome May Be an Important Link to Stroke. *Neurology Reviews*, April 2004;12:4
3. Metabolic Syndrome Doubles Stroke Risk. *CNN*, February 7, 2004 (<http://www.cnn.com>) Posted: 9:38 AM EST

4. ANA: Elevated Serum Calcium Linked to Increased Carotid-Artery Plaque Thickness. San Francisco, Ca, November 4, 2003 (www.pslgroup.com/dg/23dad2.htm)

Abstracts

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Conclusion

This grant has provided a great opportunity to study the markers of pre-clinical atherosclerosis among women from various race-ethnic backgrounds and without previous cardiovascular disease or stroke. The preliminary data has been of enormous scientific interest and has generated hypotheses for future research including: studies of progression of atherosclerosis, association studies with inflammatory or coagulation markers of atherosclerosis, genetic studies, and interventional studies in order to test various classes of drugs in primary or secondary stroke prevention among women - who have been underrepresented in most of the stroke prevention trials. This research may also help to establish specific ultrasound parameters as non-invasive screening tools for assessment of stroke risk. Finally, the FDA has recognized the use of carotid IMT as a secondary end-point in the clinical trials. This will expand the use of the subclinical measures of atherosclerosis in the research and help translate clinical research to clinical practice, making the results of this study even more attractive.

The Goddess Fund Career Development Award has considerably contributed to the development of Dr. Tanja Rundek's scientific and professional career at Columbia University. The results of the award established a novel research arena for research in neurosonology and stroke prevention. Several new grants have been established as a continuation of the work initiated and completed by Dr. Rundek with the



generous support from The Goddess Fund Career Development Award. These research results have contributed to the knowledge of subclinical markers of atherosclerosis and their specific predictive value for increased risk for stroke among women. This research will help to establish the role of carotid ultrasound markers in preventive medicine as well as in directing future research of stroke risk in women. On a personal note, Ms. Lynn Goddess has been a true supporter and a great friend. She has encouraged me at every step of this research, always believing in my success. She inspired me to go beyond traditional medical thinking and search for new knowledge and ideas. I am deeply grateful for her strength of mind, confidence, cheerfulness and inspirational outlook in life, all of which uplifted my work and spirit.

Tanja Rundek