**On-treatment HDL cholesterol and risk of atrial fibrillation in hypertensive patients with left ventricular hypertrophy**

**Supplemental Discussion and Tables**

Peter M. Okin a, Darcy A. Hille b, Kristian Wachtell c, Sverre E. Kjeldsen c, d, Stevo Julius d and Richard B. Devereux a

a Division of Cardiology, Weill Cornell Medical College, New York, NY, USA; b Merck Research Labs, West Point, PA, USA; c Department of Cardiology, Oslo University Hospital, Ullevaal, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; d Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

**Supplemental Discussion**

Prior work has found inconsistent relationships between HDL and the risk of AF in a variety of populations and settings [12-20]. In a case-control study comparing patients with paroxysmal AF with arrhythmia patients without any evidence of AF [12], risk of paroxysmal AF increased significantly across quartiles of HDL in age and gender adjusted analyses. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), baseline HDL <35 mg/dl was associated with an increased odds of both prevalent AF (adjusted OR 1.41, 95% CI 1.11-1.80, p=0.005) and incident AF (adjusted OR 1.34, p=0.005, 95% CI not provided) in multivariable logistic regression models adjusting for age, gender, race, body mass index, hypertension treatment, aspirin use, LVH and for the history of smoking, diabetes or coronary heart disease [13]. In a study of 1223 subjects individuals attending a lipid clinic who were free of AF at baseline [14], low levels of HDL cholesterol were strongly associated with the risk of new AF during 6 years median follow-up in multivariable logistic regression analyses (adjusted OR 3.79, 95% CI 1.85-7.75, p<0.001), but these observations could be skewed by the low incidence of AF (n=33). AF risk was also assessed among 7142 subjects from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study who did not have AF at baseline and were not on lipid-lowering medications [15]. During 9.6 years mean follow-up with 480 new AF cases, every 1 SD of the mean (15 mg/dl) lower HDL was associated with a 12% higher risk of new AF in multivariable Cox models. Neither total nor LDL cholesterol were significantly associated with AF risk [15]. In contrast, baseline HDL levels were not related to incident AF in a prospective cohort study of 88785 participants free of AF at baseline in China [16]; in 23738 healthy middle-aged and older women enrolled in the Women’s Health Study [19]; in a systematic review and field synopsis of 23 risk factors in 32 population-based cohorts of over 20 million participants; and was not examined in an analysis of AF risk factors among 79793 individuals without AF at baseline from 4 community-based European studies of the Biomarker for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium, despite a strong inverse association between total cholesterol and incident AF [20]. Lastly, among nearly 14000 participants in the Atherosclerosis Risk in Communities (ARIC) study [17], although increased baseline HDL was associated with a decreased risk of incident AF in Cox analyses adjusting for age, gender and race, this risk was mostly attenuated in their full multivariable Cox model with a concomitant lack of association between on-study levels of HDL treated as a time-varying covariate and incident AF in multivariable Cox analyses.

There are several other mechanisms by which the potential link between HDL and, inflammation could increase AF risk [10,36-39]. In a nested case-control study of 97 patients with AF compared to 97 age and gender matched controls from the Prevention of Renal and Vascular Endstage Disease (PREVEND) study [36], the TaqIB polymorphism of the cholesterol ester transfer protein (CETP) was significantly associated with the presence of AF. Increased CETP activity in subjects who have the B1B1 genotype of the TaqIB polymorphism could both decrease HDL levels and increase levels of oxidized LDL, increasing inflammation [36]. The increased levels of oxidized LDL associated with lower HDL could separately modulate AF risk via upregulation of miRNA-223 and its upregulation of the CACNA1C gene which encodes the L-type calcium channel protein [37]. Indeed, knockdown of endogenous miRNA-223 decreased AF susceptibility in mice whereas transfection of miRNA-223 by adenovirus-mediated expression enhanced L-type calcium currents and promoted AF in mice and this effect could be blocked by co-injection of CACNA1C-specific miR-mimic [37]. The strong association between decreased on-treatment levels of HDL and incident AF in hypertensive patients [38] and the known association of diabetes with both increased inflammation and AF [10] provides another potential link between low levels of HDL, inflammation and AF. Finally, the significant association of decreased levels of HDL with increased frequency of atrial premature contractions (APCs) in a population-based cohort and the relationship of APCs to AF risk [39] could in part account for the relationship of decreased HDL to AF risk.

**References are listed in the main article.**

**Supplemental Table 1.** Baseline demographic and clinical characteristics in relation to development of new atrial fibrillation

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | No AF  (n=7622) | New AF  (n=645) | *p-value* |
| Age (years) | 66.5±7.0 | 69.8±6.5 | <0.001 |
| Sex (% female) | 54.9 | 48.8 | 0.004 |
| Race (% black) | 6.2 | 3.3 | 0.004 |
| Randomized to Losartan (%) | 50.6 | 47.1 | 0.097 |
| History of ischemic heart disease (%) | 14.7 | 22.3 | <0.001 |
| History of myocardial infarction (%) | 5.7 | 8.2 | 0.013 |
| History of heart failure (%) | 1.3 | 2.9 | 0.002 |
| History of Stroke (%) | 3.9 | 6.0 | 0.013 |
| History of peripheral vascular disease (%) | 5.3 | 6.5 | 0.242 |
| History of diabetes mellitus (%) | 12.4 | 14.4 | 0.157 |
| Current smokers (%) | 16.6 | 15.1 | 0.355 |
| Prior antihypertensive treatment (%) | 71.5 | 76.4 | 0.008 |
| Body mass index (kg/m2) | 28.0±4.8 | 28.0±4.9 | 0.943 |
| Serum glucose (mmol/l) | 5.99±2.17 | 6.10±2.19 | 0.257 |
| Serum creatinine (µmol/l) | 86.4±19.8 | 87.3±21.9 | 0.258 |
| Total cholesterol (mmol/l) | 6.06±1.12 | 5.96±1.12 | 0.021 |
| HDL cholesterol (mmol/l) | 1.50±0.44 | 1.48±0.43 | 0.384 |
| Urine albumin/creatinine ratio (mg/mM) | 6.6±27.5 | 12.2±47.3 | 0.004 |

AF=atrial fibrillation

**Supplemental Table 2.** Baseline and change from baseline to last in-study measurement of blood pressure and electrocardiographic left ventricular hypertrophy in relation to development of new atrial fibrillation

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | No AF  (n=7622) | New AF  (n=645) | *p-value* |
| Baseline Measurements | | | |
| Systolic blood pressure (mm Hg) | 174.1±14.2 | 177.0±14.5 | <0.001 |
| Diastolic blood pressure (mm Hg) | 97.9±8.8 | 96.5±9.0 | <0.001 |
| Cornell voltage-duration product (mm•msec) | 2810±1022 | 2929±988 | 0.004 |
| Sokolow-Lyon voltage (mm) | 29.8±10.2 | 31.8±11.5 | <0.001 |
| Heart rate (bpm) | 73.7±10.9 | 72.8±11.0 | 0.034 |
| Change From Baseline to Last Measurement\* | | | |
| Systolic blood pressure (mm Hg) | -29.1±19.3 | -34.1±20.7 | <0.001 |
| Diastolic blood pressure (mm Hg) | -17.1±10.2 | -17.5±11.1 | 0.306 |
| Cornell voltage-duration product (mm•msec) | -208±827 | -104±1062 | 0.015 |
| Sokolow-Lyon voltage (mm) | -3.8±7.1 | -4.1±8.7 | 0.515 |
| Heart rate (bpm) | -5.2±12.5 | -2.8±14.8 | <0.001 |

AF=atrial fibrillation

\* change from baseline to last in-study measurement or last measurement prior to diagnosis of new atrial fibrillation

**Supplemental Table 3.** Change in HDL cholesterol levels in relation to development of new atrial fibrillation

|  |  |  |  |
| --- | --- | --- | --- |
| Change in HDL cholesterol (mmol/l) | No AF  (n=7622) | New AF  (n=645) | *p-value* |
| Baseline to Year-1 | -0.14±0.22 | -0.14±0.23 | 0.943 |
| Baseline to Year-2 | -0.14±0.24 | -0.15±0.24 | 0.787 |
| Baseline to Year-3 | -0.10±0.25 | -0.13±0.27 | 0.008 |
| Baseline to Year-4 | -0.06±0.25 | -0.09±0.27 | 0.004 |
| Baseline to Year-5 | -0.05±0.25 | -0.09±0.28 | <0.001 |

**Supplemental Table 4.** Baseline and in-treatment statin use in relation to development of new atrial fibrillation

|  |  |  |  |
| --- | --- | --- | --- |
| Statin Use (%) | No AF  (n=7622) | New AF  (n=645) | *p-value* |
| Baseline (%) | 7.7 | 6.5 | 0.299 |
| Year-1 (%) | 6.1 | 5.3 | 0.430 |
| Year-2 (%) | 24.1 | 22.2 | 0.285 |
| Year-3 (%) | 23.4 | 21.1 | 0.199 |
| Year-4 (%) | 22.5 | 20.3 | 0.209 |
| Year-5 (%) | 21.6 | 18.0 | 0.035 |