April 2, 2017

Dear ARIC Publications Committee,

Thank you very much for reviewing our proposal and providing feedback. We are resubmitting the proposal with modifications. Responses to your comments are outlined below:

1. We are concerned with using cognitive function cross-sectionally vs. longitudinally as a robust design with the ability to suggest likely causal associations. You can't do a prospective study but you could look at decline from the previous visit which is less associated with education and other factors compared to cross-sectional cognition.
   Thank you very much for this comment and for directing us to the article by Deal and colleagues. We agree with the reviewers that causation cannot be implied by cross-sectional analysis. At this point, this was not our intention. As such little work has been done on cognitive impairment in HFpEF, we felt it was important to explore potential associations first, to determine whether or not this phenomenon should be studied further. If this study identifies associations between echocardiographic markers of cardiac function and cognitive impairment among individuals with HFpEF, it would support future prospective studies designed to evaluate potential causal mechanisms.
   We acknowledge that a measure of cognitive change will give a less confounded measurement of cognitive function, but feel that our overall study questions are not well answered with a design with the evaluation of cognitive change occurring prior to the measurement of cardiac function. There is the concern that the exposure is measured well after the initial measurement of cognition, but there is also a concern about the inability to look in more detail at different cognitive domains when only three cognitive tests with repeat measurement are used. As this study is exploratory in nature, we would prefer to conduct cross-sectional analysis as our primary analysis, but we are happy to include a sensitivity analysis in which we evaluate change in these three tests and change in the averaged global Z score over the years preceding visit 5 as our outcome if preferred by the Publications Committee. This change has been made to the proposal. However, if the Publications Committee is willing to forego this analysis after reviewing our rationale, we will remove it from the proposal.
2. You may want to clarify if you will exclude cases with dementia at visit 5 since their testing will be poorer and the dementia may have started prior to visit 5 which is listed in your exclusion criteria.
   The reviewers bring up an excellent point. Therefore, we will exclude all participants with a diagnosis of dementia at ARIC visit 5 or at any prior assessment. These changes have been made to the proposal.

3. If the analysis will be done at NYU, we wanted to make sure you will sign a DMDA agreement with the UNC-DCC to cover this data use.
   Yes, I am certainly happy to sign this agreement to cover data use.

Thank you very much for your comments. We are looking forward to hearing back from you.

Sincerely,

Kenneth Faulkner, MS, RN, ANP

ARIC Manuscript Proposal #2956

PC Reviewed: 5/9/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Factors Associated with Cognitive Impairment among Individuals with Heart Failure with Preserved Ejection Fraction: The ARIC Study

b. Abbreviated Title (Length 26 characters): Cognitive Impairment in HFpEF

2. Writing Group:
Kenneth M. Faulkner, MS, RN, ANP
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Lucy S. Witt, MD, MPH
Victoria Vaughan Dickson, PhD, CRNP, FAHA, FHFSA, FAAN
Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _KF__ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Submit proposal for review	March 2017
Receipt of data	June-July 2017
Data analysis	July-October 2017
Writing and revising	November 2017-March 2018
Submit for publication	May 2018

4. Rationale:

Cognitive impairment (CI) affects as many as 58% of individuals with heart failure and influences heart failure self-care (1-8). Poor self-care contributes to high rates of hospitalization, high mortality and increased health care costs (9-13). Although prior researchers have evaluated CI in heart failure, most have focused on individuals with reduced ejection fraction (HFrEF) (14-19). The limited research on CI in heart failure with preserved ejection fraction (HFpEF) suggests that CI is as prevalent among individuals with HFpEF as it is among individuals with HFrEF, although the magnitude of CI may be greater among individuals with HFrEF (14, 20-24).

The association between CI and HFpEF is unclear. The Conceptual Model of Cognitive Deficits in Heart Failure (Figure 1) suggests that circulatory insufficiency due to a failing heart contributes to reduced cerebral perfusion and ultimately CI (25). Reduced left ventricular ejection fraction (LVEF) is highlighted as a potential contributing factor (25). As LVEF is normal among individuals with HFpEF, this model is not adequate for describing the etiology behind CI in HFpEF. Other factors may contribute to circulatory insufficiency and reduced cerebral perfusion in HFpEF, but the exact mechanisms are not well understood.

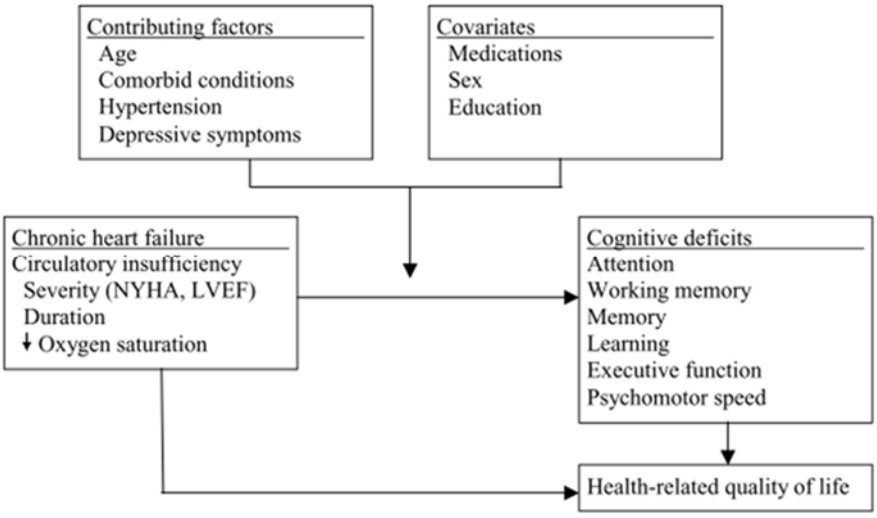

Figure 1. The Conceptual Model of Cognitive Deficits in Heart Failure

Individuals with HFpEF experience myriad abnormalities in cardiac structure and function which may promote circulatory insufficiency and contribute to reduced cerebral perfusion (26-30). These include abnormalities in diastolic function, systolic function, cardiac hemodynamics, and ventricular-vascular coupling (26, 28, 31-38). The associations between these abnormalities and CI have not been evaluated in a sample of individuals with HFpEF. Atrial fibrillation is also prevalent among individuals with HFpEF and may contribute to the

development of CI via either clinical or subclinical stroke (39-41), but the association between atrial fibrillation and CI has not been evaluated in a sample of individuals with HFpEF. It is likely that for both HFrEF and HFpEF that there are other mechanisms, distinct from impacts on flow-related cerebral perfusion or via stroke, by which CI might develop. Inflammatory changes, right-sided heart failure, and hypoxia may all contribute to CI in these populations, but these associations are beyond the scope of this study.

The purpose of this proposed secondary data analysis is to identify associations between CI and echocardiographic markers of diastolic dysfunction (LVMI, LAVI, E/A, E/E', DT), systolic dysfunction (left ventricular ejection fraction, longitudinal strain, radial strain, circumferential strain), cardiac hemodynamics (stroke volume index, cardiac index), and ventricular-vascular coupling (Ea/Ees) in a sample of individuals with HFpEF. The association between CI and atrial fibrillation in a sample of individuals with HFpEF will also be evaluated. At ARIC visit 5, participants at all 4 sites underwent echocardiographic analysis and completed extensive neurocognitive evaluation. For this reason, the data from ARIC visit 5 are ideal for evaluating these research questions.

5. Main Hypothesis/Study Questions:

1. How does the pattern of cognitive impairment (CI) differ among individuals with HFrEF, individuals with HFpEF, and individuals free of heart failure?
2. Are there associations between echocardiographic markers of diastolic dysfunction (LAVI, LVMI, E/A, E/E', DT) and CI in individuals with HFpEF?
3. Are there associations between echocardiographic markers of systolic dysfunction and cardiac hemodynamics (cardiac index, stroke volume index, radial/longitudinal/circumferential strain) and CI in individuals with HFpEF?
4. Are there associations between echocardiographic markers of ventricular/vascular coupling (Ea/Ees) and CI in individuals with HFpEF?
5. Are there associations between atrial fibrillation and CI in individuals with HFpEF?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

This will be a cross-sectional analysis of data from ARIC visit 5. Participants who completed in-person cognitive assessments at ARIC visit 5 will be included. Individuals with a history of stroke or dementia prior to ARIC visit 5 or who presented with stroke or dementia at ARIC visit 5 will be excluded, as these may influence cognitive function.

Independent variables of interest will include measures of diastolic dysfunction, systolic function, cardiac hemodynamics, and ventricular-vascular coupling. Measures of diastolic dysfunction include left ventricular mass index (LVMI), left atrial volume index (LAVI), the ratio of early diastolic trans-mitral filling velocity to the late diastolic trans-mitral filling velocity (E/A), the ratio of early diastolic trans-mitral filling velocity to early diastolic mitral annular tissue velocity (E/E'), and deceleration time (DT). Measures of systolic dysfunction and cardiac hemodynamics include stroke volume, cardiac index, and measures of ventricular strain. Ventricular-vascular coupling is measured by the ratio of arterial elastance to end-systolic elastance (Ea/Ees). Atrial fibrillation will also be included as an independent variable. Sociodemographic variables (age, race/ethnicity, sex, education, smoking history, field center), chronic comorbid illnesses (hypertension, diabetes, mellitus, chronic obstructive pulmonary

disease, anemia, depressive symptoms by CES-D score from ARIC/NCS visit 5), and medications known to influence cognitive function (antidepressants, ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics, digoxin) will be included as potential covariates. As the outcome of interest is cognitive function, the dependent variables include scores on neurocognitive tests that evaluate a wide range of cognitive domains (Delayed Word Recall Test, Logical Memory Test Part I and Part II, Incidental Learning Test, Digit Span Backwards Test, Digit Symbol Substitution Test, Trail Making Test Part A and B, Animal Naming Test, Boston Naming Test, Word Fluency Test) as well as change over time in scores and averaged global *Z*-score for the three cognitive measures that were administered at multiple visits prior to visit 5 (Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test). Standardized Z-scores will be used when appropriate and domain-specific scores as previously defined in ARIC will be examined.

Analysis will be conducted using Stata version 14 or newer (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) under the guidance of a biostatistician associated with the Rory Meyers College of Nursing at New York University. To reduce the effect of missing data on the power of this study, multiple imputation using chained equations will be performed to replace missing independent variables.

To address the first research question, an initial analysis will compare cognitive performance among individuals with HFrEF, individuals with HFpEF, and individuals free of heart failure. An analysis of variance (ANOVA) will be generated to compare mean Z-scores on each of the tests in the neurocognitive battery. This will provide domain-specific information about how CI differs among individuals with HFpEF, individuals with HFrEF, and individuals free of heart failure.

As this study is designed to explore factors that may contribute to CI in HFpEF, subsequent analyses evaluating associations between echocardiographic measures and scores on neurocognitive tests will be conducted only on individuals with HFpEF. Descriptive statistics will be generated to evaluate the characteristics of the sample with HFpEF. Means, standard deviations, and confidence intervals will be reported for continuous variables. Frequencies and percentages will be reported for categorical variables.

Bivariate analysis will evaluate associations between the independent variables (demographic variables, chronic comorbid conditions, medication profile, and echocardiographic measures). Variables which demonstrate strong collinearity will be considered for removal from further analysis due to redundancy. Associations between independent variables and scores on the battery of neurocognitive tests will also be evaluated. Independent variables that demonstrate a significant association ($p<.10$) with any of the neurocognitive tests will be included in multivariate analysis.

Regression analysis will be conducted exclusively on the HFpEF sample to evaluate the associations outlined in research questions 2-5. Multiple linear regression analysis will be conducted to quantify the magnitude of the effect of the independent variables on scores on neurocognitive tests. A separate multivariate model will be generated for each neurocognitive test, but the set of predictors will be common in all multivariate models. Independent variables that demonstrate statistically significant associations ($p<.10$) with scores on any of the neurocognitive tests in bivariate analysis will be included in all multivariate models. All sociodemographic variables (age, sex, race/ethnicity, education, smoking history, field center) will also be included in all models. Groups of predictors will be introduced into multiple linear regression analysis in a hierarchical fashion with known predictors and potential covariates being

included in the initial models. Sociodemographic variables will be included in the initial model. Comorbid conditions will be included in the second model and medications will be added in the third model. Echocardiographic measures of diastolic function will be included in the fourth model to evaluate research question 2. Echocardiographic measures of systolic function and cardiac hemodynamics will be added in the fifth model to evaluate research question 3. Echocardiographic measures of ventricular-vascular coupling will be included in the sixth model to evaluate research question 4. Finally, atrial fibrillation will be included in the final model to evaluate research question 5. The unique contribution of each predictor on performance on the neurocognitive tests will be identified. Significant associations ($p<.05$) between predictors and scores on each neurocognitive test and the magnitude of these associations after controlling for covariates will be identified in the final models. As several neurocognitive tests evaluate the same cognitive domain, *p*-values will be adjusted using a Bonferroni correction to account for multiple comparisons. The R^2 will be noted for the initial model to determine the amount of variance in CI explained by demographics. The change in R^2 will be noted for each subsequent model to identify the amount of variance explained by the addition of the new variables. The assumptions of multiple linear regression will be evaluated in this analysis. Sensitivity analysis will also be conducted to determine if atrial fibrillation and the echocardiographic measures of cardiac function are associated with change in cognitive function over time. For these analyses, the outcome variables will be change in scores and averaged global *Z*-score on the three neurocognitive tests that were assessed multiple times prior to visit 5 (Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test).

Finally, a logistic regression model will be generated to identify the associations between the predictors identified in multiple linear regression analysis and the odds of mild cognitive impairment (MCI) as determined by expert-adjudicated diagnosis. Predictors that demonstrate a significant ($p<.05$) effect on scores on neurocognitive tests will be included in the logistic regression model. The sociodemographic variables (age, sex, race/ethnicity, education, field center) will also be included. Hosmer-Lemeshow statistics will be evaluated to determine goodness of fit. Collinearity diagnostics will be examined to determine if there is substantial overlap among the predictors. Variables that demonstrate a high degree of collinearity will be evaluated for removal from the model. Potential outliers will be identified by generating and examining residuals and measures of leverage and influence. Cases with standardized residual values (ZRESID) above 2.5 or below -2.5 will be evaluated for removal from the analysis, as they may influence the regression estimates.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _XX_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _XX_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__XX__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
#1701 - Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study. Lead author: Jan Bressler. One of the co-authors, Patricia Chang, is a member of the current writing group.

#2227 - Relationship of cardiac structure and function with cognitive performance: as study of the Atherosclerosis Risk in Communities (ARIC) study. Lead author: Pardeep Jhund.

#2384 - Cardiac and Brain Structure and Function Associations: The ARIC Study. Lead author: Rebecca Gottesman. Rebecca Gottesman is a member of this writing group.

#2546 - Association of Left Atrial Enlargement with Lower Cognitive Function and Subclinical Cerebral Infarcts: The ARIC Study. Lead author: Lin Y. Chen.

#2679 - Neurocognitive function and quality of life in heart failure: the ARIC study. Lead author: Lucy S. Witt. Lucy Witt and Patricia Chang (co-author) are members of the current writing group.

#2856 - Left Ventricular Hypertrophy and its Association with Cognitive Decline and Dementia Risk over 20 years: The ARIC Neurocognitive Study (ARIC-NCS). Lead author: Faye L. Norby.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _XX_ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _XX_ No.

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ARIC Manuscript Proposal #2956

PC Reviewed: 5/9/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Factors Associated with Cognitive Impairment among Individuals with Heart Failure with Preserved Ejection Fraction: The ARIC Study

b. Abbreviated Title (Length 26 characters): Cognitive Impairment in HFpEF

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _KF__ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Submit proposal for review	March 2017
Receipt of data	June-July 2017
Data analysis	July-October 2017
Writing and revising	November 2017-March 2018
Submit for publication	May 2018

4. Rationale:

Cognitive impairment (CI) affects as many as 58% of individuals with heart failure and influences heart failure self-care (1-8). Poor self-care contributes to high rates of hospitalization, high mortality and increased health care costs (9-13). Although prior researchers have evaluated CI in heart failure, most have focused on individuals with reduced ejection fraction (HFrEF) (14-19). The limited research on CI in heart failure with preserved ejection fraction (HFpEF) suggests that CI is as prevalent among individuals with HFpEF as it is among individuals with HFrEF, although the magnitude of CI may be greater among individuals with HFrEF (14, 20-24).

The association between CI and HFpEF is unclear. The Conceptual Model of Cognitive Deficits in Heart Failure (Figure 1) suggests that circulatory insufficiency due to a failing heart contributes to reduced cerebral perfusion and ultimately CI (25). Reduced left ventricular ejection fraction (LVEF) is highlighted as a potential contributing factor (25). As LVEF is normal among individuals with HFpEF, this model is not adequate for describing the etiology behind CI in HFpEF. Other factors may contribute to circulatory insufficiency and reduced cerebral perfusion in HFpEF, but the exact mechanisms are not well understood.

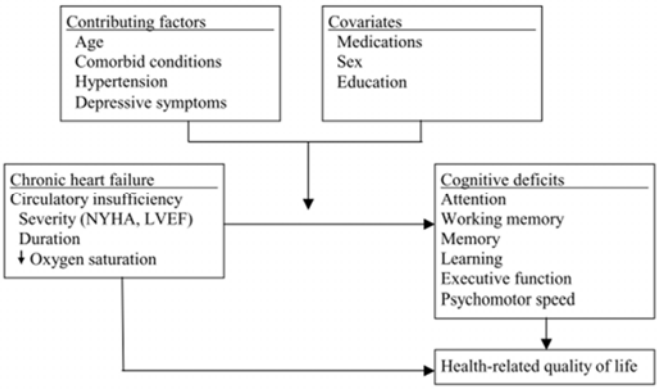

Figure 1. The Conceptual Model of Cognitive Deficits in Heart Failure

Individuals with HFpEF experience myriad abnormalities in cardiac structure and function which may promote circulatory insufficiency and contribute to reduced cerebral perfusion (26-30). These include abnormalities in diastolic function, systolic function, cardiac hemodynamics, and ventricular-vascular coupling (26, 28, 31-38). The associations between these abnormalities and CI have not been evaluated in a sample of individuals with HFpEF. Atrial fibrillation is also prevalent among individuals with HFpEF and may contribute to the

development of CI via either clinical or subclinical stroke (39-41), but the association between atrial fibrillation and CI has not been evaluated in a sample of individuals with HFpEF. It is likely that for both HFrEF and HFpEF that there are other mechanisms, distinct from impacts on flow-related cerebral perfusion or via stroke, by which CI might develop. Inflammatory changes, right-sided heart failure, and hypoxia may all contribute to CI in these populations, but these associations are beyond the scope of this study.

The purpose of this proposed secondary data analysis is to identify associations between CI and echocardiographic markers of diastolic dysfunction (LVMI, LAVI, E/A, E/E', DT), systolic dysfunction (left ventricular ejection fraction, longitudinal strain, radial strain, circumferential strain), cardiac hemodynamics (stroke volume index, cardiac index), and ventricular-vascular coupling (Ea/Ees) in a sample of individuals with HFpEF. The association between CI and atrial fibrillation in a sample of individuals with HFpEF will also be evaluated. At ARIC visit 5, participants at all 4 sites underwent echocardiographic analysis and completed extensive neurocognitive evaluation. For this reason, the data from ARIC visit 5 are ideal for evaluating these research questions.

5. Main Hypothesis/Study Questions:

1. How does the pattern of cognitive impairment (CI) differ among individuals with HFrEF, individuals with HFpEF, and individuals free of heart failure?
2. Are there associations between echocardiographic markers of diastolic dysfunction (LAVI, LVMI, E/A, E/E', DT) and CI in individuals with HFpEF?
3. Are there associations between echocardiographic markers of systolic dysfunction and cardiac hemodynamics (cardiac index, stroke volume index, radial/longitudinal/circumferential strain) and CI in individuals with HFpEF?
4. Are there associations between echocardiographic markers of ventricular/vascular coupling (Ea/Ees) and CI in individuals with HFpEF?
5. Are there associations between atrial fibrillation and CI in individuals with HFpEF?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

This will be a cross-sectional analysis of data from ARIC visit 5. Participants who completed in-person cognitive assessments at ARIC visit 5 will be included. Individuals with a history of stroke or dementia prior to ARIC visit 5 or who presented with stroke or dementia at ARIC visit 5 will be excluded, as these may influence cognitive function.

Independent variables of interest will include measures of diastolic dysfunction, systolic function, cardiac hemodynamics, and ventricular-vascular coupling. Measures of diastolic dysfunction include left ventricular mass index (LVMI), left atrial volume index (LAVI), the ratio of early diastolic trans-mitral filling velocity to the late diastolic trans-mitral filling velocity (E/A), the ratio of early diastolic trans-mitral filling velocity to early diastolic mitral annular tissue velocity (E/E'), and deceleration time (DT). Measures of systolic dysfunction and cardiac hemodynamics include stroke volume, cardiac index, and measures of ventricular strain. Ventricular-vascular coupling is measured by the ratio of arterial elastance to end-systolic elastance (Ea/Ees). Atrial fibrillation will also be included as an independent variable. Sociodemographic variables (age, race/ethnicity, sex, education, smoking history, field center), chronic comorbid illnesses (hypertension, diabetes, mellitus, chronic obstructive pulmonary

disease, anemia, depressive symptoms by CES-D score from ARIC/NCS visit 5), and medications known to influence cognitive function (antidepressants, ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics, digoxin) will be included as potential covariates. As the outcome of interest is cognitive function, the dependent variables include scores on neurocognitive tests that evaluate a wide range of cognitive domains (Delayed Word Recall Test, Logical Memory Test Part I and Part II, Incidental Learning Test, Digit Span Backwards Test, Digit Symbol Substitution Test, Trail Making Test Part A and B, Animal Naming Test, Boston Naming Test, Word Fluency Test) as well as change over time in scores and averaged global *Z*-score for the three cognitive measures that were administered at multiple visits prior to visit 5 (Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test). Standardized Z-scores will be used when appropriate and domain-specific scores as previously defined in ARIC will be examined.

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Analysis will be conducted using Stata version 14 or newer (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) under the guidance of a biostatistician associated with the Rory Meyers College of Nursing at New York University. To reduce the effect of missing data on the power of this study, multiple imputation using chained equations will be performed to replace missing independent variables.

To address the first research question, an initial analysis will compare cognitive performance among individuals with HFrEF, individuals with HFpEF, and individuals free of heart failure. An analysis of variance (ANOVA) will be generated to compare mean Z-scores on each of the tests in the neurocognitive battery. This will provide domain-specific information about how CI differs among individuals with HFpEF, individuals with HFrEF, and individuals free of heart failure.

As this study is designed to explore factors that may contribute to CI in HFpEF, subsequent analyses evaluating associations between echocardiographic measures and scores on neurocognitive tests will be conducted only on individuals with HFpEF. Descriptive statistics will be generated to evaluate the characteristics of the sample with HFpEF. Means, standard deviations, and confidence intervals will be reported for continuous variables. Frequencies and percentages will be reported for categorical variables.

Bivariate analysis will evaluate associations between the independent variables (demographic variables, chronic comorbid conditions, medication profile, and echocardiographic measures). Variables which demonstrate strong collinearity will be considered for removal from further analysis due to redundancy. Associations between independent variables and scores on the battery of neurocognitive tests will also be evaluated. Independent variables that demonstrate a significant association ($p<.10$) with any of the neurocognitive tests will be included in multivariate analysis.

Regression analysis will be conducted exclusively on the HFpEF sample to evaluate the associations outlined in research questions 2-5. Multiple linear regression analysis will be conducted to quantify the magnitude of the effect of the independent variables on scores on neurocognitive tests. A separate multivariate model will be generated for each neurocognitive test, but the set of predictors will be common in all multivariate models. Independent variables that demonstrate statistically significant associations ($p<.10$) with scores on any of the neurocognitive tests in bivariate analysis will be included in all multivariate models. All sociodemographic variables (age, sex, race/ethnicity, education, smoking history, field center) will also be included in all models. Groups of predictors will be introduced into multiple linear regression analysis in a hierarchical fashion with known predictors and potential covariates being

included in the initial models. Sociodemographic variables will be included in the initial model. Comorbid conditions will be included in the second model and medications will be added in the third model. Echocardiographic measures of diastolic function will be included in the fourth model to evaluate research question 2. Echocardiographic measures of systolic function and cardiac hemodynamics will be added in the fifth model to evaluate research question 3. Echocardiographic measures of ventricular-vascular coupling will be included in the sixth model to evaluate research question 4. Finally, atrial fibrillation will be included in the final model to evaluate research question 5. The unique contribution of each predictor on performance on the neurocognitive tests will be identified. Significant associations (p<.05) between predictors and scores on each neurocognitive test and the magnitude of these associations after controlling for covariates will be identified in the final models. As several neurocognitive tests evaluate the same cognitive domain, p-values will be adjusted using a Bonferroni correction to account for multiple comparisons. The R^2 will be noted for the initial model to determine the amount of variance in CI explained by demographics. The change in R^2 will be noted for each subsequent model to identify the amount of variance explained by the addition of the new variables. The assumptions of multiple linear regression will be evaluated in this analysis. Sensitivity analysis will also be conducted to determine if atrial fibrillation and the echocardiographic measures of cardiac function are associated with change in cognitive function over time. For these analyses, the outcome variables will be change in scores and averaged global *Z*-score on the three neurocognitive tests that were assessed multiple times prior to visit 5 (Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test).

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Finally, a logistic regression model will be generated to identify the associations between the predictors identified in multiple linear regression analysis and the odds of mild cognitive impairment (MCI) as determined by expert-adjudicated diagnosis. Predictors that demonstrate a significant (p<.05) effect on scores on neurocognitive tests will be included in the logistic regression model. The sociodemographic variables (age, sex, race/ethnicity, education, field center) will also be included. Hosmer-Lemeshow statistics will be evaluated to determine goodness of fit. Collinearity diagnostics will be examined to determine if there is substantial overlap among the predictors. Variables that demonstrate a high degree of collinearity will be evaluated for removal from the model. Potential outliers will be identified by generating and examining residuals and measures of leverage and influence. Cases with standardized residual values (ZRESID) above 2.5 or below -2.5 will be evaluated for removal from the analysis, as they may influence the regression estimates.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _XX_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _XX_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__XX__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#1701 - Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study. Lead author: Jan Bressler. One of the co-authors, Patricia Chang, is a member of the current writing group.

#2227 - Relationship of cardiac structure and function with cognitive performance: as study of the Atherosclerosis Risk in Communities (ARIC) study. Lead author: Pardeep Jhund.

#2384 - Cardiac and Brain Structure and Function Associations: The ARIC Study. Lead author: Rebecca Gottesman. Rebecca Gottesman is a member of this writing group.

#2546 - Association of Left Atrial Enlargement with Lower Cognitive Function and Subclinical Cerebral Infarcts: The ARIC Study. Lead author: Lin Y. Chen.

#2679 - Neurocognitive function and quality of life in heart failure: the ARIC study. Lead author: Lucy S. Witt. Lucy Witt and Patricia Chang (co-author) are members of the current writing group.

#2856 - Left Ventricular Hypertrophy and its Association with Cognitive Decline and Dementia Risk over 20 years: The ARIC Neurocognitive Study (ARIC-NCS). Lead author: Faye L. Norby.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _XX_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _XX_ No.

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