ARIC Manuscript Proposal # 1477r

	PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
I.	**SC Reviewed: _____**	**Status: _____**	**Priority: ____**

1.a. Full Title: Assessment of novel heart failure classification schema for hospitalized patients: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Novel HF classifications

2. Writing Group:

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

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3. Timeline:

Following approval of this manuscript by the ARIC Publications Committee this work can begin.

4. Rationale:

HF is a clinical syndrome, a result of complex pathological processes that culminate in the failure of the heart to circulate blood at normal pressure. The ACC/AHA advocate the use of pertinent symptoms and signs in the systematization of HF, plus objective response to treatment when in doubt[1]. As unrecognized ventricular dysfunction and HF are frequent among individuals with common conditions, many with manifestations such as chronic obstructive pulmonary disease (COPD), the signs and symptoms of HF although sensitive have low specificity [2]. This problem is accentuated due to their high prevalence in the elderly, the obese and in women[3]. There is some evidence of misdiagnosis of HF by physicians relative to objective criteria[4]. Furthermore, there is no standard definition of diastolic dysfunction, which is mostly a diagnosis of exclusion of systolic heart failure (ejection fraction >30%) in the presence of symptoms of cardiac congestion[5]. Importantly, population based studies have found that at least half of the individuals with LV dysfunction on echocardiography have never been diagnosed as having heart failure[6, 7].

There is manifest discordance in the classification of HF according to several available classification schema relative to physician-adjudicated classification[8], also illustrated on ARIC data by yet unpublished results from ARIC ms. #1331. ARIC's surveillance of hospitalized HF collects information sufficient to classify putative HF events as HF present vs. absent according to somewhat divergent criteria, namely Framingham, modified Boston and NHANES. This is accomplished by a combination of computer aided classification and a review by a panel of qualified physicians. The latter define the presence or absence of HF according to a fourth set of criteria, namely ARIC's unpublished classification criteria that in addition to specifying whether a hospitalized event qualifies as HF, also assigns the rubrics of (a) definite decompensated heart failure, (b) possible decompensated heart failure, (c) chronic stable heart failure, (d) heart failure unlikely and (e) unclassifiable, based on the reviewer's "clinical judgment" for which they consider all the data abstracted from the medical records.

In contrast, none of the other criteria used by ARIC speaks to the acute/decompensated vs. chronic nature of the HF event, and none considers contemporaneous diagnostic tools such as echocardiograms or biomarkers as criteria elements. As a result, although the Framingham, modified Boston and NHANES are established and widely used classification schema, their relevance to contemporary classifications of HF events may be in question, and their continued relevance as metrics in the taxonomy of HF is of concern to any study that aims to quantify the population burden of HF from this point forward.

Two relatively recent developments deserve attention in the efforts by ARIC to classify HF in its cohort and in community surveillance, a revision of the Framingham criteria that incorporates biomarkers and ehocardiographic information and the publication of a synthesis of HF classification criteria used in clinical trials.

A revised but unpublished version of the classic Framingham criteria is being used by Framingham investigators (and others). Its configuration follows the logic of the original Framingham criteria for classification of HF and introduces LVEF, diastolic dysfunction and BNP levels as additional criterion elements. Although this classification schema is unpublished it is gaining attention and its properties should be tested empirically by ARIC.

In December 2005 a group of cardiovascular clinical trialists, biostatisticians, National Institutes of Health (NIH) scientists, regulators, and pharmaceutical industry scientists published their suggestions for a definition for heart failure for use in observational studies and clinical trials[9]. In addition to signs, symptoms, therapy and response to therapy the proposed systematization relies extensively on biomarker and echocardiographic information, and emphasizes the distinction between diagnoses of new onset HF, new events of HF, and HF events in a patient with known HF. The publication suggests classification threshold values for biomarkers and echocardiographic parameters, but does not specify the criteria by which these threshold levels were chosen. It also recommends the use of its classification scheme but it does not provide operational criteria that would enable its standardized implementation. The breadth of expertise reflected in the recommendations published by Zannad et al. and the notoriety achieved by these "criteria" recommend their systematic exploration by the ARIC study and their test on ARIC's unique abstracted and adjudicated HF data to examine the concordance of five sets of criteria that have greatest contemporary relevance in the classification of HF: Zannad's emerging trialists' criteria, ARIC's unpublished HF classification criteria, Framingham, modified Boston and NHANES. Because of their potential relevance to HF in the outpatient setting the Gothenburg criteria will also be considered. See Appendix I

It should be noted that the HF trialists' criteria as published by Zannad and collaborators are not yet suitable for implementation. As mentioned above, a detailed logic algorithm or specifics that

would allow for a version in programming language appear to be lacking from the materials published by Zannad et al.[9] Preparation of such algorithms is one of the goals of this proposal and would consider circumstances such as incomplete or missing data, which are not spelled out in these (nor other) published classification criteria.

Additional considerations argue for the work proposed here. ARIC should also consider the asymmetry built into the criteria it currently employs to classify the presumed HF events it samples as part of HF surveillance. As mentioned above, the three "classic" HF criteria used by ARIC do not discriminate between acute vs. chronic HF and they fail to consider echocardiographic and biomarker information. While the former ("classic") criteria can provide historical continuity in HF classification and to some degree comparability to other studies relative to the unchartered and unpublished "ARIC criteria" of HF, the current practice of conditioning the set of events to be reviewed by the HF MMCC according to agreement on the three "classic" criteria establishes a hybrid system that may not serve the ARIC study well. Since the Framingham, Boston, and NHANES classification schema use criteria elements different from ARIC's classification, a significant proportion of putative HF events in ARIC's Community Surveillance are not classified by the ARIC criteria. Adding complexity, this gating process is not driven by one criterion but by a less transparent agreement on three criteria. As a consequence of the current adjudication-reduction approach the HF events selected to bypass a classification that takes in to account the abstracted biomarkers and echocardiographic information are those at the extremes of an unknown classification continuum, namely the ones considered as HF present or absent by each of the Framingham, Boston, and NHANES criteria. Thus in ARIC Community Surveillance, neither the biomarker nor the echocardiographic information abstracted at significant effort and expense are considered in the classification of these putative events.

Beyond the interest that this work holds for ARIC's surveillance procedures, an assessment of the proposed trialists HF classification criteria and their concordance with the other HF classification criteria based on ARIC's unique HF surveillance data for calendar years 2005 and 2006, is of considerable interest to the field. This ms. proposal provides a framework to compare the concordance of these HF classification schema, as stated below.

5. Main Hypothesis/Study Questions:

The study questions apply to the following (7) HF classification schema: Framingham, Modified Framingham (unpublished), Modified Boston, NHANES, ARIC, HF Trialists, and Gothenburg.

a. Estimate the agreement between a working version of the trialists criteria and the remaining HF classification schema listed above on 2005-2006 HF Surveillance data in ARIC.
b. Estimate the agreement between the revised Framingham criteria and the remaining HF classification schema listed above on 2005-2006 HF Surveillance data in ARIC.
c. Examine the agreement of a simple classification algorithm that includes hospital discharge (ICD) codes, BNP, ejection fraction, signs/symptoms and diuretic use with each of the above 6 classification schema.

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).

The analysis set is restricted to the 2005-2006 HF Cohort and Community Surveillance data in ARIC; cohort members will not be identified nor analyzed separately. The analyses will include

agreement “rates” and estimates of sensitivity, specificity, PV+ and PV- (as routinely used in the analyses of these data by ARIC).

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

8.a. Will the DNA data be used in this manuscript? 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

____X__ 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)?

Ms#1331 Comparison of Hospitalized Heart Failure Diagnostic Criteria

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ 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/

12. 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.

So noted.

1. Hunt, S.A., et al., *ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society.* Circulation, 2005. **112**(12): p. e154-235.
2. Rutten, F.H., et al., *Heart failure and chronic obstructive pulmonary disease: An ignored combination?* Eur J Heart Fail, 2006. **8**(7): p. 706-11.

3. Dahlstrom, U., *Frequent non-cardiac comorbidities in patients with chronic heart failure.* Eur J Heart Fail, 2005. **7**(3): p. 309-16.
4. Remes, J., et al., *Validity of clinical diagnosis of heart failure in primary health care.* Eur Heart J, 1991. **12**(3): p. 315-21.
5. Vasan, R.S. and D. Levy, *Defining diastolic heart failure: a call for standardized diagnostic criteria.* Circulation, 2000. **101**(17): p. 2118-21.
6. McDonagh, T.A., et al., *Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population.* Lancet, 1997. **350**(9081): p. 829-33.
7. Mosterd, A., et al., *Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study.* Eur Heart J, 1999. **20**(6): p. 447-55.
8. Mosterd, A., et al., *Classification of heart failure in population based research: an assessment of six heart failure scores.* Eur J Epidemiol, 1997. **13**(5): p. 491-502.
9. Zannad, F., et al., *Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition.* Eur Heart J, 2008. **29**(3): p. 413-21.

Appendix

Variables required to define HF diagnosis/event using Zannad et al[1]

Variable group	Number	Variable Name
A	1	History of heart failure
B	1	Shortness of breath/Dyspnea on exertion
B	2	Paroxysmal nocturnal dyspnoea
B	3	Orthopnea
B	4	Fatigue
B	5	Reduced exercise tolerance
B	6	Pulmonary edema
B	7	Jugular venous distension
B	8	Rales
B	9	S3 heart sounds
B	10	Hepato-jugular reflux
B	11	Altered hemodynamics
B	12	Peripheral edema
B	13	Cardiomegaly
C	1	Loop diuretics (lasix)
C	2	ACE inhibitor/ ARB
C	3	B-blockers
C	4	History of hypertension
D	1	BNP levels (pg/mL)*
D	2	NT-pro BNP (ng/L) *
D	3	Age
D	4	Left ventricular ejection fraction*
D	5	Diastolic dysfunction**
D	6	LV mass (linear method)*
D	7	LV mass (2D method) *
D	8	E/A*
D	9	Mitral (E wave) deceleration time*
E	1	Death
E	2	Acute coronary syndrome
E	3	Pulmonary embolism

* It is emphasized that BNP and ECHO should be analyzed by a core laboratory whenever feasible, particularly if the study endpoints are related to BNP or ECHO parameters. An ECHO core laboratory may be more important than a core laboratory for BNP due to the variation associated with ECHO interpretation. Ideally, core lab measurements for BNP and ECHO would be obtained on all patients. If not possible, random ECHO quality checks and central readings should be obtained in a subset of patients and/or centers.

** Though there is no cardiologist diagnosed diastolic dysfunction variable in Zannad et al, it may be used if available.

Variable name	Classification per Zannad et al[1]	Diagram number
BNP	≥400	BNP1
BNP	≥100 to <400	BNP2
NT-proBNP	≥450 (age <50y), or ≥900 (age 50y to <75y), or ≥1800 (age >75y)	NT-proBNP1
NT- proBNP	Elevated* but lower than above age specific threshold defined above (NT-proBNP1)	NT-proBNP2
Diastolic dysfunction	LV mass >95g/m2 (linear method) Female, or LV mass >88 g/m2 (2D method) Female, or LV mass >115 g/m2 (linear method) Male, or LV mass >102 g/m2 (2D method) Male	DD1
Diastolic dysfunction	E/A >1	DD2
Diastolic dysfunction	mitral (E wave) deceleration time <200 ms	DD3
Systolic dysfunction	Left ventricular ejection fraction <40%	LVEF1
Death	During HF hospitalization with pump failure, or During HF hospitalization without ACS, or pulmonary emboli	Death1

* A precise definition of elevated is not given in Zannad et al. As there are age, gender, BMI, and renal disease dependencies the impact on classification of values (say) >100 and below the threshold levels of NT-proBNP1 should be assessed…

Heart failure classification recommended by Zannad et al.

Case/Event definition	Criteria
New onset HF diagnosis	A1 = 0 AND [(B = 1 and (C1=1 or C2=1 or(C3=1 and C4=0)))] AND [(BNP = 1 or NT-proBNP1 = 1) OR LVEF1=1 OR ((BNP2=1 or or NT-proBNP2 = 1) and (LVEF1=1 or DD1=1 or DD2 = 1 or DD3 = 1))]
New HF event	A1 = 0 **AND** {Death1 = 1 **OR** {(Sum (B1-B13)≥ 2 AND C1=1*) **AND** [(BNP = 1 or NT-proBNP1 = 1) OR LVEF1=1 OR ((BNP2=1 or or NT-proBNP2 = 1) and (LVEF1=1 or DD1=1 or DD2 = 1 or DD3 = 1))]}}
HF event	A1 = 1 **AND** {Death1 = 1 **OR** {(Sum (B1-B13)≥ 2 AND C1=1*)

* or use of vaso-active drug for symptoms, which is difficult to define in ARIC Surveillance and thus not included at this point.

1. Zannad, F., et al., *Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition.* Eur Heart J, 2008. **29**(3): p. 413-21.

ARIC Surveillance Variables to be used

Zannad		HFAB form	Variable Name
A	1	7.a/b/c	History of HF
B	1	23.d	Shortness of breath, Dyspnea on exertion
B	2	23.h	Paroxysmal nocturnal dyspnoea
B	3	23.i	Orthopnea (breathing problems lying down LV)
B	4		Fatigue
B	5	22.e	Reduced exercise tolerance
B	6	28.b/c	Pulmonary edema
B	7	22.b	Jugular venous distension
B	8	23j/k	Rales
B	9	24.a	S3
B	10	22c	Hepato-jugular reflux
B	11	22.d	Altered hemodynamics
B	12	22.a	Peripheral edema (lower extremity)
B	13	28.d	Cardiomegaly (enlarged heart)
C	1	68	Loop diuretics (lasix)
C	2	59	ACE inhibitor/ARB
C	3	65	B-blockers
C	4	63	History of hypertension
C	5	73.a/b	IV vasoactive agents
D	1	39a	BNP levels(pg/mL)
D	2	40a	NT-pro BNP(ng/L)
D	3	0.c - DOB	age
D	4	29/30/32 .b 33/34/35/36 .b	Left ventricular ejection fraction
D	5	29.d.14 29.c.1	diastolic dysfunction
D	6		LV mass(linear method)
D	7		LV mass(2D method)
D	8		E/A
D	9		Mitral (E wave) deceleration time
E	1	0.d/f	Death
E	2		Acute coronary syndrome
E	3		Pulmonary embolism