Studies Using Large Datasets:
How to obtain the data and use them well

Meredith A. Brisco-Bacik, MD, MSCE

Assistant Professor of Medicine, Cardiology
Director HF Clinical Research
Advanced Heart Failure and Cardiac Transplantation
DOM Research Curriculum

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Outline

1) Why should I use data that already exist?
2) What are the types of data sources out there?
3) Discussions of data I have personally used and analyzed (NIH BioLINCC, National Data/Registries, Clinical Trial Data)
    - How to choose an appropriate research project or question
    - How to obtain the data
    - What to expect following data access through publication of results
4) Conclusions/Questions

1. Why should I use data that already exist?

TIME:
As residents you don't have much of it, prospective work can take years and and you should be focusing on your training

MONEY:
Clinical research is expensive as is statistical support

SAMPLE SIZE:
Temple may not have enough patients with condition "X" for extensive analyses

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1. Are there disadvantages to using data that already exist?

- If the data were not designed to answer your specific question, your results are likely to be "hypothesis-generating"
- A specific variable may not be captured in the manner you require
  - Ex. You are interested in renal dysfunction after transplant. You need creatinine to calculate eGFR but only variable recorded is Cr>2.0, yes/no
- The data collection is finished. Missing data are often an issue and you cannot "go back"
- The more people who have access, the greater likelihood someone else may "scoop" you

2. What types of data are available?

NIH Data and Specimens:
To "increase the return from NIH outcomes and population research"
Publicly available specimens and data from studies and trials

Claims Data - National Inpatient Sample:
https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp
Largest all-payer inpatient care database in the US. 7 million hospital stays. Costs about $650

Claims Data – CMS:
https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles.html
Medicare baseline data and follow up data. Costs about $250 per file per year

National Data around a Procedure or Condition:
https://www.sts.org/registries-research-center/sts-research-center/access-publications
https://optn.transplant.hrsa.gov/data/request-data/
https://www.ishlt.org/registries/international-registry-for-mechanically-assisted-c
These data are available. Some are free, some cost money, some require an official application with a project idea. Highly variable

Sponsored Clinical Trial Data for Secondary Analyses:
Clinical trials are expensive, so many trials have publication committees and applications for secondary analyses. Here you DON'T often get raw data

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3. Data that I have used and published

1) An overview of the data source
2) How to formulate an appropriate research question for the particular data source
3) How to obtain the data, what is involved, application etc.
4) My own personal example and potential impact of using the described dataset

Caveat: These are my own personal experiences and words of advice
This is in no way a comprehensive assessment of all that is possible
The data I chose to work with were appropriate for my research interests and may not be appropriate for yours

NIH/NHLBI:BioLINCC-Overview of data

BioLINCC
Biologic Specimen and Data Repository Information Coordinating Center

The BioLINCC Handbook

A Guide to the NHLBI Biologic Specimen and Data Repositories

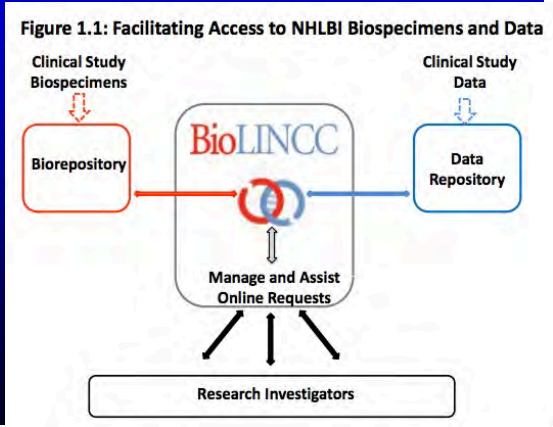
https://biolincc.nhlbi.nih.gov

NIH National Heart, Lung, and Blood Institute

https://biolincc.nhlbi.nih.gov/studies/

BioLINCC_Handbook_V3.5_20170510

- NHLBI has a policy for data sharing of funded studies that are large or expensive
- Data must be shared 3 years after the end of the study or 2 years after the main trial paper has been published
- Data is submitted to the program official and then deidentified
- Data often includes baseline data, visits, outcomes data and laboratory information
- Some studies also have biospecimens



NIH/NHLBI:BioLINCC-Research Question

- Know the data and what has been published
- Look at the study info on the BioLINCC website

1. Relief and Recurrence of Congestion During and After Hospitalization for Acute **Heart Failure**: Insights From **Diuretic Optimization** Strategy Evaluation in Acute Decompensated **Heart Failure** (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated **Heart Failure** (CARESS-HF).
   Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, DeVore AD, Khazanie P, Redfield MM, Goldsmith SR, Bart BA, Anstrom KJ, Felker GM, Hernandez AF, Stevenson LW.

10. Effect of admission oral **diuretic** dose on response to continuous versus bolus intravenous **diuretics** in acute **heart failure**: an analysis from **diuretic optimization** strategies in acute **heart failure**.
    Shah RV, McNulty S, O'Connor CM, Felker GM, Braunwald E, Givertz MM.
    Am **Heart** J. 2012 Dec;164(6):862-8. doi: 10.1016/j.ahj.2012.08.019. Epub 2012 Oct 29.
    PMID: 23194486 **Free PMC Article**

Heart Failure Network (HFN) Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF)

Request Data

Study Type	Collection Type	Study Period
Clinical Trial	Open BioLINCC Study *See bottom of this webpage for request information*	February 2008 – February 2010
NHLBI Division	**Date Prepared**	**Last Updated**
DCVS	April 24, 2014	April 24, 2014
Clinical Trial URLs	**Primary Publication URLs**	**Study Website**
https://clinicaltrials.gov/ct2/s...	https://www.ncbi.nlm.nih.gov/pub...	https://www.hfnetwork.org/

Resources Available
Study Datasets Only

Study Publications (7)

Study Documents
- Data Dictionary (PDF - 244.3 KB)
- Forms (PDF - 5.0 MB)
- Protocol (PDF - 902.3 KB)

Persons using assistive technology may not be able to fully access information in the study documents. For assistance, Contact BioLINCC and include the web address and/or publication title in your message. If you need help accessing information in different file formats such as PDF, XLS, DOC, see Instructions for Downloading Viewers and Players.

Consent

Commercial Use Data Restrictions No

Data Restrictions Based On Area Of Research No

Objectives

The DOSE study sought to evaluate the most effective dosing (high vs. low) and administration (continuous infusion vs. intermittent boluses) combination of the diuretic Furosemide in the treatment of patients with acute decompensated heart failure.

- Examine the data dictionaries
- Examine the protocol
- Formulate your research question

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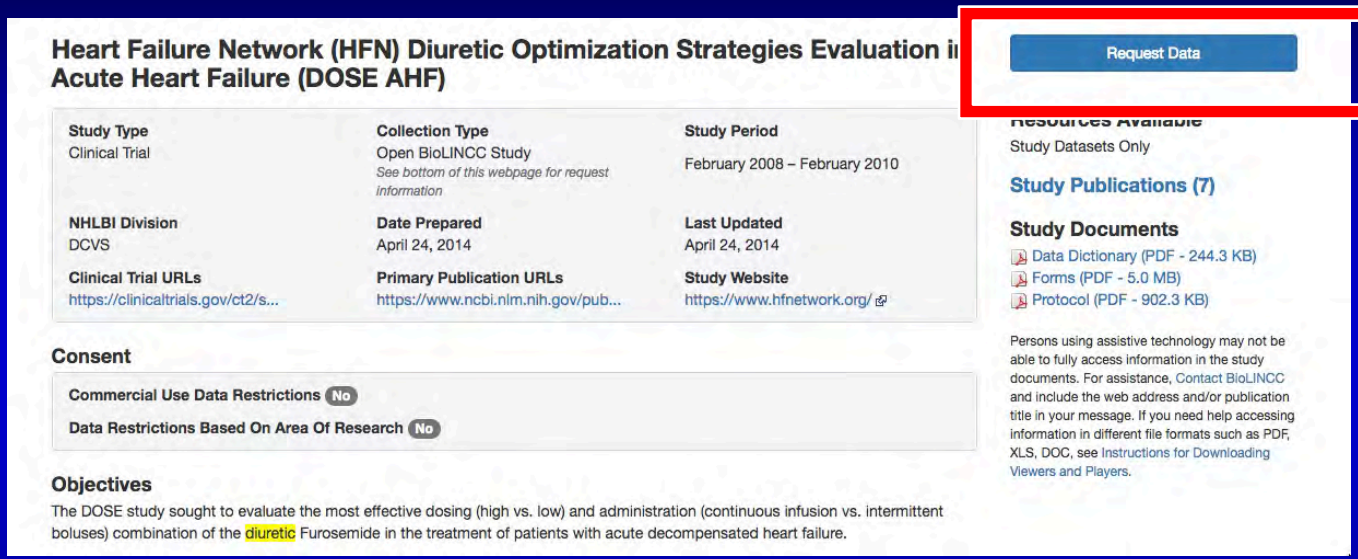
NIH/NHLBI: How to get the data



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https://clinicaltrials.gov/ct2/s...	https://www.ncbi.nlm.nih.gov/pub...	https://www.hfnetwork.org/

Consent

Commercial Use Data Restrictions: No

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- You must create a profile and account with BioLINCC
- If you press the request data button, it will prompt you, but you can also request multiple datasets

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NIH/NHLBI: How to get the data

Request Identifier

Request Name*

Temple Cardiorenal Request

Create a nickname for your reference.

Requestor Information

Name*

Meredith A. Brisco-Bacik

Title

Assistant Professor of Medicine

Institution*

Temple University School of Medicine

Email*

meredith.brisco@tuhs.temple.edu

Department

Medicine/Cardiology

Address*

3500 N. Broad Street MERB 1057 Philadelphia PA 19140 USA

Phone

215-910-2750

Fax

Website

Support Information

Institution type*

- Non-Profit Organization
- Commercial Organization
- Academic

Number of years in scientific research

- 0-5
- 5-10
- 10+

Approximately how many years has the lead investigator been involved in scientific research?

Is funding currently available for this research?*

- Yes
- No

Primary Funding Source for this Research*

Institutional/Departmental

If funding is not yet available, please indicate anticipated primary funding source.

Extramural Award Type

Other Funding Type / Other Extramural Award Type

NIH FOA #

Other Funding Comments

Request Details

Study*

(BEST) Beta-Blocker Evaluation in Survival Trial (BEST)
(DIG) Digitalis Investigation Group (DIG)
(ESCAPE) Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE)
(HFN-CARRESS) Heart Failure Network (HFN) CARdiorenal REScue Study in Acute Decompensated Heart Failure (CARRESS)
(HFN-DOSE AHF) Heart Failure Network (HFN) Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF)

Resources from multiple studies may be requested via one request form using the above drop down menu.

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NIH/NHLBI: How to get the data

Describe this request*

In collaboration with Dr. Jeffrey Testani, I have worked extensively with NHLBI limited datasets both at UPENN and the Medical University of South Carolina. I recently took a new faculty position at Temple University and I would like to obtain access to these datasets in order to continue my cardiorenal research

A brief overview of your research needs.

Design and analysis plan*

Studies will focus on studying cardiorenal interactions including predictors of cardiorenal dysfunction, differentiation of the cardiorenal syndrome and effect modifiers of cardiorenal interactions and their relationship with mortality.

Include the participant inclusion/exclusion criteria, expected study visit periods, key analytic variables, primary and secondary outcome measure, follow-up period (if applicable), and intended statistical methods. Inadequately described requests may be deferred until a complete description is included.

Will the results be used for a commercial purpose?*

- Yes
- No - the results will not be used for a commercial purpose.

A "Yes" response defines this as a "Commercial Purpose" request.

Information Security: Please check the information security practices to be used*

- Institute supported, controlled access server
- Institute supported, password protected desktop computer
- Encrypted, password protected laptop computer
- Encrypted portable media (encrypted external hard drive, encrypted thumb drive)
- Unencrypted portable media backup (CD, DVD, thumb drive) stored in locked file cabinet
- Private (institutional) or commercial encrypted cloud

Study data must be maintained in a secure and controlled environment

"Cardiorenal Investigations in Publicly Available Datasets"
PI: Meredith A. Brisco-Bacik, MD MSCE

Objective: The overall objective of this research plan is to better define cardiorenal phenotypes and their prognostic importance in heart failure (HF).

Background: Renal dysfunction is common in heart failure and identifies high-risk patients. However, multiple different mechanisms capable of initiating a reduction in glomerular filtration rate (GFR) exist in heart failure. For example, renal dysfunction can result from neurohormonal activation and venous congestion secondary to the heart failure itself. Alternatively, comorbid conditions like diabetes and hypertension, which are highly prevalent in heart failure, can also decrease GFR. Although the primary mechanisms underlying HF-induced renal dysfunction (the cardiorenal syndrome) vs. co-incident primary renal dysfunction differ, the reduction in GFR can be identical and indistinguishable. Differentiation of these different causes of renal dysfunction could alter therapeutic strategies. Unfortunately, no methodology currently exists to distinguish cardiorenal syndrome from primary renal dysfunction unrelated to the heart failure itself. The requested clinical trials contain measures of renal dysfunction, neurohormonal activation, venous congestion as well as detailed clinical outcomes, including mortality. They therefore provide the pertinent information required to complete the objective of this proposal.

Analysis plan:
Although the exposures and outcomes examined will differ depending on which clinical trial dataset is used, in general, we will focus on the following exposures and outcomes of interest:

Exposures: Blood urea nitrogen to creatinine ratio, diuretic efficiency, diuretic dose, proteinuria, change in proteinuria, hepatic congestion, hemoconcentration, timing of hemoconcentration, neurohormones, GFR and renal dysfunction
Outcomes: Mortality (all-cause), CV mortality, hospitalization for heart failure, worsening in renal function, improvement in renal function
Covariates: Demographics, medications, physical exam, laboratory data, invasive hemodynamics when available, imaging (ejection fraction on echocardiography) etc.

Statistical Analysis (depending on the outcome): Descriptive statistics, Student's t-test, Mann-Whitney U test, chi-square, correlation coefficients, logistic regression, linear regression, Cox-proportional hazards survival analysis

You upload this in addition

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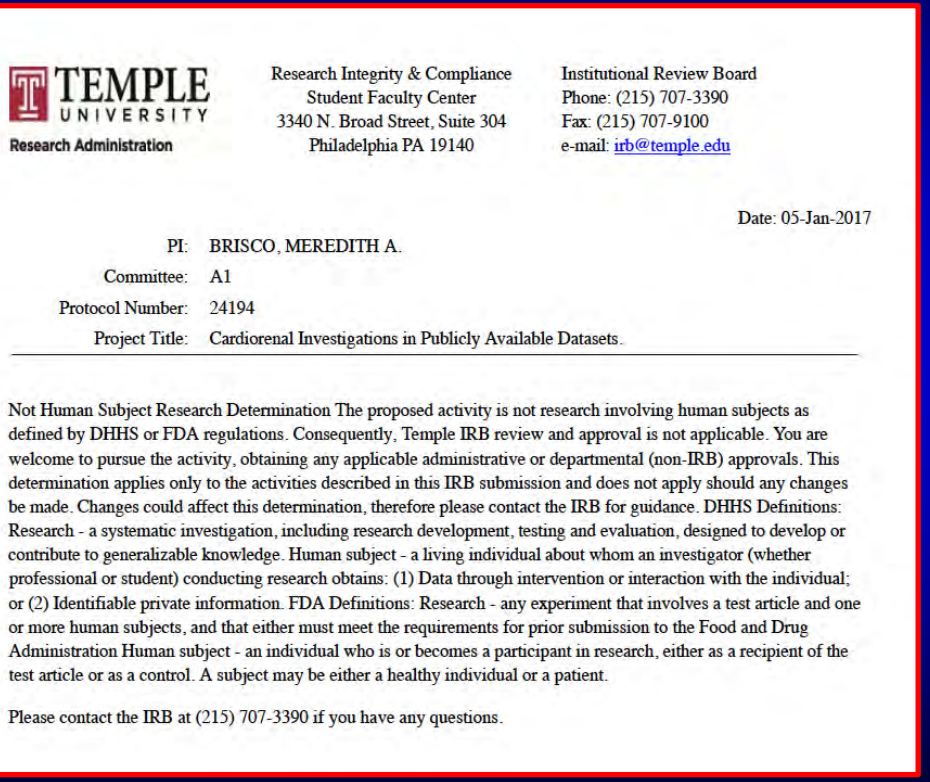
NIH/NHLBI: IRB approval

- You need to obtain IRB approval
- As data is already de-identified BY THE NIH, this research is exempt or not even "research"
- STILL, you need a letter from our IRB stating such to upload to the NIH
- Call our IRB to expedite



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Research Administration

Research Integrity & Compliance
Student Faculty Center
3340 N. Broad Street, Suite 304
Philadelphia PA 19140

Institutional Review Board
Phone: (215) 707-3390
Fax: (215) 707-9100
e-mail: irb@temple.edu

Date: 05-Jan-2017

PI: BRISCO, MEREDITH A.
Committee: A1
Protocol Number: 24194
Project Title: Cardiorenal Investigations in Publicly Available Datasets.

Not Human Subject Research Determination The proposed activity is not research involving human subjects as defined by DHHS or FDA regulations. Consequently, Temple IRB review and approval is not applicable. You are welcome to pursue the activity, obtaining any applicable administrative or departmental (non-IRB) approvals. This determination applies only to the activities described in this IRB submission and does not apply should any changes be made. Changes could affect this determination, therefore please contact the IRB for guidance. DHHS Definitions: Research - a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Human subject - a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual; or (2) Identifiable private information. FDA Definitions: Research - any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration Human subject - an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

Please contact the IRB at (215) 707-3390 if you have any questions.

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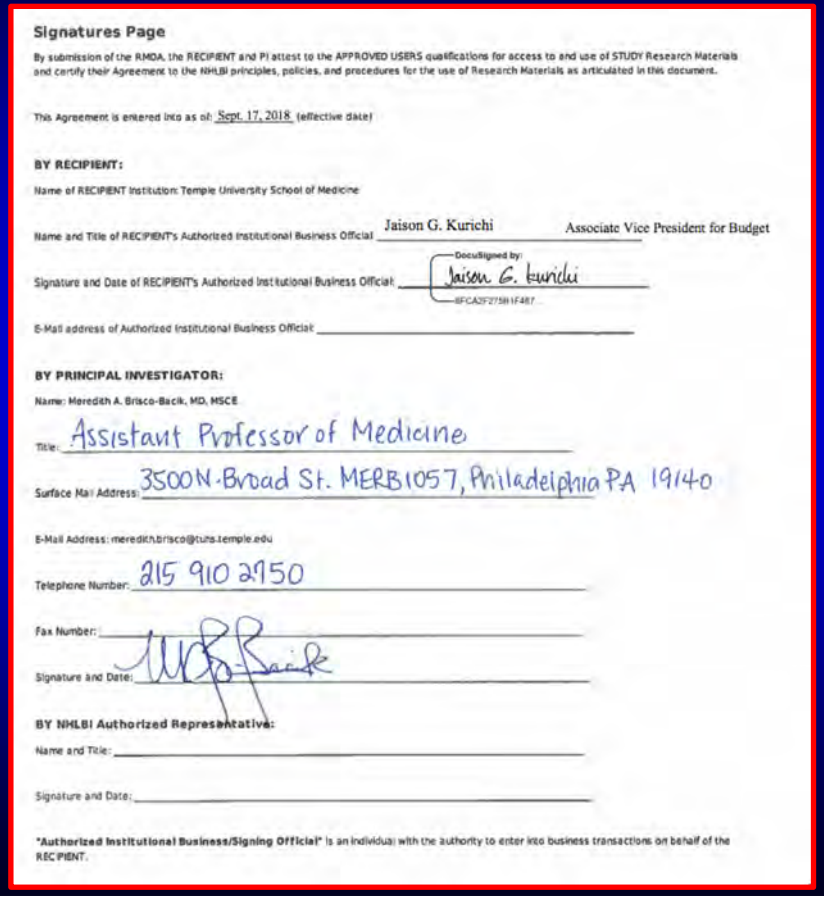
BioLINCC: Get the RMDA signed



Signatures Page

By submission of the RMDA, the RECIPIENT and PI attest to the APPROVED USERS qualifications for access to and use of STUDY Research Materials and certify their Agreement to the NHLBI principles, policies, and procedures for the use of Research Materials as articulated in this document.

This Agreement is entered into as of: Sept. 17, 2018 (effective date)

BY RECIPIENT:

Name of RECIPIENT Institution: Temple University School of Medicine

Name and Title of RECIPIENT's Authorized Institutional Business Official: Jaison G. Kurichi Associate Vice President for Budget

Signature and Date of RECIPIENT's Authorized Institutional Business Official: DocuSigned by: Jaison G. Kurichi

E-Mail address of Authorized Institutional Business Official:

BY PRINCIPAL INVESTIGATOR:

Name: Meredith A. Brisco-Bacik, MD, MSCE

Title: Assistant Professor of Medicine

Surface Mail Address: 3500 N. Broad St. MERB 1057, Philadelphia PA 19140

E-Mail Address: meredith.brisco@tuhs.temple.edu

Telephone Number: 215 910 2750

Fax Number:

Signature and Date:

BY NHLBI Authorized Representative:

Name and Title:

Signature and Date:

"Authorized Institutional Business/Signing Official" is an individual with the authority to enter into business transactions on behalf of the RECIPIENT.

- The RMDA is a Research Materials Distribution Agreement generated on the website
- It must be signed by the business official here at Temple
- You upload this to the site and often this is the rate-limiting step

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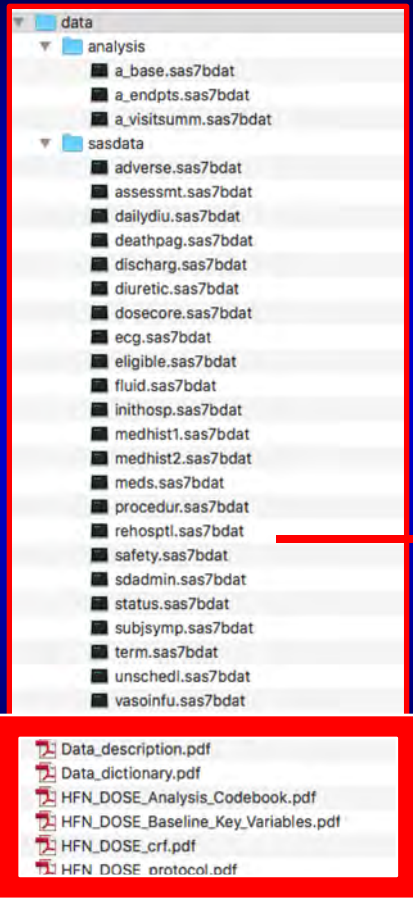
BioLINCC: From Data download to publication



Request Status	Requestor (Institution)	Currently Requested Studies	Assigned To
Fulfilled	Meredith A. Brisco-Bacik (Temple University School of Medicine)	BEST , DIG , ESCAPE , HFN-CARRESS , HFN-DOSE AHF , HFN-ROSE , PEACE , SCD-HeFT , SOLVD	BioLINCC and Requestor

Date Requested	Last Modified	Related Requests
March 01, 2018	September 24, 2018	N/A

Dataset Download Links

Studies of Left Ventricular Dysfunction (SOLVD) default (ZIP - 53.6 MB)
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) default (ZIP - 25.3 MB)
Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy (PEACE) default (ZIP - 3.9 MB)
Heart Failure Network (HFN) Renal Optimization Strategies Evaluation in Acute Heart Failure and Reliable Evaluation of Dyspnea (ROSE) default (ZIP - 9.8 MB)
Heart Failure Network (HFN) Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE AHF) default (ZIP - 5.8 MB)
Heart Failure Network (HFN) CARdiorenal REScue Study in Acute Decompensated Heart Failure (CARRESS) default (ZIP - 9.3 MB)
Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) default (ZIP - 23.1 MB)
Digitalis Investigation Group (DIG) default (ZIP - 10.7 MB)
Beta-Blocker Evaluation in Survival Trial (BEST) default (ZIP - 13.1 MB)

Actual Data Files:

These are SAS data files. If you don't work in SAS you will need to download and convert the data to SPSS or STATA.
https://stattransfer.com/overview/

Data Dictionary Etc:

These files explain your data, the variables etc.
You will want to READ these carefully as you explore the data

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NOW WHAT?

Learn your data

Perform your analyses

Write your manuscript

Important Notes: Once you have the data, you are on your own
You do not need permission to submit a manuscript or abstract
No one from the NIH is checking your results

Clinical Investigation

Relevance of Changes in Serum Creatinine During a Heart Failure Trial of Decongestive Strategies: Insights From the DOSE Trial

MEREDITH A. BRISCO, MD, MSCE,[1] MICHAEL R. ZILE, MD,[2] JENNIFER S. HANBERG, BA,[3] F. PERRY WILSON, MD, MSCE,[3,4] CHIRAG R. PARIKH, MD, PhD,[3,4] STEVEN G. COCA, DO, MS,[5] W.H. WILSON TANG, MD,[6] AND JEFFREY M. TESTANI, MD, MTR[3,4]

Philadelphia, Pennsylvania; Charleston, South Carolina; New Haven, Connecticut; New York, New York; and Cleveland, Ohio

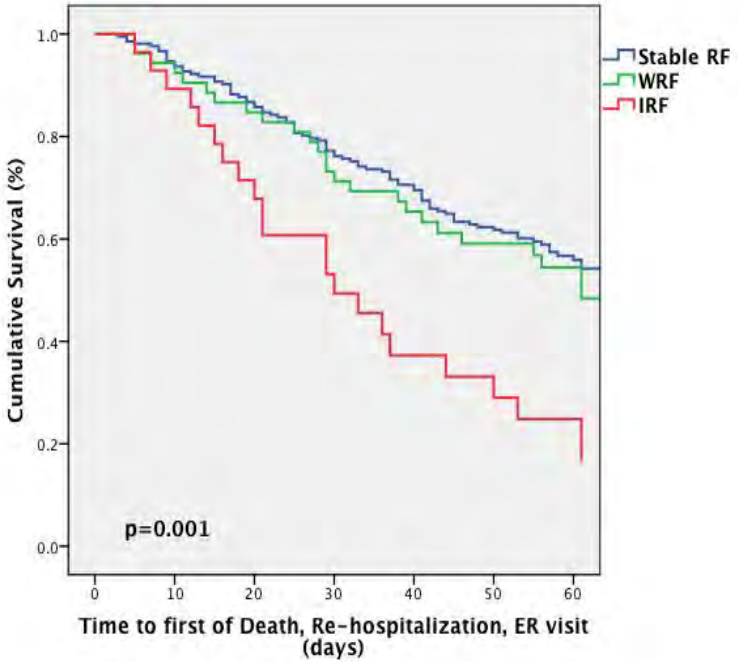
Editorial

Surrogate Endpoints: Not the Real Thing

STEPHEN S. GOTTLIEB, MD

Baltimore, Maryland

- 301 patients with 2 or more serum Cr available
- WRF and IRF defined using 0.3 mg/dl change
- 18% experienced WRF and 9.1% experienced IRF at 72 hours
- Over 60 days of follow up, 139 patients (45%) had composite outcome of death, rehospitalization or ER visit



Increasing creatinine = Better Outcomes
HR=0.81 per 0.3 mg/dl *increase*, p=0.026

Brisco et al *J Card Fail* 2016;10:753-60.

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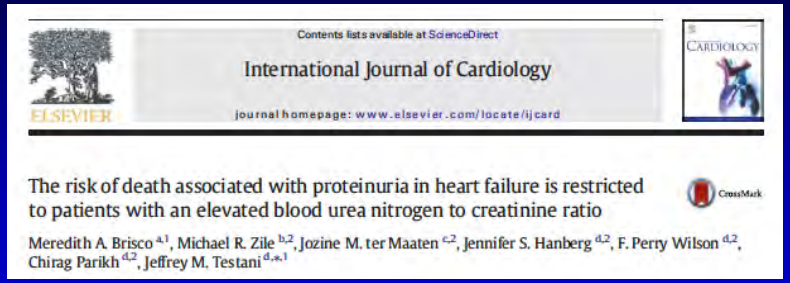
What are some other examples of impact?



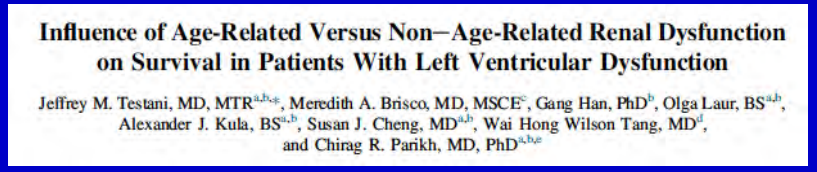
Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The risk of death associated with proteinuria in heart failure is restricted to patients with an elevated blood urea nitrogen to creatinine ratio

Meredith A. Brisco [a,1], Michael R. Zile [b,2], Jozine M. ter Maaten [c,2], Jennifer S. Hanberg [d,2], F. Perry Wilson [d,2], Chirag Parikh [d,2], Jeffrey M. Testani [d,*,1]



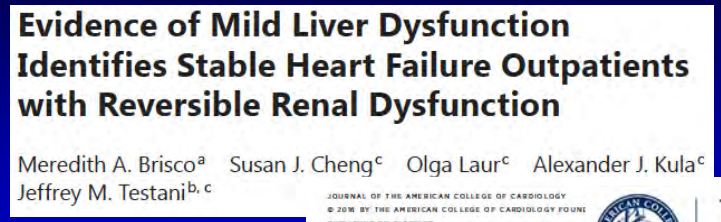
Influence of Age-Related Versus Non–Age-Related Renal Dysfunction on Survival in Patients With Left Ventricular Dysfunction

Jeffrey M. Testani, MD, MTR[a,b,*], Meredith A. Brisco, MD, MSCE[c], Gang Han, PhD[b], Olga Laur, BS[a,b], Alexander J. Kula, BS[a,b], Susan J. Cheng, MD[a,b], Wai Hong Wilson Tang, MD[d], and Chirag R. Parikh, MD, PhD[a,b,e]

Circulation

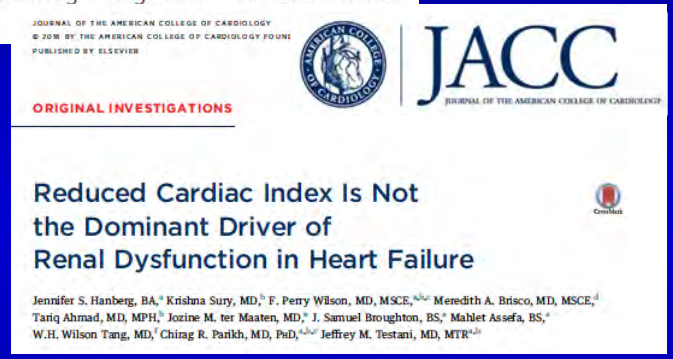
ORIGINAL RESEARCH ARTICLE

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury



Evidence of Mild Liver Dysfunction Identifies Stable Heart Failure Outpatients with Reversible Renal Dysfunction

Meredith A. Brisco[a] Susan J. Cheng[c] Olga Laur[c] Alexander J. Kula[c] Jeffrey M. Testani[b, c]



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PUBLISHED BY ELSEVIER

JACC

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

ORIGINAL INVESTIGATIONS

Reduced Cardiac Index Is Not the Dominant Driver of Renal Dysfunction in Heart Failure

Jennifer S. Hanberg, BA,[a] Krishna Sury, MD,[b] F. Perry Wilson, MD, MSCE,[a,b,c] Meredith A. Brisco, MD, MSCE,[d] Tariq Ahmad, MD, MPH,[b] Jozine M. ter Maaten, MD,[b] J. Samuel Broughton, BS,[a] Mahlet Assefa, BS,[a] W.H. Wilson Tang, MD,[f] Chirag R. Parikh, MD, PhD,[a,b,c] Jeffrey M. Testani, MD, MTR[a,b]

All of these manuscripts and more originated from BioLINCC data.
Some of the studies are 10-20 years old.

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UNOS STAR Files: Overview of data

- UNOS makes Standard Transplant Analysis and Research (STAR) Files available for each organ transplanted in the US
- Each file contains information on all waiting list registrations and transplants since October 1, 1987 with a 2 month lag.
- These files are deidentified without hospital identifiers
- There is one record per annual follow up per patient which amounts to extremely large datasets

UNOS™ Transplant Pro

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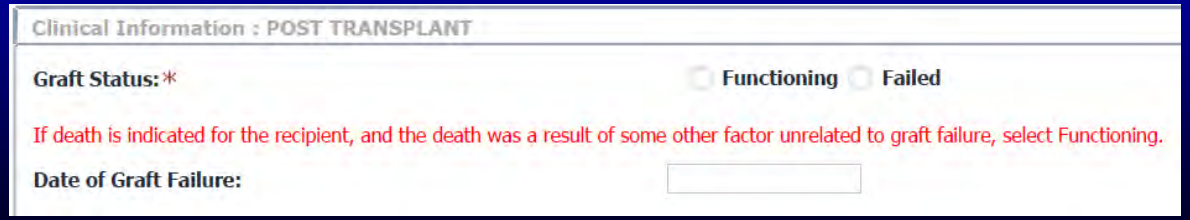
UNOS: Choosing a Research Question

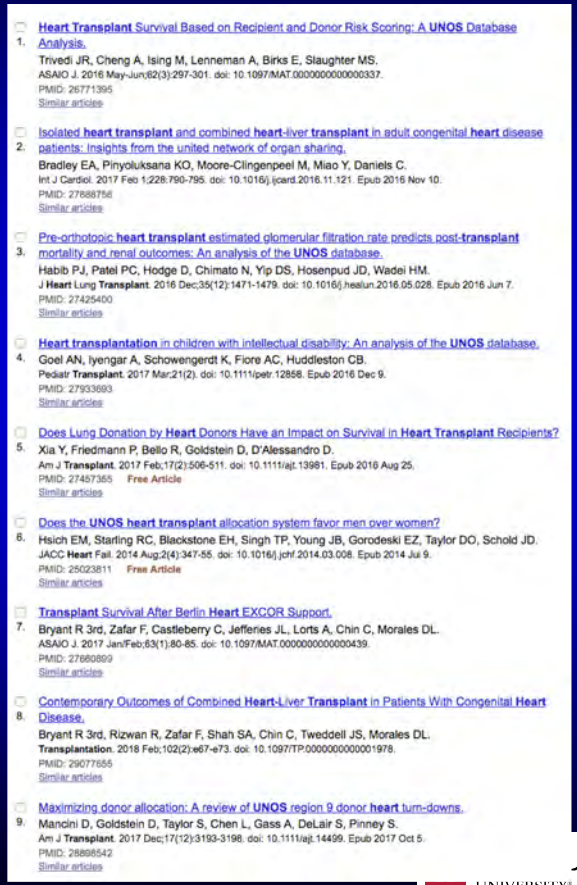
- Know the data and what has been published
- Examine what and how data is collected

https://transplantpro.org/technology/data-collection-forms/

The Primary Outcome Definition is IMPORTANT

Ex. The issue of graft failure in the UNOS data….





UNOS: How to get the data

- This is probably one of the easier registries to access:

  https://optn.transplant.hrsa.gov/data/request-data/

1. Fill out the form online
2. A CD arrives with the STAR files requested
3. Depending on your IRB you may want to secure documentation or approval, here UNOS is exempt

Data Request

If you are at an OPTN Member transplant center, OPO or histocompatibility lab, and have access to UNet℠, please log in to Secure Enterprise and submit your data request using the UNOS Service Portal.

All fields below are required.

First name **Last name**

Email address **Phone number**

Profession

Please select...

Is this request for a STAR file?

Yes

No

STAR (Standard Transplant Analysis and Research) files are DVDs with datasets that contain de-identified patient-level information for transplant recipients and waiting list candidates back to 10/1/1987. Use of a STAR file requires knowledge of database software capable of manipulating files with thousands of records and hundreds of variables, such as SAS or SPSS. Please note that the size of the STAR files precludes the use of software such as Microsoft Excel and Access.

If you wish to confirm the data you want is available, you can review PDF copies of the data collection forms here: Data Collection Forms

I'm not a robot

reCAPTCHA

The submit button will be disabled until you complete the CAPTCHA.

Submit

UNOS: What's on the CD?

Data	
Filename	UNOS FINAL FINAL Dataset.dta
Label	
Notes	
Variables	668
Observations	23,056
Size	67.46M
Memory	128M

File Sizes:
Take note, in this final cleaned dataset there are over 23,000 observations. Data doesn't start this way…

Data Dictionary Etc:
These files will explain how variables are coded and collected

Actual Data Files:
These are SAS data files. If you don't work in SAS you will need to download and convert the data to SPSS or STATA.
https://stattransfer.com/overview/

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UNOS: A word on data cleaning…

Data Cleaning to Work with Data

```
*Start with the baseline file**

**Getting rid of the lung transplants**
tab organ
encode organ, gen(organtype)
tab organtype
drop if organtype==1|organtype==3
tab organtype
drop organ

**Getting rid of the kids**
tab AGE_GROUP
encode AGE_GROUP, gen(agegrp)
drop if agegrp==2|agegrp==3
drop AGE_GROUP agegrp

**To get one line per patient**
sort  PT_CODE retxdate
bysort  PT_CODE: gen n=_n
bysort  PT_CODE: gen N=_N
tab n
gen retxp=1 if n>1
replace retxp=0 if n==1
tab retxp
drop if retxp==1
duplicates report PT_CODE
drop retxp
drop n N

**Getting rid of patients who died on the waitlist and weren't transplanted**
drop if DEATH_DATE<.
```

Variable Creation for your analysis

```
**Gender mismatch*
gen sexmismatchYN=.
replace sexmismatchYN=1 if sex==1 & sex_donor==2
replace sexmismatchYN=1 if sex==2 & sex_donor==1
replace sexmismatchYN=0 if sex==1 & sex_donor==1
replace sexmismatchYN=0 if sex==2 & sex_donor==2

***Calculating GFR***
rename CREAT_TRR creat_baseline
rename CREAT_DON creat_donor
rename MOST_RCNT_CREAT creat_listing

gen unadjustedgfr_baseline=(175*(creat_baseline^(-1.154))*(age^(-.203)))
gen gfr_baseline=.
replace gfr_baseline=unadjustedgfr_baseline*1.212*.742 if blackrace==1 & sex==1
replace gfr_baseline=unadjustedgfr_baseline*1.212 if blackrace==1 & sex==2
replace gfr_baseline=unadjustedgfr_baseline*.742 if blackrace==0 & sex==1
replace gfr_baseline=unadjustedgfr_baseline if blackrace==0 & sex==2

gen donorunadjustedgfr=(175*(creat_donor^-1.154)*(AGE_DON^-.203))
gen donorgfr=.
replace donorgfr=donorunadjustedgfr*1.212*.742 if blackrace_donor==1 & sex_donor==1
replace donorgfr=donorunadjustedgfr*1.212 if blackrace_donor==1 & sex_donor==2
replace donorgfr=donorunadjustedgfr*.742 if blackrace_donor==0 & sex_donor==1
replace donorgfr=donorunadjustedgfr if blackrace_donor==0 & sex_donor==2

gen unadjustedgfr_listing=(175*(creat_listing^-1.154)*(INIT_AGE^-.203))
gen gfr_listing=.
replace gfr_listing=unadjustedgfr_listing*1.212*.742 if blackrace==1 & sex==1
replace gfr_listing=unadjustedgfr_listing*1.212 if blackrace==1 & sex==2
replace gfr_listing=unadjustedgfr_listing*.742 if blackrace==0 & sex==1
replace gfr_listing=unadjustedgfr_listing if blackrace==0 & sex==2
```

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NOW WHAT?

Learn your data

Perform your analyses

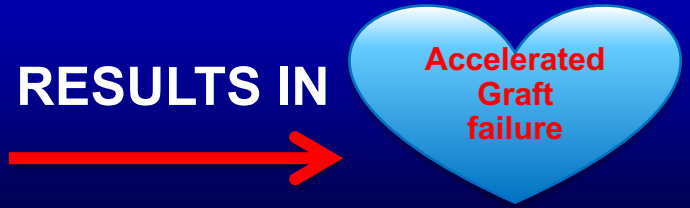
Write your manuscript

Important Notes: Once you have the data, you are on your own
You do not need permission to submit a manuscript or abstract
You must however cite the data in the methods appropriately

UNOS Data: Eval of Renocardiac Syndrome

IF IN DONOR:

THEN in RECIPIENT:



Laur and Brisco et al *J Card Fail* 2016;5:368-75.

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Donors with RD have greater disease burden but have similar allograft characteristics

	Overall Cohort	Donor RD present		P value
Donor characteristics:	N = 35914	No (N = 29736)	Yes (N = 6178)	
Age (mean ± SD), per 10-year increment	31.3 ± 12.4	30.6 ± 12.3	34.6 ± 12.2	<0.001
Female gender (%)	10631 (29.6)	8732 (29.4)	1899 (30.7)	0.03
Black race (%)	4729 (13.2)	3815 (12.8)	914 (14.8)	<0.001
BMI	26.5 ± 9.3	26.2 ± 9.4	27.8 ± 8.5	<0.001
Diabetes Mellitus	811 (2.3)	595 (2.0)	216 (3.5)	<0.001
Hypertension	4380 (12.3)	3151 (10.7)	1229 (20.1)	<0.001
Cigarette use	9815 (27.6)	8050 (27.4)	1765 (28.9)	0.01
Serum creatinine, mg/dl	1.0 ± 0.5	0.9 ± 0.4	2.0 ± 1.5	<0.001
Proteinuria	7985 (32.4)	5852 (28.8)	2133 (49.4)	<0.001
Graft characteristics:				
Allograft ischemic time (hours)	3.1 ± 1.0	3.1 ± 1.0	3.2±1.0	0.04
Graft LVEF (%)	61.6 ± 7.7	61.5 ± 7.7	61.7 ± 7.6	0.12

Donor RD – 17.2%

Laur and Brisco et al *J Card Fail* 2016;5:368-75.

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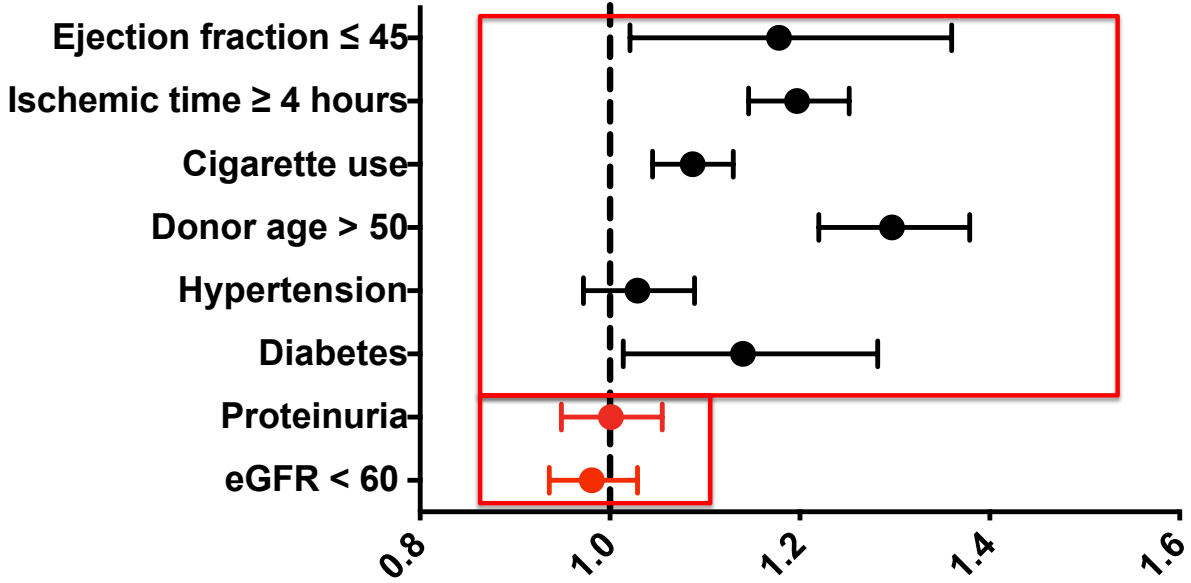
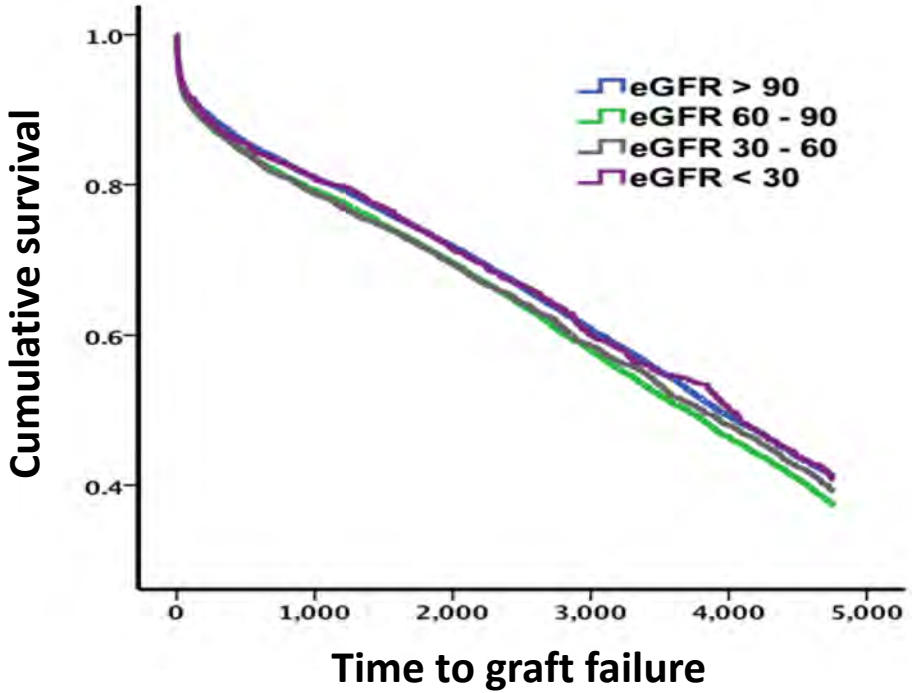
Donor RD and proteinuria are not associated with worsened graft survival on multivariate analysis



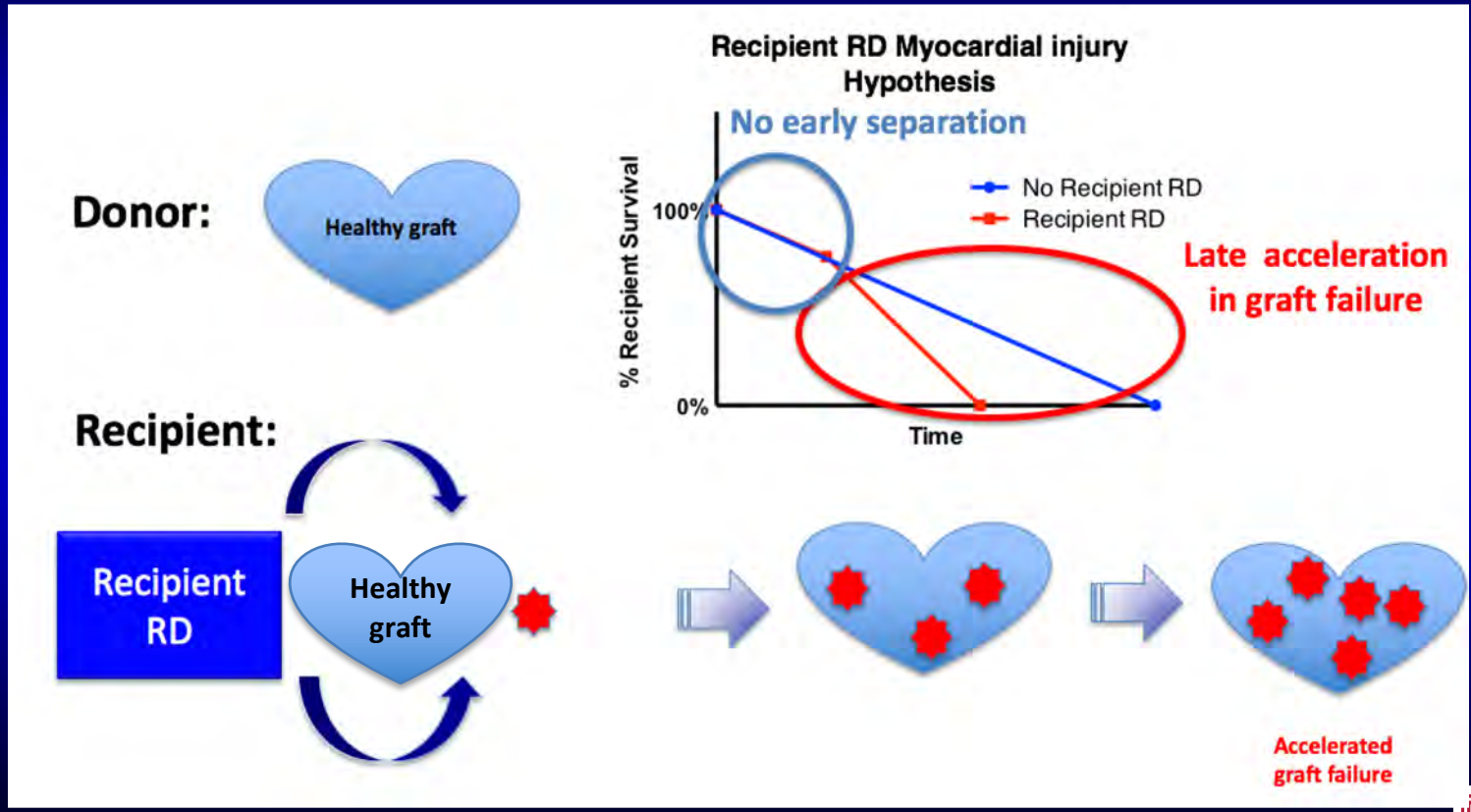
Laur and Brisco et al *J Card Fail* 2016;5:368-75.

Donor RD - KM graphs stratified by donor eGFR stages: No dose response effect



Laur and Brisco et al *J Card Fail* 2016;5:368-75.

If prolonged RD in recipients causes myocardial damage, we should see graft failure worsening with time



Laur and Brisco et al *J Card Fail* 2016;5:368-75.

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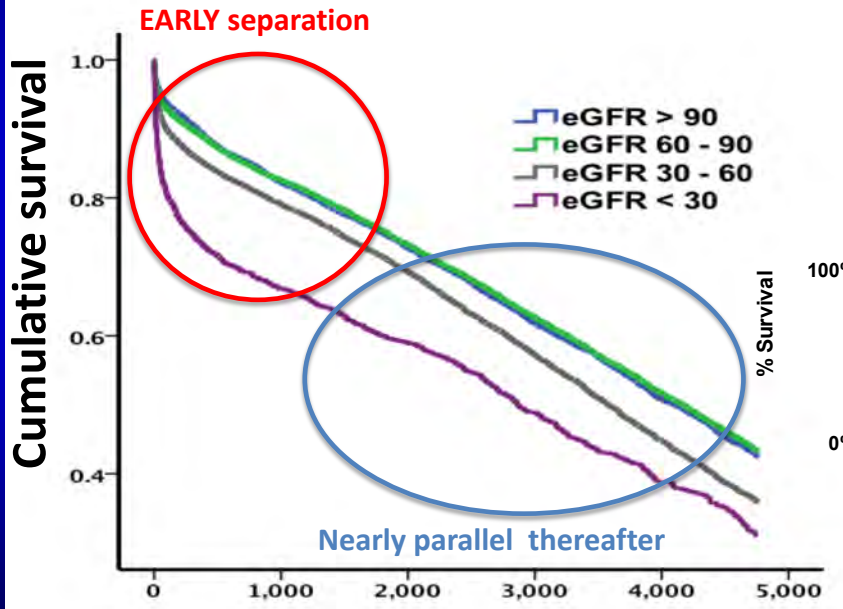
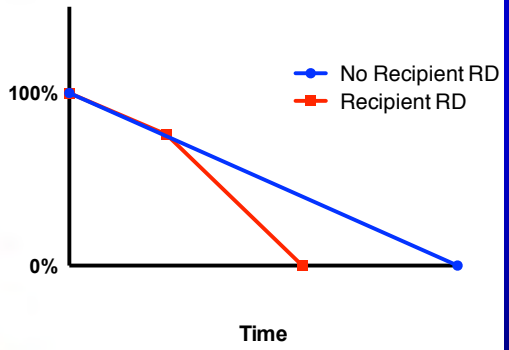
Recipient RD – no accelerated graft failure late after transplantation



Theoretical survival if RD did cause myocardial damage long-term:



OPPOSITE pattern observed

Laur and Brisco et al *J Card Fail* 2016;5:368-75.

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What is the impact?

Clinical Investigation

The Impact of Donor and Recipient Renal Dysfunction on Cardiac Allograft Survival: Insights Into Reno-Cardiac Interactions

OLGA LAUR, MD,[1,#] MEREDITH A. BRISCO, MD, MSCE,[2,#] ALEXANDER J. KULA, BS,[1] SUSAN J. CHENG, MD,[1] ABEEL A. MANGI, MD,[1] LAVANYA BELLUMKONDA, MD,[1] DANIEL L. JACOBY, MD,[1] STEVEN COCA, DO, MS,[1] W.H. WILSON TANG, MD,[3] CHIRAG R. PARIKH, MD, PhD,[1] AND JEFFREY M. TESTANI, MD, MTR[1]

Editorial

Donor Hearts: Time to Look at Them in a Different Light?

GONZALO V. GONZALEZ-STAWINSKI, MD

Dallas, Texas

Ventricular Assist Device Utilization in Heart Transplant Candidates: Nationwide Variability and Impact on Waitlist Outcomes

Investigator: Veli K. Topkara, MD

Twitter Journal Club: May 3, 2018

Circulation: Heart Failure

EMERGING INVESTIGATORS

Ventricular Assist Device Utilization in Heart Transplant Candidates

Nationwide Variability and Impact on Waitlist Outcomes

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Sponsored Clinical Trial Data: An Overview

- Industry (with some exceptions) are less likely to “hand over” datasets from their clinical trials:
  - **BAD-Side**: You never know data as well and industry may not be interested in research with a negative statement or outcome
  - **GOOD-Side**: Industry statisticians work directly with you on analyses but they physically do the analytic work.
- It is harder to discover what variables, endpoints etc. a particular clinical trial collected (i.e. you can’t look it up on a website), BUT:
  - Looking at the original publications from the trial and methods section will help
- The ”way in” to a secondary analysis is by being a good enrolling site in the parent clinical trial
  - If Temple participated, coordinators will have CRFs, your “in” to what was collected

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Clinical Trial Data: Research Question

- Know the data and what has been published
- Look for a "Rationale and Study Design" paper for additional info
- Obtain the CRFs from study coordinator to glean more on the data
- Formulate your research question

3. **Clinical** management of continuous-flow left ventricular assist devices in advanced heart failure.
Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, Starling RC, Chen L, Boyle AJ, Chillcott S, Adamson RM, Blood MS, Camacho MT, Idrissi KA, Petty M, Sobieski M, Wright S, Myers TJ, Farrar DJ; **HeartMate II Clinical Investigators**.
J Heart Lung Transplant. 2010 Apr;29(4 Suppl):S1-39. doi: 10.1016/j.healun.2010.01.011. Epub 2010 Feb 24.
PMID: 20181499
Similar articles

12. Japanese Multicenter Outcomes With the **HeartMate** II Left Ventricular Assist Device in Patients With Small Body Surface Area.
Ono M, Sawa Y, Nakatani T, Tominaga R, Matsui Y, Yamazaki K, Saiki Y, Niinami H, Matsumiya G, Arai H; Japanese **HeartMate II Investigators**.
Circ J. 2016 Aug 25;80(9):1931-6. doi: 10.1253/circj.CJ-16-0203. Epub 2016 Jul 4.
PMID: 27373233 **Free Article**
Similar articles

13. Right ventricular failure in patients with the **HeartMate** II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes.
Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, Massey T, Milano CA, Moazami N, Sundareswaran KS, Farrar DJ; **HeartMate II Clinical Investigators**.
J Thorac Cardiovasc Surg. 2010 May;139(5):1316-24. doi: 10.1016/j.jtcvs.2009.11.020. Epub 2010 Feb 4.
PMID: 20132950 **Free Article**
Similar articles

14. Pre-operative risk factors of bleeding and stroke during left ventricular assist device support: an analysis of more than 900 **HeartMate** II outpatients.
Boyle AJ, Jorde UP, Sun B, Park SJ, Milano CA, Frazier OH, Sundareswaran KS, Farrar DJ, Russell SD; **HeartMate II Clinical Investigators**.
J Am Coll Cardiol. 2014 Mar 11;63(9):880-8. doi: 10.1016/j.jacc.2013.08.1656. Epub 2013 Dec 11.
PMID: 24316083 **Free Article**
Similar articles

15. Pump replacement for left ventricular assist device failure can be done safely and is associated with low mortality.
Moazami N, Milano CA, John R, Sun B, Adamson RM, Pagani FD, Smedira N, Slaughter MS, Farrar DJ, Frazier OH; **HeartMate II Investigators**.
Ann Thorac Surg. 2013 Feb;95(2):500-5. doi: 10.1016/j.athoracsur.2012.09.011. Epub 2012 Dec 20.
PMID: 23261114
Similar articles

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Clinical Trial Data: The Proposal

- Clinical trials usually have publication committees who ultimately decide which secondary analysis proposals are approved
- You have to complete a research proposal application that your mentor (usually a local PI or subI) must submit
- If Temple didn't enroll well or the sponsor was disappointed in your mentor, **DO NOT** submit an application for a secondary analysis

HMII TRIAL

HEARTMATE II APPLICATION FORM FOR PROPOSED TOPICS FOR ABSTRACTS and PUBLICATIONS	Please e-mail application to David J. Farrar, Ph.D., david.farrar@thoratec.com, or fax (925) 847-8574
NAME OF APPLICANTS: Meredith A. Brisco, M.D. Lee R. Goldberg, M.D., MPH	DATE: November 9, 2010
CLINICAL SITE: Hospital of the University of Pennsylvania	PHONE: 215-615-0820 FAX: 215-615-828 E-MAIL: Meredith.Brisco@uphs.upenn.edu Lee.Goldberg@uphs.upenn.edu
ABSTRACT (__) ; PRESENTATION (__) ; INVITED SPEAKER (__) ; MANUSCRIPT (x) .	
FORUM OR TARGET JOURNAL: Circulation or JACC or Journal of Heart and Lung Transplantation	
ABSTRACT DEADLINE: N/A	PRESENTATION DATE: N/A

HEARTMATE II PUBLICATION POLICY

QUESTION TO BE ANSWERED, OR PROPOSED TOPIC or TITLE OF ABSTRACT/MANUSCRIPT: (for multiple topics, indicate your first choice, second choice, etc)

FIRST AND ONLY CHOICE
Proposed Title: Atrial and Ventricular Arrhythmias in Patients with HeartMate II Left Ventricular Assist Devices

Question to be Answered:
What is the incidence and prevalence of atrial and ventricular arrhythmias in patients with HMII LVADs as both bridge to transplant and destination therapies? What are the clinical predictors for both ventricular and atrial arrhythmias and is their presence associated with differential survival and or quality of life when compared to those patients without arrhythmias?

Background
Treatment of advanced heart failure with continuous-flow left ventricular assist devices (LVADs) both as bridge to transplant and destination therapy is associated with improved survival with fewer adverse events as compared to older pulsatile assist devices. [Slaughter 2009, Miller 2007] As the technology continues to improve, the number of patients both exposed to and treated with these advanced therapies is likely to increase. Arrhythmias are a known complication of severe cardiomyopathy and although LVADs unload the myopathic heart, arrhythmias, specifically ventricular, are common in patients with these devices.

Clinical Trial Data: The Proposal

PROPOSED AUTHOR(S) AND YOUR ROLE. IF PROPOSED LEAD AUTHOR, ARE YOU WILLING TO ASSUME RESPONSIBILITY FOR MANUSCRIPT PREPARATION AND COMPLETION?

Meredith A. Brisco (Lead Author): Yes. Under the mentorship of Lee Goldberg, M.D., I will assume responsibility for the manuscript's preparation and completion. My role will be the previously stated responsibility as well as ensuring the statistical analysis is motivated by clinical relevance.

Lee R. Goldberg (Last Author): Trial design and analysis. Supervisor and mentor to Meredith Brisco who will assume co-responsibility for the manuscript's preparation and completion.

PATIENT SUBGROUP(S) (who are the patients to be examined?):
Patients with advanced heart failure refractory to optimal medical management, who underwent placement of a HeartMate II continuous-flow LVAD for either bridge to transplant or destination therapy, including patients enrolled after the subsequent initial publications from the trial, are eligible for analysis. Those patients who received an LVAD primarily for incessant ventricular arrhythmias will likely be excluded from the analysis.

Defining your role and patients:
The sponsor wants to know who is responsible for the project. You cannot "drop the ball" here.

ANALYSIS PLAN (Proposed lead authors must provide types of analyses needed, variables to be analyzed, statistics required, etc)

Analysis Plan:
You won't physically perform the analyses but you need to describe the analyses you desire

Atrial Arrhythmias

1. Calculation of overall incidence of atrial arrhythmias over the available duration of follow-up
2. Kaplan-Meier Curve construction in those with and without atrial arrhythmias with comparison using the log-rank test.
3. Time to event analysis/Cox Proportional Hazards modeling with the primary endpoint development of atrial arrhythmias. Predictor variables of particular interest will include essential demographics (sex, age, beta blocker use, amiodarone use) as well as type of cardiomyopathy, bridge or destination device, preoperative afib, atrial flutter or atrial tachycardia, concomitant presence of sleep apnea if known.
5. Of those patients with AE forms filled out and submitted, report the percentage of atrial events out of all AE arrhythmia events.
6. Comparison of QOL scores in those patients with and without atrial arrhythmias.
7. Comparison of categorical variables of interest between those with and without atrial arrhythmias using Fisher's exact test.
8. Comparison of continuous variables of interest between those with and without atrial arrhythmias using Student's t test.

This application is an opportunity to make an impression. You never know who might see it on the committee.

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What to expect if application approved

- You will work with a statistician and other members of an analytic team assigned to your proposal, likely via teleconference
- Powerpoints (or other media) of figures and results of your analysis will be provided
- It is a partnership and a back in forth is usually involved
- Once it is time for manuscript preparation, they usually write the methods and create the tables and figures but you will handle the rest
- The sponsor/team must approve the manuscript before submission
- Don’t be surprised if other authors are “added”

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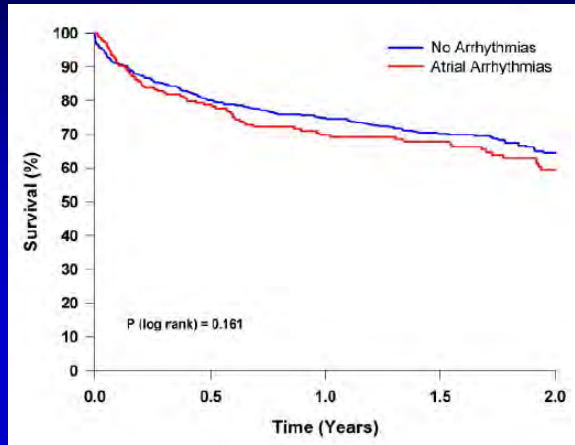
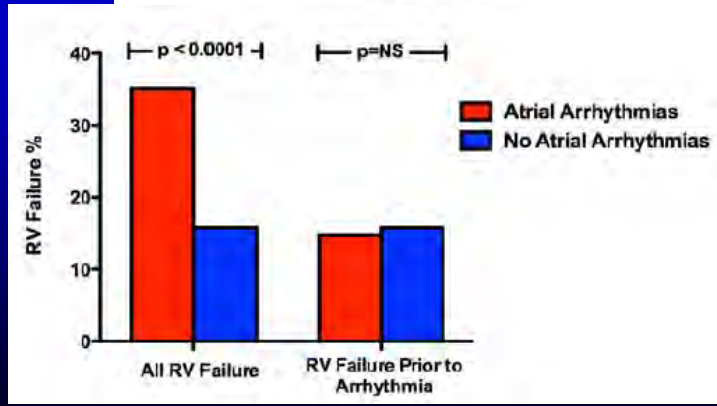
Clinical Trial Data: Atrial Arrhythmias in LVAD Patients

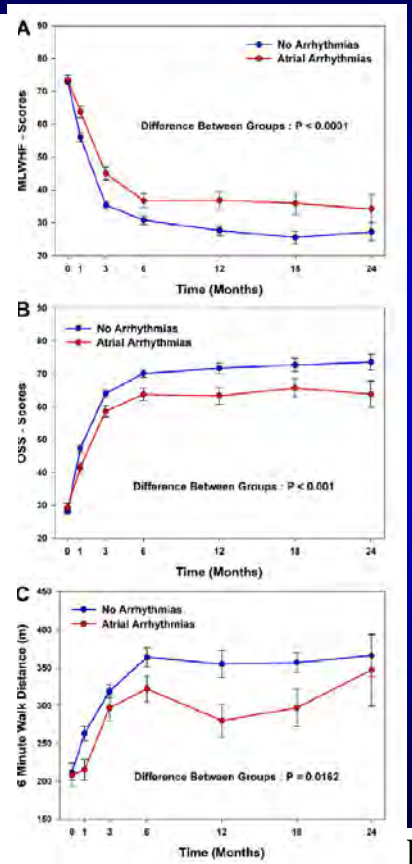
The incidence of AAs after CF-LVAD was unknown, as was their clinical impact

In 1125 patients from the original HM2 trial we performed a comprehensive analysis

AAs after CF-LVAD do not impact survival but do affect quality of life and functional status



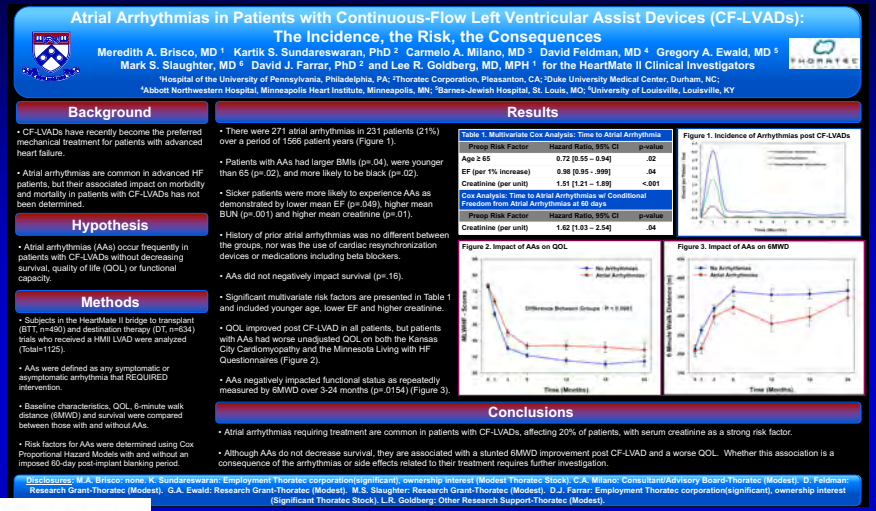




Brisco et al *J Card Surg* 2014

What is the impact?

- This was my first lead author poster presentation at AHA
- We ultimately went on to publish our manuscript which strengthened my CV in fellowship
- Relationships formed led to my recruitment into EMERG



Atrial Arrhythmias in Patients with Continuous-Flow Left Ventricular Assist Devices (CF-LVADs): The Incidence, the Risk, the Consequences

Meredith A. Brisco, MD [1] Kartik S. Sundareswaran, PhD [2] Carmelo A. Milano, MD [3] David Feldman, MD [4] Gregory A. Ewald, MD [5] Mark S. Slaughter, MD [6] David J. Farrar, PhD [2] and Lee R. Goldberg, MD, MPH [1] for the HeartMate II Clinical Investigators

[1]Hospital of the University of Pennsylvania, Philadelphia, PA; [2]Thoratec Corporation, Pleasanton, CA; [3]Duke University Medical Center, Durham, NC; [4]Abbott Northwestern Hospital, Minneapolis Heart Institute, Minneapolis, MN; [5]Barnes-Jewish Hospital, St. Louis, MO; [6]University of Louisville, Louisville, KY

Background

- CF-LVADs have recently become the preferred mechanical treatment for patients with advanced heart failure.
- Atrial arrhythmias are common in advanced HF patients, but their associated impact on morbidity and mortality in patients with CF-LVADs has not been determined.

Hypothesis

- Atrial arrhythmias (AAs) occur frequently in patients with CF-LVADs without decreasing survival, quality of life (QOL) or functional capacity.

Methods

- Subjects in the HeartMate II bridge to transplant (BTT, n=490) and destination therapy (DT, n=634) trials who received a HMII LVAD were analyzed (Total=1125).
- AAs were defined as any symptomatic or asymptomatic arrhythmia that REQUIRED intervention.
- Baseline characteristics, QOL, 6-minute walk distance (6MWD) and survival were compared between those with and without AAs.
- Risk factors for AAs were determined using Cox Proportional Hazard Models with and without an imposed 60-day post-implant blanking period.

Results

- There were 271 atrial arrhythmias in 231 patients (21%) over a period of 1566 patient years (Figure 1).
- Patients with AAs had larger BMIs (p=.04), were younger than 65 (p=.02), and more likely to be black (p=.02).
- Sicker patients were more likely to experience AAs as demonstrated by lower mean EF (p=.049), higher mean BUN (p=.001) and higher mean creatinine (p=.01).
- History of prior atrial arrhythmias was no different between the groups, nor was the use of cardiac resynchronization devices or medications including beta blockers.
- AAs did not negatively impact survival (p=.16).
- Significant multivariate risk factors are presented in Table 1 and included younger age, lower EF and higher creatinine.
- QOL improved post CF-LVAD in all patients, but patients with AAs had worse unadjusted QOL on both the Kansas City Cardiomyopathy and the Minnesota Living with HF Questionnaires (Figure 2).
- AAs negatively impacted functional status as repeatedly measured by 6MWD over 3-24 months (p=.0154) (Figure 3).

Table 1. Multivariate Cox Analysis: Time to Atrial Arrhythmia

Preop Risk Factor	Hazard Ratio, 95% CI	p-value
Age ≥ 65	0.72 [0.55 – 0.94]	.02
EF (per 1% increase)	0.98 [0.95 - .999]	.04
Creatinine (per unit)	1.51 [1.21 – 1.89]	<.001
Cox Analysis: Time to Atrial Arrhythmias w/ Conditional Freedom from Atrial Arrhythmias at 60 days		
Preop Risk Factor	Hazard Ratio, 95% CI	p-value
Creatinine (per unit)	1.62 [1.03 – 2.54]	.04

Figure 1. Incidence of Arrhythmias post CF-LVADs

Figure 2. Impact of AAs on QOL

Figure 3. Impact of AAs on 6MWD

Conclusions

- Atrial arrhythmias requiring treatment are common in patients with CF-LVADs, affecting 20% of patients, with serum creatinine as a strong risk factor.
- Although AAs do not decrease survival, they are associated with a stunted 6MWD improvement post CF-LVAD and a worse QOL. Whether this association is a consequence of the arrhythmias or side effects related to their treatment requires further investigation.

Disclosures: M.A. Brisco: none. K. Sundareswaran: Employment Thoratec corporation(significant), ownership interest (Modest Thoratec Stock). C.A. Milano: Consultant/Advisory Board-Thoratec (Modest). D. Feldman: Research Grant-Thoratec (Modest). G.A. Ewald: Research Grant-Thoratec (Modest). M.S. Slaughter: Research Grant-Thoratec (Modest). D.J. Farrar: Employment Thoratec corporation(significant), ownership interest (Significant Thoratec Stock). L.R. Goldberg: Other Research Support-Thoratec (Modest).

The Incidence, Risk, and Consequences of Atrial Arrhythmias in Patients with Continuous-Flow Left Ventricular Assist Devices

Meredith A. Brisco, M.D., M.S.C.E.,* Kartik S. Sundareswaran, Ph.D.,†
Carmelo A. Milano, M.D.,‡ David Feldman, M.D.,§ Jeffrey M. Testani, M.D., M.T.R.,¶
Gregory A. Ewald, M.D.,|| Mark S. Slaughter, M.D.,# David J. Farrar, Ph.D.,†
Lee R. Goldberg, M.D., M.P.H.,⊥ for the HeartMate II Clinical Investigators

- Secondary analyses of clinical trials like this one are published every week

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Final Thoughts…

- Analyses of registry data, claims data or clinical trial data are relevant and valuable research endeavors with their own unique advantages and limitations
- Do your homework and know your data
- Regardless of the type of research you pursue, knowledge of statistics and/or statistical software is an invaluable tool

Questions?

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