ATHN-1: A Cross-Sectional Analysis of Cardiovascular Disease in Hemophilia

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ATHN-1 CVD Study
Breakfast Breakout Agenda

-Congrats on completing enrollment!

-Data summary from ASH abstract

-Goals for data collection and analysis

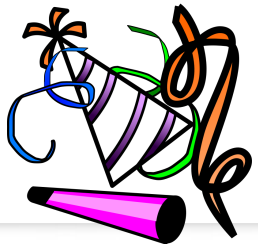
-Next Steps: Exploring renal insufficiency in a prospective cohort study

-Questions and Discussion

We completed Enrollment: above target goal!

SITE	Enrollment
Bloodworks Northwest	23
HTC of Western PA (Pittsburgh)	22
Georgetown University	20
Orthopedic Hospital	19
Indiana Hemophilia and Thrombosis Center	17
University of North Carolina	17
University of Colorado	13
University of Pennsylvania	10
Emory University	10
Ohio State	10
University of Michigan	9
HTC of Central Pennsylvania (Penn State/Hershey)	8
University of California, San Diego	6
Henry Ford Hospital	5
Blood Center of Wisconsin	4
Vanderbilt University	3
Mary M. Gooley HTC	3
Louisiana Comprehensive HTC/Tulane	2
Gulf States HTC	2

203 participants enrolled as of 12OCT2015



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Disease and Severity of 202 enrolled subjects

Disease and Severity	N	%
Severe	111	55.0
Moderate	89	44.1
Mild (6%)	2	0.99
Hemophilia A	124	61.4
Hemophilia B	78	38.6

Results from the ASH abstract

(n=165)

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ATHN-1 Population Characteristics at n=165

Characteristic	n	%
Caucasian	148	89.7%
African American	14	8.5%
Mean age	61 years, range 54-73	
Use of prophylaxis	50	30.3%
Current inhibitor	8	4.9%
Hepatitis C		61.2%
HIV		28.5%

CVD Risk Factors, ATHN-1 (n=165)

Risk Factor	% Subjects
Hypertension (HTN)	61.2%
Dyslipidemia	35.1%
Diabetes (DM)	21.8%
Ever smoked	49.1%
Does not engage in at least moderate physical activity (> 90 minutes/week)	55.2%
Family history of CVD	43.0%
Obese BMI (≥ 30 kg/m^2)	30.3%
Elevated waist circumference (≥ 102 cm)	32.1%

Lab Testing Results (n=165)

Lab Test	Percentage of patients with abnormal results	Mean	SD	Normal range
Creatinine	26.7%	1.1	0.5	0.51-1.18
CRP	9.7%	5.2	13.7	0-10.0
Cholesterol	23.0%	174.1	38.8	< 200
Triglycerides	27.9%	129.1	68.3	< 150
HDL	42.4%	43.2	11.8	> 40
LDL (calc.)	21.8%	105.1	34.7	< 130

Vascular disease in 165 subjects

- Reported past vascular events:
  - Prior angina or atrial fib/flutter: 14 subjects (8.5%)
  - Leg DVT: 5 (3.0%)
  - MI or PE: 4 (2.4%)
  - Stenting for CAD: 3 (1.8%)
  - TIA: 2 (1.2%)
  - Cardiac angioplasty/stent/CABG or PAD: 1 (0.6%)

Low Prevalence of CVD in Hemophilia

- CVD is defined as **Angina**, **MI, TIA**, or ischemic/ embolic stroke
  - 16 subjects met this definition, for a **prevalence rate of 9.7%**
  - Significantly lower than the prevalence rate of 23% found in similarly aged men in the ARIC cohort (p-value < 0.001)
  - None of the men with CVD were on antiplatelet or AC medication

Predictors of CVD in Hemophilia

Variable	OR (95% CI) for CVD
Ever smoker*	**3.5 (1.1-11.3)**
Hypertension (HTN)	2.0 (0.6-6.6)
Dyslipidemia	2.0 (0.7-5.6)
Positive family history	1.4 (0.5-3.8)
Lower HDL	1.4 (0.5-3.9)
Diabetes Mellitus	1.2 (0.4-4.0)
Higher TG	1.2 (0.4-3.7)
Low level physical activity	1.1 (0.4-3.3)
Obese BMI	Not significant

*versus never smokers

Predictors of CVD in Hemophilia

Variable	OR (95% CI) for CVD
Using prophylaxis (3/50 on prophy vs. 13/115)	0.5 (0.1-1.8)
HIV+ (2/47 HIV+ vs. 14/115 HIV-)	0.3 (0.07-1.5)

Current use of anti-HTN medications (42.4% of all subjects), cholesterol lowering agents (17.6%), and DM medications (13.3%) did not decrease CVD risk.

Analysis of cause and effect is limited by the cross-sectional design

Conclusions as of ASH Abstract submission

- Older men with moderate to severe hemophilia commonly report risk factors for CVD, including HTN (61.2%), dyslipidemia (35.2%) and renal insufficiency (26.7%)

- Despite this, the prevalence of reported CVD is low at 9.7%, suggesting that men with hemophilia may be protected from forming pathogenic thrombi.

- Smoking significantly increased the OR of CVD events among men with hemophilia.

Next steps in this analysis

- More data are needed to determine if the approach to prophylaxis or other therapies should be altered in this population.

- Have begun the process of formally comparing the prevalence of CVD and CV risk factors with similarly aged men in the ARIC database now that enrollment is complete.

CKD in hemophilia

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Next Step: Focus on Renal Insufficiency

- In preliminary analysis of 109 subjects, we found a striking prevalence of renal insufficiency
  - mean serum creatinine is 1.12 (range 0.45-4.42 mg/dL) and mean eGFR is 78.1 (range 12.7-126.5 ml/min/1.73 m^2).
  - 23% of patients have an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2.
  - 30% have an abnormally elevated creatinine
- We do not know if this is persistent (i.e. chronic kidney disease (CKD))

Potential stages of CKD in our cohort

Stage	GFR (ml/min/ m^2)	Prevalence general population (%)	Hemophilia cohort (%)
I	> 90	1.78	-
II	60-89	3.24	36.7
III	30-59	7.69	21.1
IV	15-29	0.35	0.9
V	< 15	0.25	0.9

CKD is defined as a GFR < 60 for ≥ 3 months

In men, the CKD-EPI equation is eGFR= 141 x min (Creatinine/0.9 or 1)$^{-0.4411}$ x max (Creatinine/0.9 or 1)$^{-1.209}$ x 0.993^{age} x 1.159 [if black].

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ATHN 1 RESEARCH STUDY

Coresh et al. JAMA 2007; 298: 2038

Limited data exists on renal disease in hemophilia

- Soucie et al. found in a 3 year surveillance period, U.S. men with hemophilia were 50x more likely to die from renal disease than the general population (SMR 50; 95% CI 26.8-92.8)
- Kulkarni et al. found increased hospitalizations for renal disease in men with hemophilia compared to age matched controls (179% more likely for acute kidney injury (AKI), 169% more likely for CKD)

Soucie et al. Blood 2000; 96: 437-442
Kulkarni et al. Haemophilia 2003; 9: 703-10

Risk factors for CKD in the US

- Diabetes (44.9%)
- HTN (27.2%)
- Less common: glomerulonephritis, obstruction, vasculitis, neoplasm

- CVD and CKD are linked
  - Management of CV risk factors is very important to halt both CKD and CVD

Hemophilia risk factors for renal disease

- Unique risk factors in the hemophilia population:
  - urinary tract bleeding?
  - Anti-fibrinolytic agents?
  - Nephrotic syndrome from ITI in FIX inhibitors?
  - Chronic viral infections (HIV and HCV)

- In our cohort, subjects with renal disease, defined as a GFR < 60, were more likely to be older (p=0.02), but did not have statistically significantly higher rates of DM, HTN, HIV or HCV, *suggesting that the key CKD risk factors in the hemophilia population may be different than the general population*

A Cross-Sectional Analysis of Cardiovascular Disease in the Hemophilia Population (CVD in Hemophilia Study) Protocol Extension ATHN-1

Forming a prospective cohort

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Specific Aims for the new proposal

1) Determine the prevalence of CKD by assessing renal function at two time points over a two year period in a prospective cohort of 200 male subjects with moderate or severe hemophilia A or B aged 54-73 years;

2) Determine the prevalence of risk factors for CKD at those two time points and complications of CKD including end stage renal disease (ESRD);

Specific Aims for the new proposal

3) Compare prevalence data and risk factors for CKD in subjects with hemophilia with similarly aged male subjects in the Atherosclerosis Risk in Communities Cohort (ARIC).

This proposal will allow us to turn our study from a cross-sectional study to a prospective cohort study

Prospective Cohort Study: Follow Up Visit #1

- Reconsent original enrollees to collect updated data
  - Current plan is to hopefully re-approach every 2-3 years

- Update (since date of last visit)

- PE (VS, waist circumference, BMI)
- Current medications and indication
- CVD risk factors (including HbA1c)
- History of arterial and venous thrombosis (including details of angina diagnosis)
- Liver disease
- HIV, malignancy, inhibitor status

New Data Elements Proposed

- **Specific to CKD:**
  - history of hematuria by decade
  - history of kidney stones
  - Max creatinine by year for the past 10 years (if available)
  - Past or current use of NSAIDs and of antifibrinolytic agents
  - Obstructive symptoms and history of prostatic disease
  - history of (intrinsic) renal disease, ever seen a nephrologist, had a renal biopsy, or underwent dialysis
    - Details of the renal disease diagnosis

Additional Lab Data Proposed

- Serum creatinine (to be assayed locally)
  - within 12 months prior or 1 month post the date of the follow-up visit. This will be considered standard of care.

- To further corroborate a diagnosis of CKD, we will collect the highest recorded serum creatinine level each year over the past 10 year period, as available.

- Possibly in the future: Spot urine albumin and creatinine (to be run centrally)

Power calculations

- We will have 90% power to detect a difference in GFR of 5.69 ml/min/m^2 between the hemophilia and ARIC cohort, and ~100% power to evaluate a difference in prevalence of CKD

Power	True prevalence in hemophilia cohort				
True prevalence in controls	10%	15%	20%	23%	30%
5%	81%	100%	100%	100%	100%
10%	5%	61%	98%	100%	100%
15%	50%	5%	50%	83%	100%
20%	98%	40%	5%	20%	91%

Funding

- Bayer Early Career Investigator Award awarded to Dr. Sood
- Additional applications for funding are pending, including with Bayer and consideration of an R21
- As an update to the current CVD study, this is planned to be submitted as an amendment to the current IRB application

Thank you!

- Centers for Disease Control for generously funding this Study
  - Our program officers: Azfar Siddiqi and Vanessa Byams
- Bayer Early Career Investigator Award is funding the prospective cohort study going forward
- ATHN
  - CEO Diane Aschman
  - Director of Operations Crystal Watson
  - Biostatistician Dunlei Cheng

Thank you!

ATHN-1 Site	PI	Study Coordinators
Orthopedic	Quon	Lucy Lacanilao
Colorado	Manco-Johnson	Kristi Norton
Georgetown	Kessler	Helena Jacobs, Claire Hunn
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IHTC	Shapiro	Jackie Buckley
Tulane	Leissinger	Carol deKernion
Michigan	Sood	Rebecca Hauke
UNC	Key	Robin Kellerman, Cheryl Jeanneret, Brenda Nielsen
Rochester	Kouides	Debbie Bennett
Hershey	Eyster	Gail Long
Penn	Cuker	Mary Kelty
Pittsburgh	Ragni	Jacqueline Washington
BWNW	Konkle	Sarah Galdzicka
BCW	Gill	Karen Stephany
Gulf States	Escobar	Madeline Cantini, Krishna Cannon
UCSD	Von Drygalski	Thomas Cramer, Kristen Fulton
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Ohio State	Wang	Melanie Heinlein, Clare Messick

Comments/Questions?

Thank you for your attention and for all of your hard work thus far!

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Securing Data.
Advancing Knowledge.
Transforming Care.