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SICKLE CELL CARDIOMYOPATHY: PAST PRESENT AND FUTURE

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APRIL 29, 2015

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Case Western Reserve University Est. 1826

DISCLOSURES

None

OUTLINE

- Background
- Pathophysiology
- Sickle Cell Cardiomyopathy
- Current Management
- Future insights into the management of sickle cell cardiomyopathy
- Summary

SICKLE CELL DISEASE

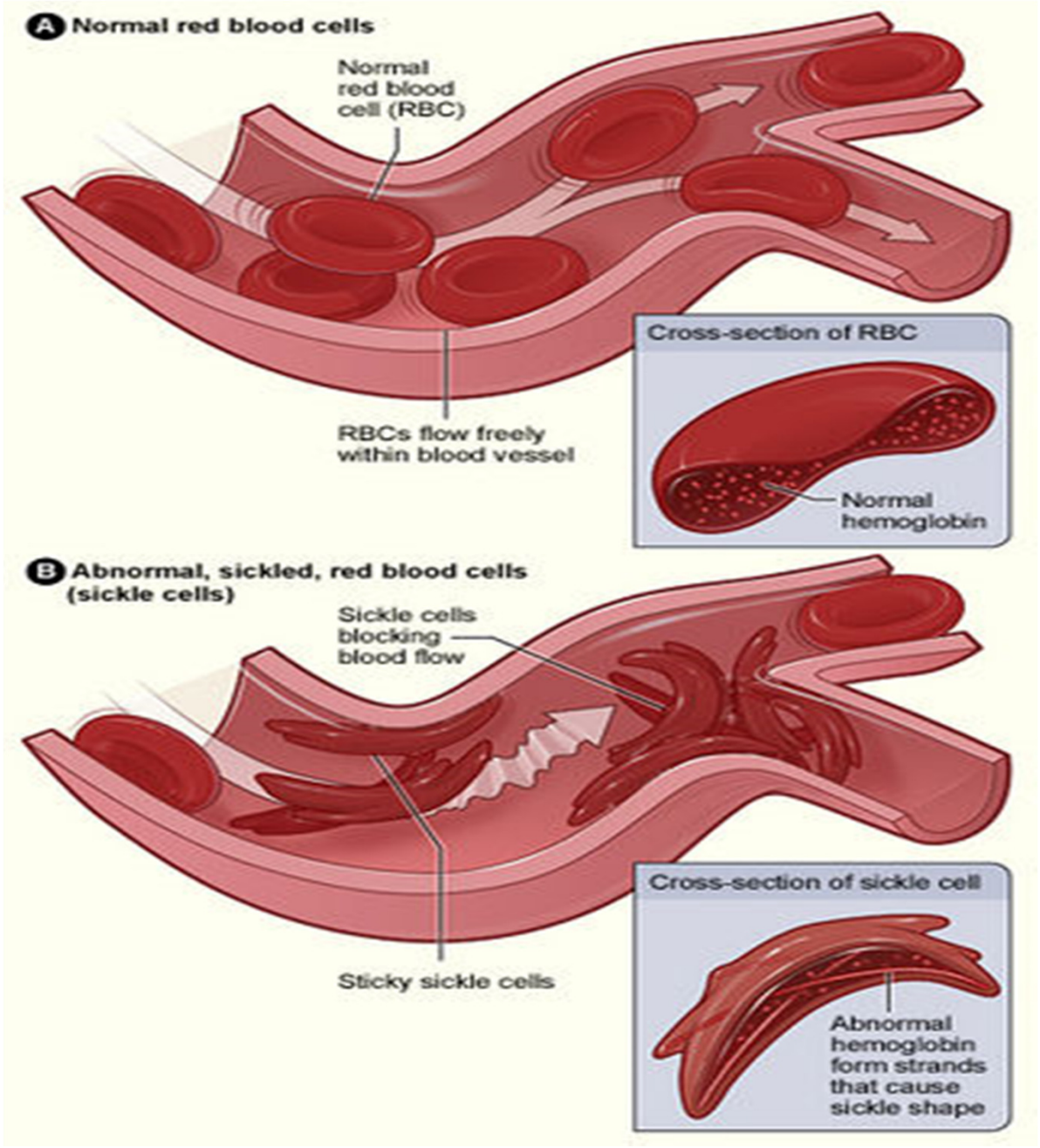
- **The condition was first described in the medical literature by the American physician James B. Herrick in 1910,**
- **In the 1940s and 1950s contributions by Nobel prize-winner Linus Pauling made it the first disease where the exact genetic and molecular defect was elucidated.**

SICKLE CELL DISEASE

- Autosomal recessive pattern of inheritance from parents
- Sickle cell trait/carrier- person with a single abnormal copy, does not experience symptoms
- The gene defect is a mutation of a single nucleotide of the β-globin gene, which results in glutamic acid being substituted by valine at position 7
- Results in abnormality in the oxygen-carrying hemoglobin molecule in red blood cells

PATHOPHYSIOLOGY

- In sickle-cell disease, low-oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity.
- These rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischemia.
- This leads to hemolytic anemia
- Bone marrow cannot compensate fast enough to match the rate of destruction
- Healthy red blood cells typically function for 90–120 days, but sickled cells only last 10–20 days


A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

COMPLICATIONS OF SICKLE CELL DISEASE

- Vascular occlusion of small and large vessels can lead to chronic damage of a number of organs including brain, lung, bone, kidney, liver, spleen, and retina
- Sickle cell crises and pain
- Increased risk of infections
- Iron overload due to multiple transfusions of the liver and heart

MAGNITUDE OF THE PROBLEM

- **Almost 300,000 children are born with a form of sickle-cell disease every year, mostly in sub-Saharan Africa, but also in other countries such as the West Indies and in people of African origin elsewhere in the world**

- **In 2013 it resulted in 176,000 deaths up from 113,000 deaths in 1990.**

SICKLE CELL CARDIOMYOPATHY

- **Patients with HbSS are at a higher risk for cardiomyopathy and heart failure**

- **HF results from microvascular disease, macrovascular disease, inflammation, iron overload**

TYPES OF SICKLE CELL CARDIOMYOPATHY

- Elevated cardiac output and cardiomegaly
- Dilated cardiomyopathy
- Progressive cardiac dysfunction and iron overload
- Diastolic dysfunction
- Pulmonary hypertension
- Pulmonary vasculopathy and cor pulmonale

IDENTIFICATION OF CARDIOMYOPATHY IN SICKLE CELL PATIENTS

Echocardiography is a useful and irreplaceable non-invasive technique to study the changes in cardiac structure and function in SCD patients.

CURRENT MANAGEMENT

- **Hydroxyurea: increases Fetal hemoglobin synthesis**
- **Transfusion therapy: shown to decrease the number and severity of attacks in a study in 1995 (Charache *et al.*) and shown to possibly increase survival time in a study in 2003 (Steinberg *et al.*)**
- **Iron chelation therapy**
- **Exchange transfusions**

FUTURE OF SICKLE CELL CARDIOMYOPATHY MANAGEMENT

Burden of HF remains unknown in HbSS and sickle cell variants

We sought to identify prevalence of HF in SS and variants

PREVALANCE OF HEART FAILURE IN SICKLE CELL PATIENTS

METHODS

Patients may be identified by: disease, prescription drug use, lab testing, disease progression, or outcome

We identified adult patients with:

- sickle cell (HbSS),
- sickle cell trait (HbS),
- sickle cell – thalassemia (HbSβ) and
- sickle cell hemoglobin C (HbSC) variants

We assessed their association with HF and systolic dysfunction (SD) using coded SNOMED

METHODS

One of the largest healthcare commercial databases in the world derived from numerous and diverse financial, operational, and medical record source systems.

Unique Lives 50 Million	U.S. Population 15%	Healthcare Networks 26
Providers 317 Thousand	Hospitals 360	Longitudinal Data Points 315 Billion
Live Connectors 2,000+	Combined Customer NPR $69 Billion	Pre-built Analytics 1,000+



A FEW WORDS ABOUT SNOMED…

- Comprehensive clinical terminology

Systematically organized computer processable collection of medical terms providing codes, terms, synonyms and definitions used in clinical documentation and reporting.

It allows a consistent way to index, store, retrieve, and aggregate clinical data across specialties and sites of care.

PATIENT POPULATION

All adults 18 years or older

HbS, HbSS, HbSC, HbSB

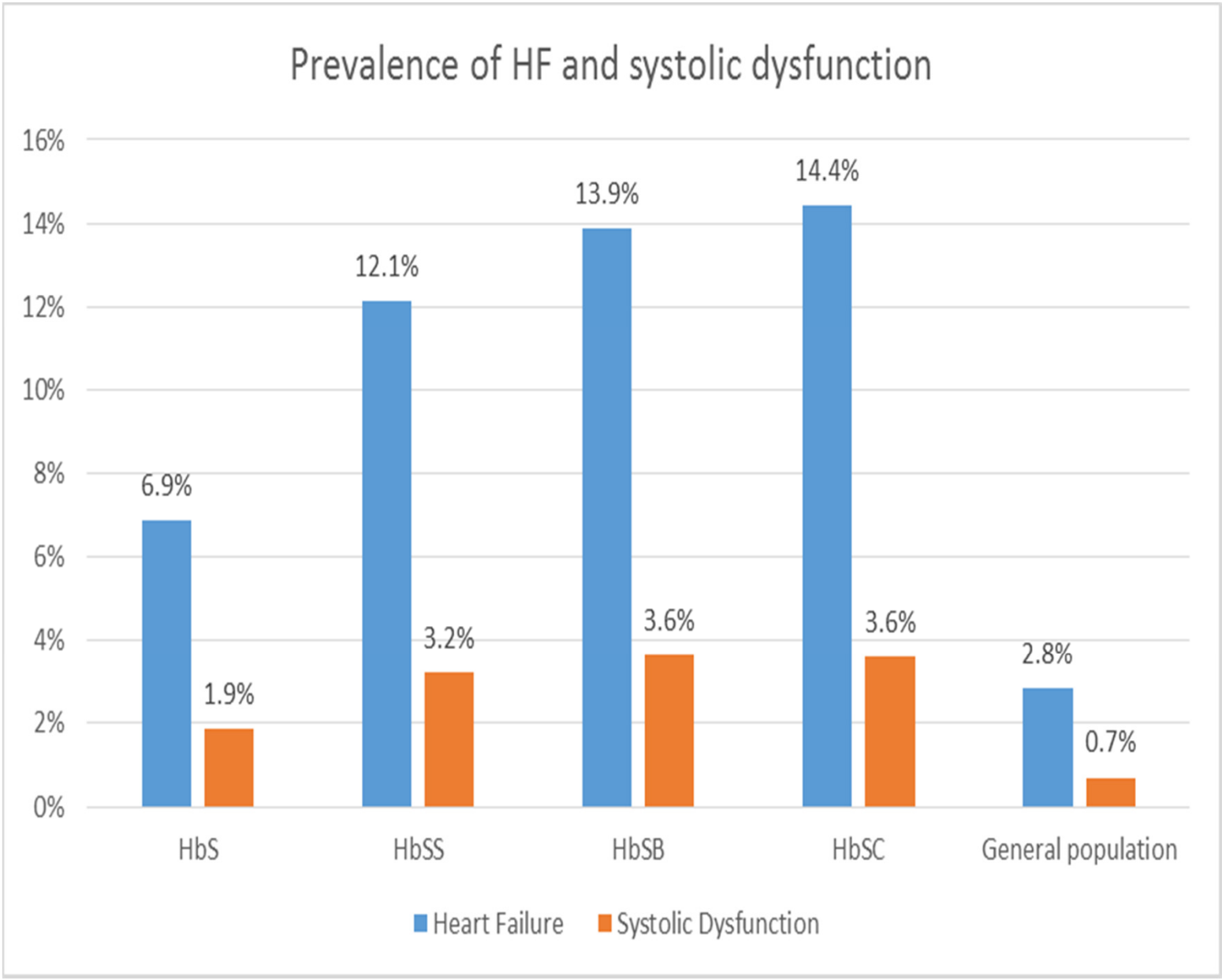
Heart Failure

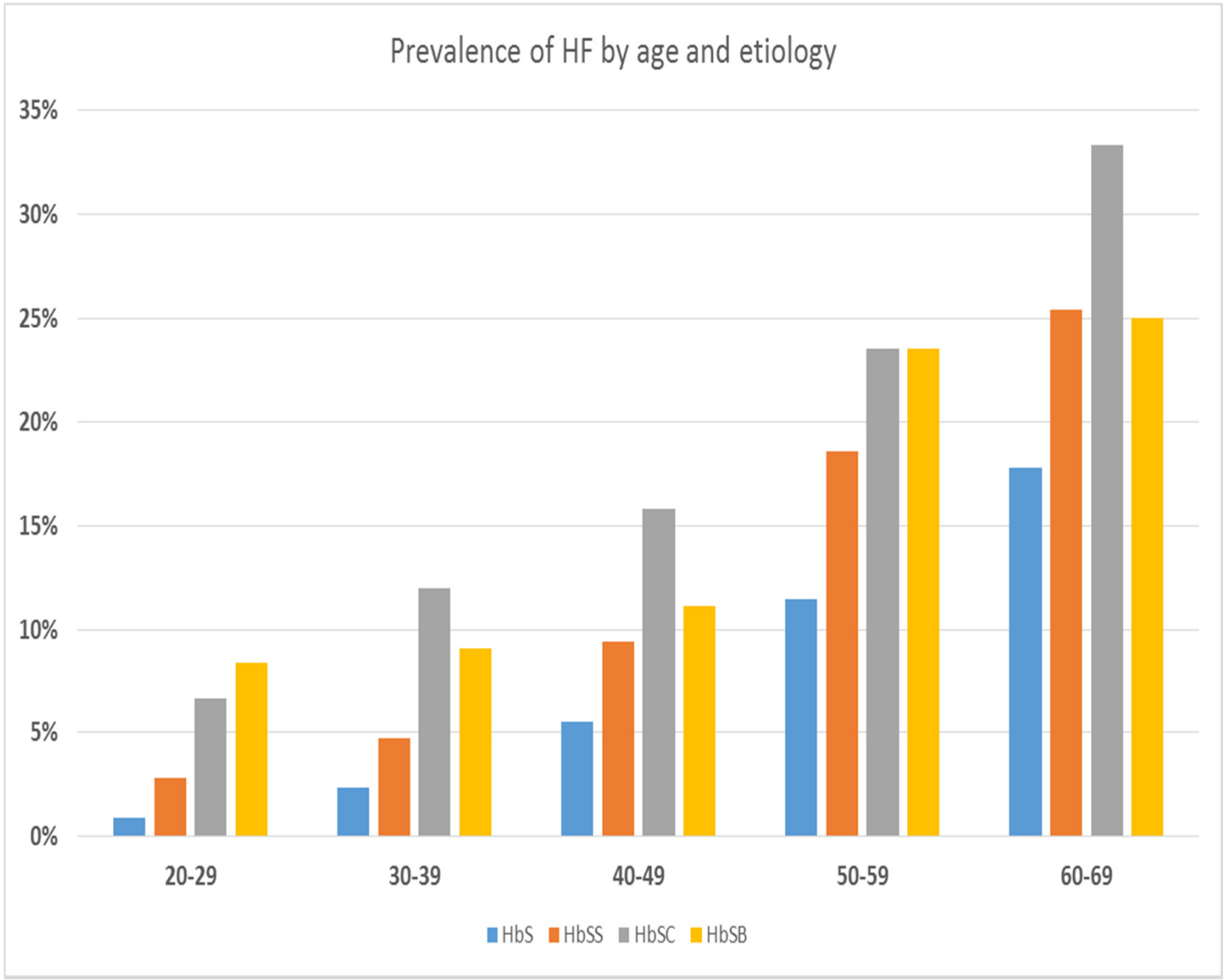
Systolic Dysfunction : Left ventricular Ejection Fraction <50%

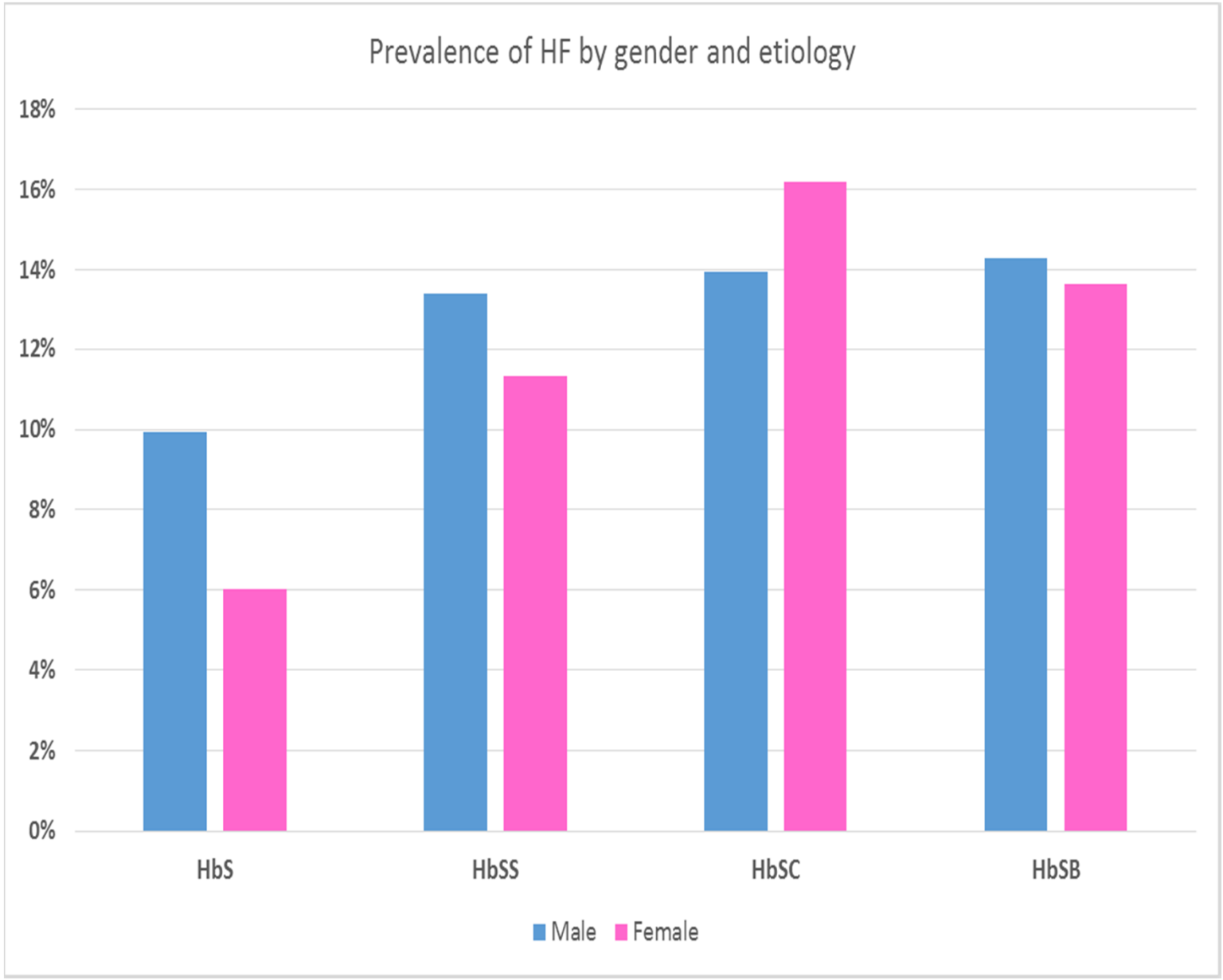
Treatment

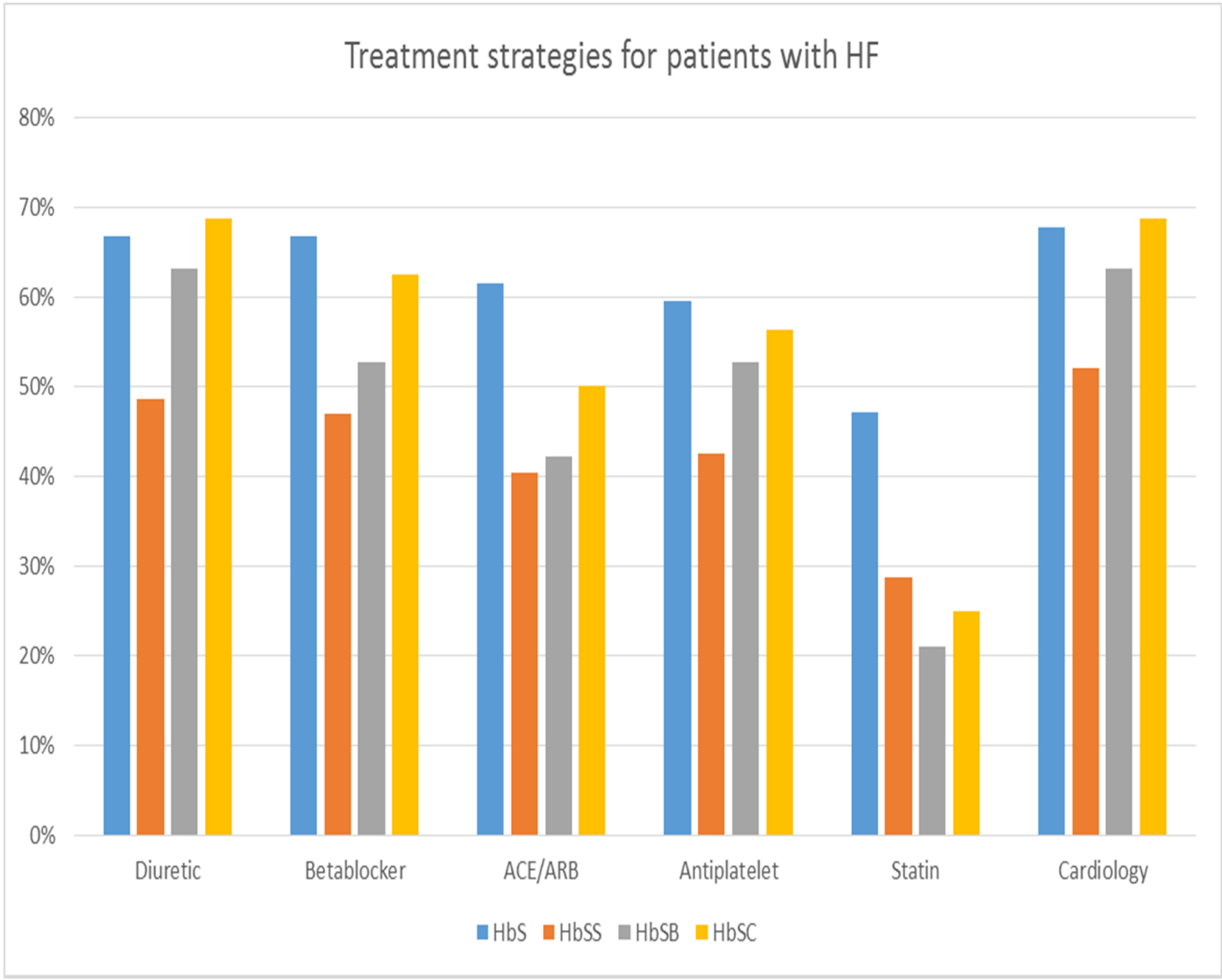
45,276,950 patients in the database

Dx	n
HbS	30320
HbSS	14900
HbSB	1370
HbSC	1110


Prevalence of HF and systolic dysfunction
16%
14%
12%
10%
8%
6%
4%
2%
0%
6.9%
1.9%
12.1%
3.2%
13.9%
3.6%
14.4%
3.6%
2.8%
0.7%
HbS
HbSS
HbSB
HbSC
General population
Heart Failure
Systolic Dysfunction


Prevalence of HF by age and etiology
35%
30%
25%
20%
15%
10%
5%
0%
20-29
30-39
40-49
50-59
60-69
HbS
HbSS
HbSC
HbSB


Prevalence of HF by gender and etiology
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
HbS
HbSS
HbSC
HbSB
Male
Female


Treatment strategies for patients with HF
80%
70%
60%
50%
40%
30%
20%
10%
0%
Diuretic
Betablocker
ACE/ARB
Antiplatelet
Statin
Cardiology
HbS
HbSS
HbSB
HbSC

CONCLUSIONS

Patients with sickle cell variants are at an increased risk for HF and systolic dysfunction.

Risk of HF increases with age, and varies by gender across diseases

Patients with HbSS disease may be undertreated for their HF

Referral to cardiologist in high risk patients is essential

LIMITATIONS OF THE STUDY

Dependent on coded terminology

Needs further validation with larger studies

REVERSAL OF CARDIAC IRON OVERLOAD IN SICKLE CELL CARDIOMYOPATHY

BACKGROUND: MECHANISM OF CARDIAC IRON OVERLOAD IN SICKLE CELL DISEASE

Iron overload occurs in patients with sickle cell disease requiring multiple blood transfusions

During iron overloading, transferrin becomes saturated and toxic non-transferrin- bound iron (NTBI) begins to appear in the circulation.

NTBI readily enters cardiomyocytes, and is rapidly bound by ferritin and transported to lysosomes for degradation and long-term storage.

When the antioxidant capacity of the cell is exceeded, reactive oxygen species are formed damaging organelles, interfering with electrical and mechanical processes, and triggering myocyte apoptosis.

BACKGROUND: CARDIAC IRON OVERLOAD

Iron accumulates in the ventricular wall, papillary muscles, ventricular septum and predominantly the epicardium

It is greater in contractile rather than in conducting myocardium.

The degree of the heart block (first degree) and supraventricular arrhythmias are correlated with the level of iron deposition in the atrial myocardium.

DIAGNOSIS OF CARDIAC IRON OVERLOAD

EKG: Arrhythmias and heart block, late presentation

ECHO:

- Diastolic dysfunction appears early in the course of iron overload
- Systolic dysfunction occurs very late

Signs of cardiac toxicity by echo appear after severe cardiac iron deposition and the process is more difficult to reverse

Cardiac biopsy can measure subclinical levels of iron overload- however invasive and sampling error

Cardiac MRI: T2*

MRI TO DIAGNOSE CARDIAC IRON OVERLOAD

T2* allows direct cardiac iron measurement using MRI, rather than indirect methods such as measuring serum ferritin level or liver iron concentration,

Allows recognition of preclinical cardiac iron and proactive modifications of iron chelation therapy.

Leonardi *et al.* found that there was poor correlation between echocardiographic diastolic dysfunction parameters and T2*.

T2* MEASUREMENT BY MRI

T2* is a relaxation parameter which is shortened in tissues containing particulate iron, which disturbs the local magnetic microenvironment.

Cardiac T2* correlates inversely with cardiac iron concentration (Wood et al, 2005b; Ghugre et al, 2006).

T2* Decay: >40 normal

20-40 abnormal

<20 severe iron overload

Low T2 associated with ventricular dysfunction, and myocardial arrhythmias (Anderson et al, 2001).

IRON CHELATION FOR CARDIAC IRON OVERLOAD

Iron chelation and regular phlebotomy without standard systolic heart failure therapy improved biventricular failure in a patient with cardiac hemochromatosis (*Chow et al*).

Tashiro A *et al*. showed clinical improvement, as well as hemosiderin depletion after 3 months of iron chelation with deferoxamine in a patient who suffered from secondary cardiac hemochromatosis in sideroblastic anemia.

There are no reports of sickle cell patients with MRI evidence of cardiac iron overload which is reversed by iron chelation therapy

AIM

To non invasively diagnose left ventricular dysfunction and cardiac iron overload by ECHO and cardiac MRI and study the effects of aggressive iron chelation on Sickle cell patients with Cardiac hemosiderosis and left ventricular systolic dysfunction

METHODS

Identified 2 patients with sickle cell disease and symptomatic heart failure.

Echo to assess cardiac function.

Cardiac MRI to assess for iron overload.

Started on iron agents - deferasirox, and deferiprone

Followed by echocardiography and CMR for improvement.

PATIENT 1

52-year-old Non smoker African American female known to have hemoglobin SS disease, and hypertension

History of frequent recurrent blood transfusions.

Referred for management of heart failure symptoms

ECHO: LVEF 55-60%, diastolic dysfunction

CMR on 9/9/2013 ➔ LVEF 53%.

Cardiac T2* 25 ms, suggestive of excessive iron deposition in the myocardium

Ferritin level = 1534 ug/L.


FoV 276*340
C: 443.0, W: 1015.0
LF
Image no: 1
09/09/2013 - 02:53:05 PM
Slice 1 of 25
P
46

Started on Deferasirox.

Patient was already on an ACE inhibitor for hypertension and microalbuminuria. Beta blocker and diuretic were initiated for symptomatic heart failure.

FOLLOW UP

Much improved symptoms of heart failure

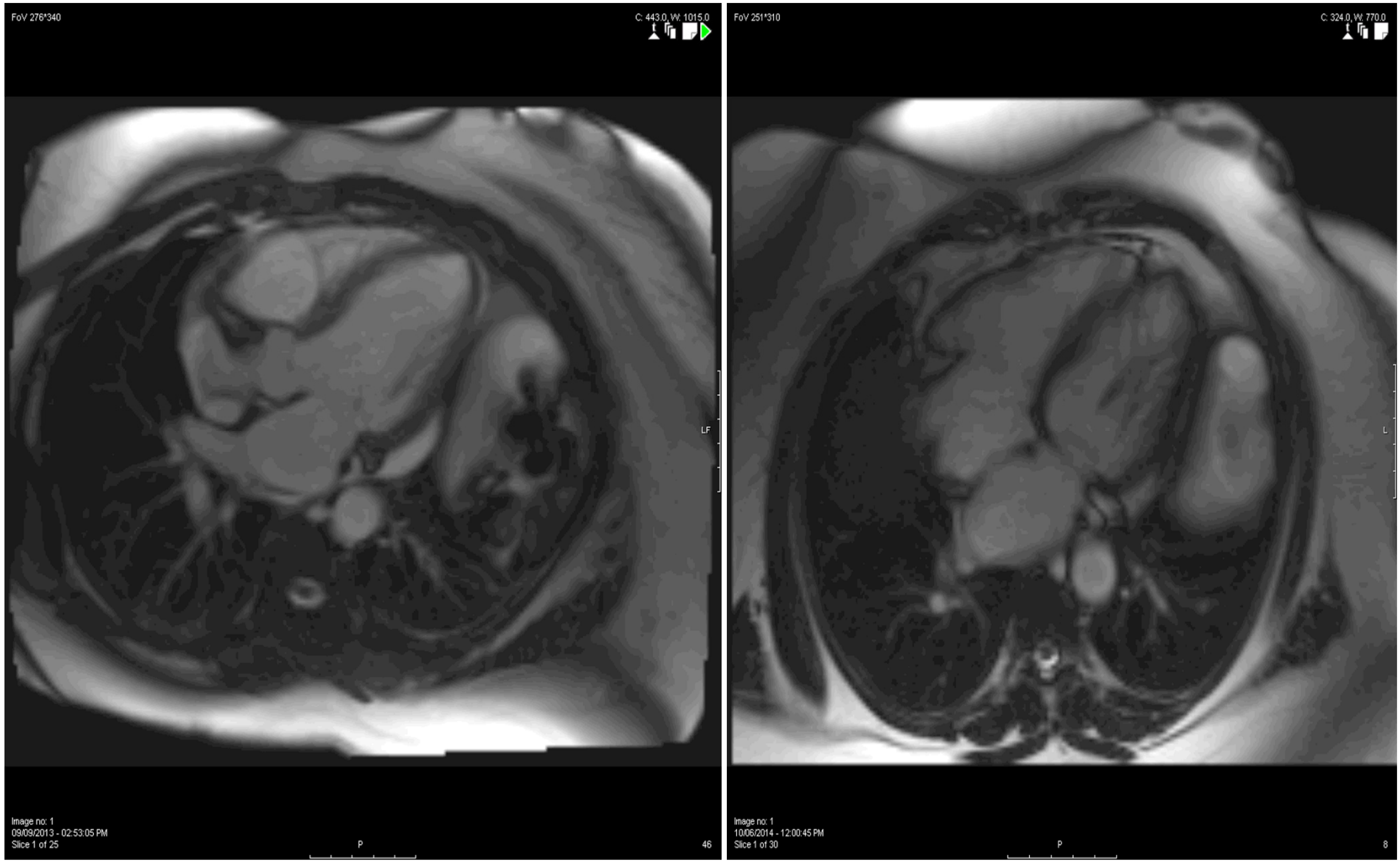
Repeat CMR 10/6/2014 after 12 months of iron chelation therapy showed LVEF improved to 66%

T2* improved to 33 ms.

Follow up ferritin 855 ug/L.


FoV 251*310
C: 324.0, W: 770.0
L
Image no: 1
10/06/2014 - 12:00:45 PM
Slice 1 of 30
P
8

CMR BEFORE AND AFTER IRON CHELATION



PATIENT 2

45-year-old African-American male smoker known to have hemoglobin SS disease, hypertension, chronic kidney disease stage III

Multiple transfusions for recurrent sickle cell crises

Referred for heart failure symptoms

TTE 3/20/14 LVEF 15-20%

Initiated on heart failure therapy including beta blocker, hydralazine/Imdur (no ACE or spironolactone due to advanced CKD)

CMR on 3/24/2014 showed severely dilated LV, Left ventricular ejection fraction (LVEF) was 27%

T2* 20 ms - Severe iron deposition.

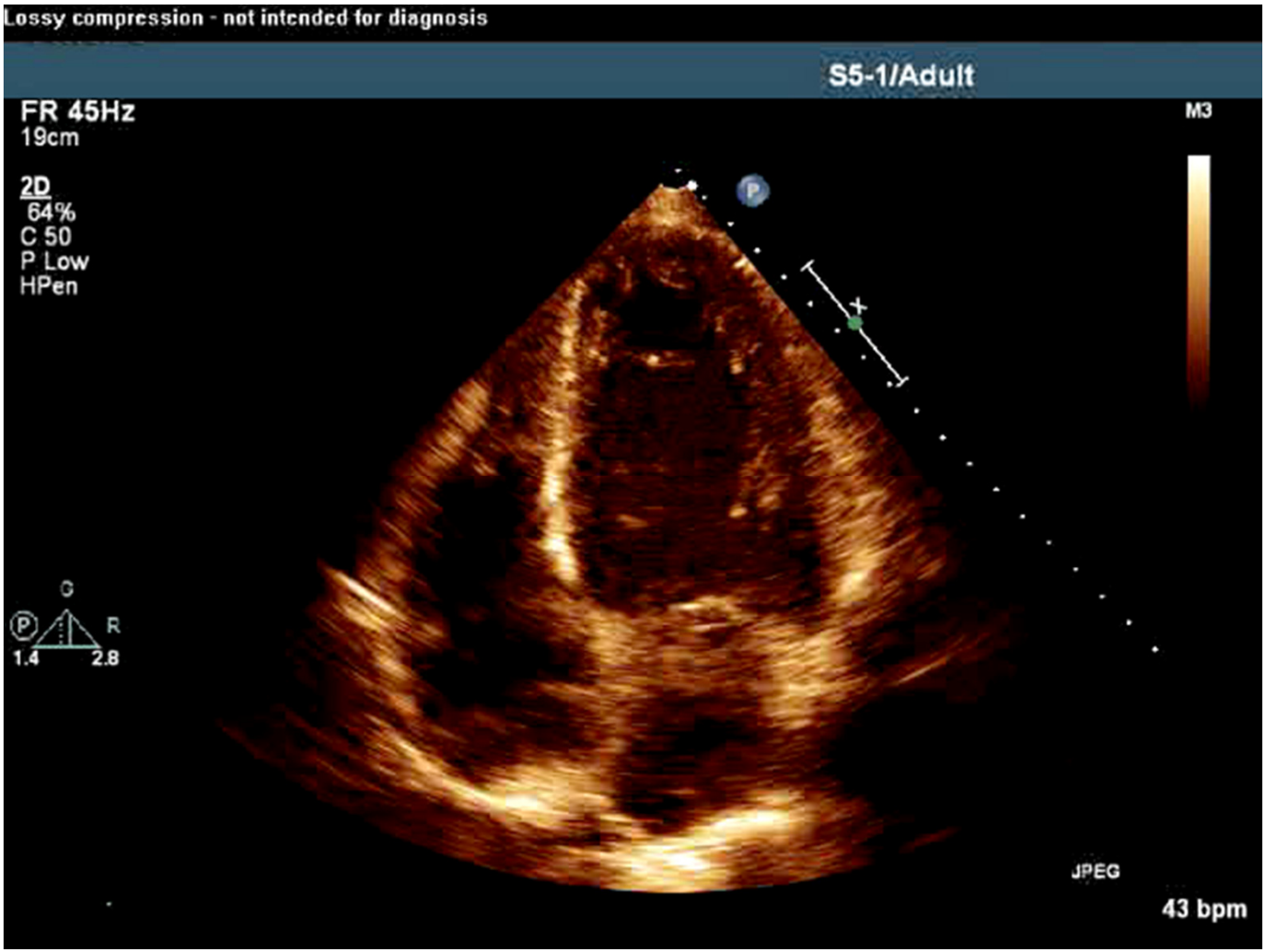
Ferritin level=1905 ug/L.

7/8/2014 Global systolic dysfunction LVEF 20-25% without significant improvement.

Patient started on deferiprone therapy as no improvement in LVEF despite heart failure regimen on repeat ECHO.

Left heart catheterization deferred due to advanced CKD

Primary prevention automatic implantable defibrillator (AICD) was deferred until follow up after chelation therapy.


Lossy compression - not intended for diagnosis
S5-1/Adult
FR 45Hz
19cm
2D
64%
C 50
P Low
HPen
M3
G
P
R
1.4
2.8
JPEG
43 bpm

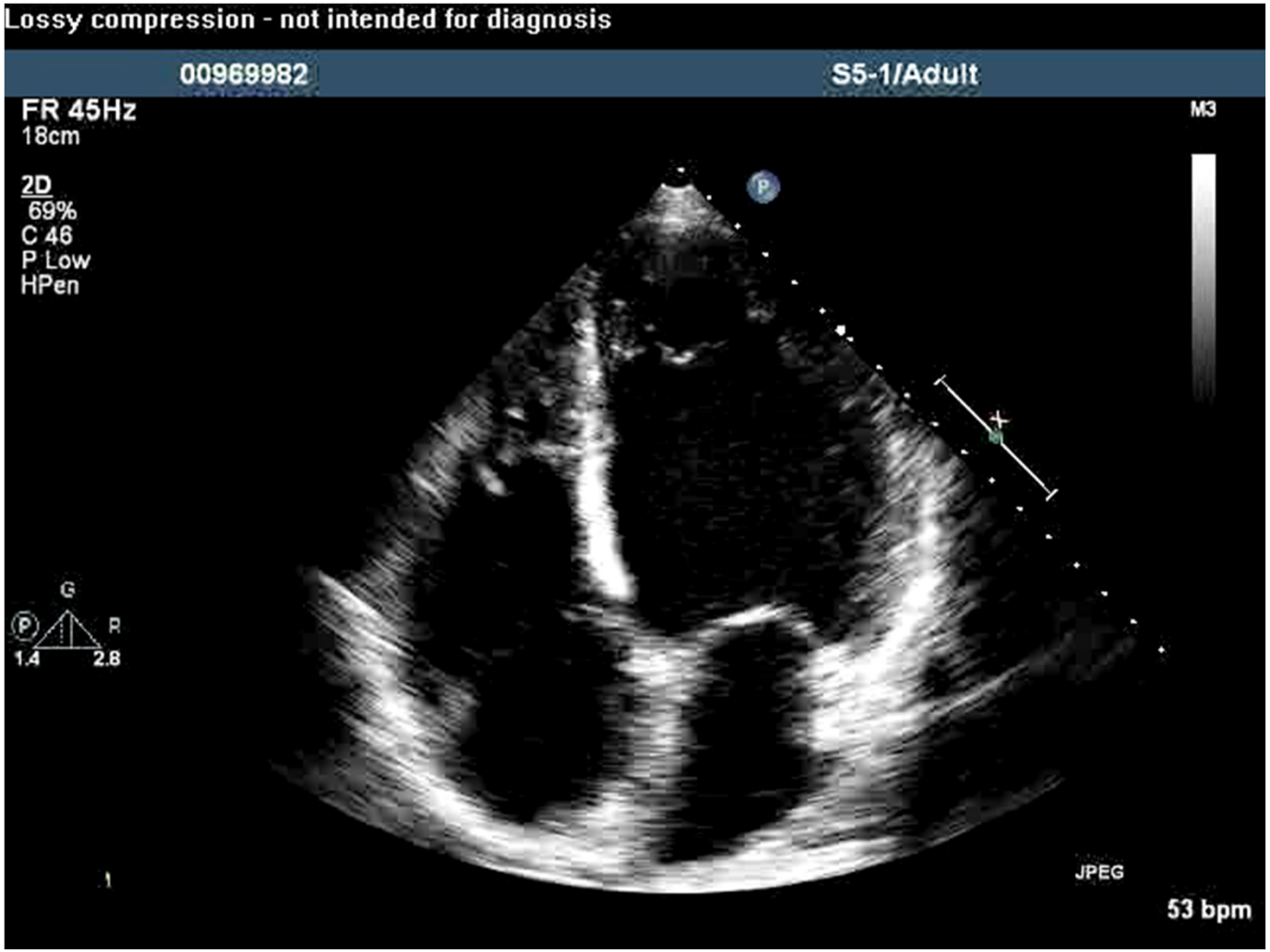
FOLLOW UP

Follow-up ECHO on 10/8/2014 (after 4 months of iron chelation) showed remarkable improvement in the left ventricular ejection fraction of 45%.

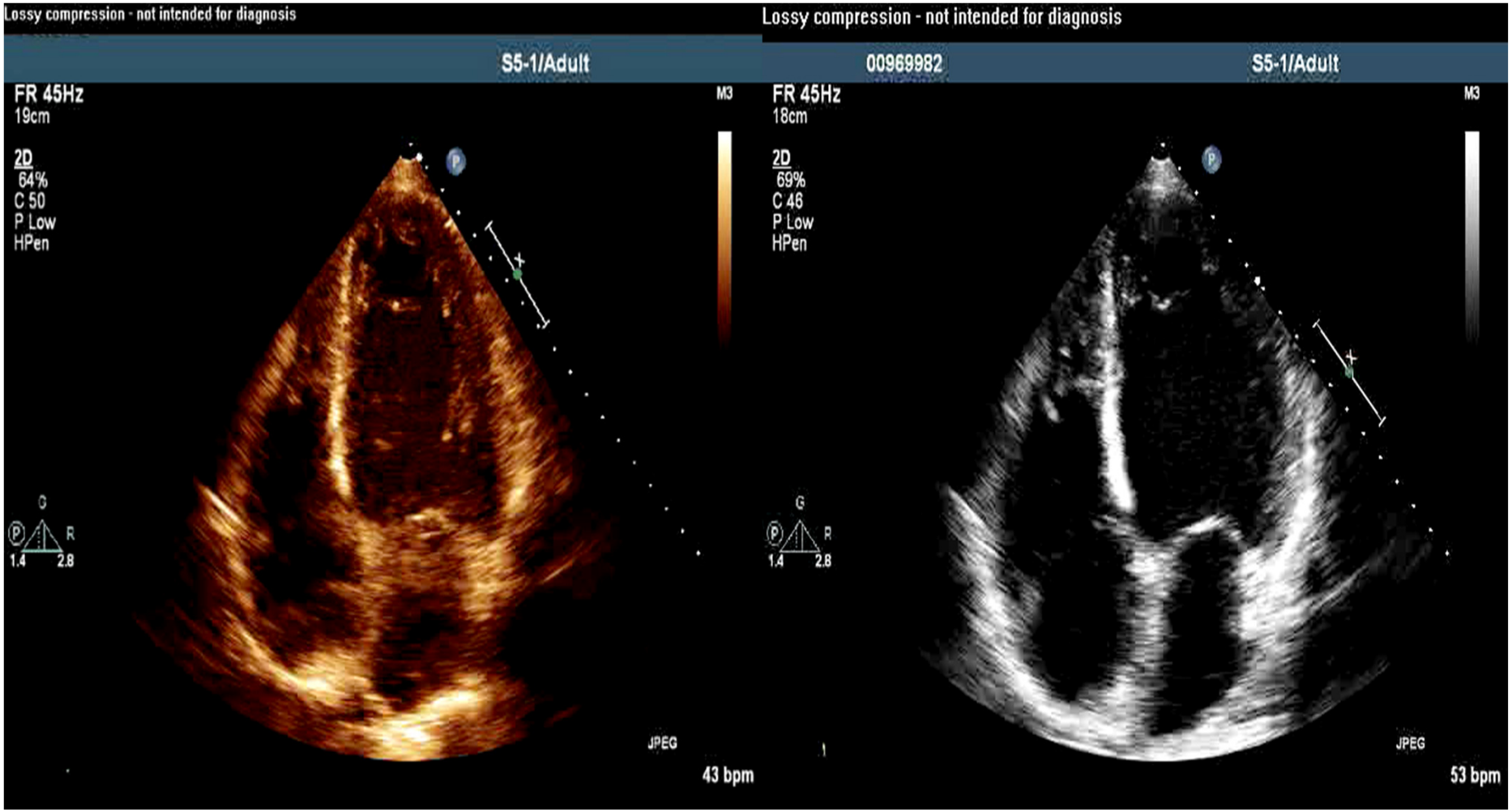
Symptoms of heart failure resolved

Ferritin= 1292 ug/L.

Awaiting CMR


Lossy compression - not intended for diagnosis
00969982
S5-1/Adult
FR 45Hz
18cm
2D
69%
C 46
P Low
HPen
M3
G
P
R
1.4
2.8
JPEG
53 bpm

ECHO BEFORE AND AFTER IRON CHELATION



SUMMARY

Both patients had improvement in their left ventricular function post initiation of iron chelation therapy

Duration of iron chelation therapy to improve left ventricular function was variable in both patients and is likely dependent on patient related factors

Role of standard heart failure medications in these patients is not clear

FURTHER STUDIES NEEDED...

Larger studies needed to assess the benefits of iron chelation therapy in sickle cell patients with cardiac iron overload and left ventricular dysfunction

Further studies to assess the role of standard heart failure medications in these patients

TAKE HOME POINTS

Our case series points towards the role of iron chelation in managing left ventricular dysfunction due to iron overload cardiomyopathy in sickle cell disease

MRI in sickle cell disease

- Uses T2* to directly measure cardiac iron
- Sensitive tool to identify patients with subclinical cardiac iron concentration
- May help stratify their risk of subsequent cardiac dysfunction
- Early detection of cardiac iron overload may lead to earlier aggressive treatment and may help reduce patient morbidity and mortality

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Thanks' for your kind attention!!!!!!



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