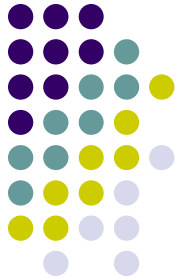
ΑΙΜΟΧΡΩΜΑΤΩΣΗ

ΣΠΥΡΟΜΗΤΡΟΣ ΓΕΩΡΓΙΟΣ
ΚΑΡΔΙΟΛΟΓΟΣ ,F.E.S.C, ΔΙΕΥΘΥΝΤΗΣ ΕΣΥ
ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ Γ.Ν.ΚΑΤΕΡΙΝΗ

TERMINOLOGY

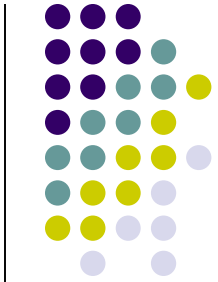


- **Hemochromatosis refers to iron overload generally**.

- **Hereditary hemochromatosis (HH)**, most commonly due to **mutations in the HH gene (*HFE*)**, is a disorder in which **increased intestinal iron absorption can lead to total-body iron overload**

- Deposition in **parenchymal tissues, including the heart**

EPIDEMIOLOGY



- Hereditary hemochromatosis is a common disorder with ***recessive inheritance*** that affects 1 in 400 individuals of northern European ancestry.
- Less common in individuals with African or Hispanic ancestry and extremely uncommon in individuals with Asian ancestry
- Extremely common in the Caucasian population, approaching a **gene frequency of 7%** and a **disease prevalence of 0.2 to** 0.7 % in the general Caucasian population

CENTRAL ILLUSTRATION: Diagnostic Approach in Various Causes of Restrictive Cardiomyopathy When Patients Present With Heart Failure With Preserved Ejection

RESTRICTIVE CARDIOMYOPATHY (RCM)
A rare form of heart muscle disease characterized by rigid heart walls and restrictive filling of the ventricles

Age of Onset	Symptoms	Diagnostic Tools	Etiologies	Management
< 30 years of age (due largely to genetic abnormalities) **> 65 years of age**	No symptoms of RCM, or very mild symptoms Over time leads to heart failure that can cause symptoms of: Exercise intolerance Dyspnea Fatigue Arrhythmias Lower extremity edema	Medical history Echocardiogram MRI FDG-PET imaging Cardiac catheterization Endomyocardial biopsy **Important to rule out:** Hypertensive heart disease Hypertrophic cardiomyopathy Constrictive pericarditis High output heart failure	**Primary/idiopathic:** Endomyocardial fibrosis Idiopathic restrictive disease **Secondary/Infiltrative:** Amyloidosis Sarcoidosis Hemochromatosis Scleroderma Carcinoid heart disease Glycogen storage diseases such as Fabry disease Radiation induced Metastatic malignancy Iron overload	**Therapy is directed towards the specific underlying disease etiologies and to:** Relieve congestive symptoms (Loop diuretics, Sodium and fluid restriction) Rhythm control with the use of antiarrhythmic agents Permanent atrioventricular sequential pacer implantation Heart transplantation

Pereira, N.L. et al. J Am Coll Cardiol. 2018;71(10):1149-66.

Causes of iron overload

Cause	Mechanism
Increased intake	
Transfusional overload (eg, in inherited bone marrow failure syndromes, hemolytic anemias, myelodysplastic syndrome, aplastic anemia)	Iatrogenic, used to treat severe anemia
Iron-loaded diet (eg, "African iron overload")	Dietary, from iron in barrels used to store homemade beer; may have genetic component
Repeated hemin infusions (eg, to treat acute intermittent porphyria)	Iatrogenic, used to treat acute porphyric attacks
Increased absorption (with normal intake)	
Hereditary hemochromatosis due to *HFE* mutation (eg, C282Y/C282Y; C282Y/H63D)	Incompletely understood effects on iron absorption
Hereditary hemochromatosis due to rare mutations (eg, ferroportin, hemojuvelin, hepcidin, ceruloplasmin)	Alterations in known regulators of intestinal iron absorption
Thalassemia major or intermedia	Ineffective erythropoiesis leading to suppression of hepcidin; transfusional iron overload may also contribute
Sideroblastic anemia (inherited or acquired)	Ineffective erythropoiesis leading to suppression of hepcidin
Inherited anemias (eg, CDA, DBA)	Ineffective erythropoiesis leading to suppression of hepcidin
Gestational alloimmune liver disease (GALD)*	Maternal alloantibody causing liver injury in utero
Chronic liver disease, especially alcoholic liver disease, chronic hepatitis, and non-alcoholic fatty liver disease (NAFLD)	Incompletely understood, possible reduced hepcidin production?

Refer to UpToDate content on iron overload, iron balance, and specific disorders for further details.

HFE: hereditary hemochromatosis gene; CDA: congenital dyserythropoietic anemia; DBA: Diamond-Blackfan anemia.
* Many cases of GALD were previously called neonatal hemochromatosis; however, the conditions are not synonymous.

Courtesy of Stan Schrier, MD.

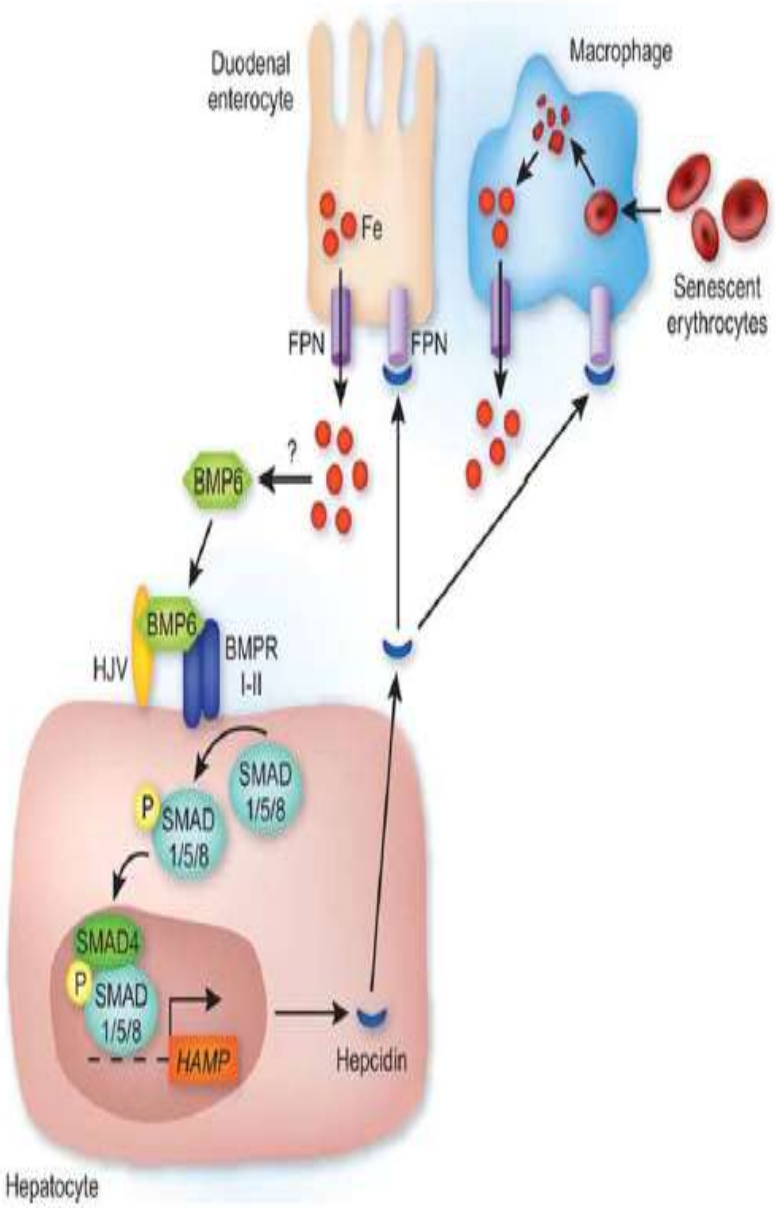
TABLE 1 Conditions Associated With Iron Overload Cardiomyopathy

Primary Hemochromatosis	
Classical (Type 1)	
Mutation:	*HFE* gene (C282Y or H63D)
Inheritance:	Autosomal recessive
Nonclassical (Type 2)	
Mutation:	Subtype A-hemojuvelin [iron-regulatory protein] (*HJV* gene)
	Subtype B- hepcidin (*HAMP* gene)
Inheritance:	Autosomal recessive
Nonclassical (Type 3)	
Mutation:	Transferrin receptor (*TfR2* gene)
Inheritance:	Autosomal recessive
Nonclassical (Type 4)	
Mutation:	Ferroportin [iron exporter protein] (*SLC40A1*)
Inheritance:	Autosomal dominant
Secondary Iron-Overload	
Acquired anemias	
Hemoglobinopathies: Alpha and beta thalassemia and sickle cell anemia, sideroblastic anemia	
Acquired anemias	
Myelodysplastic syndromes	

HFE gene mutation **is <u>necessary but not sufficient</u> for** the development of hemochromatosis (clinical iron overload).

It generally **<u>takes decades of excess iron absorption</u>** without concomitant blood loss for clinically significant tissue iron deposition to occur.

Clinical manifestations of HH generally do not occur until after the age of **<u>40 years in men and after menopause in women</u>**



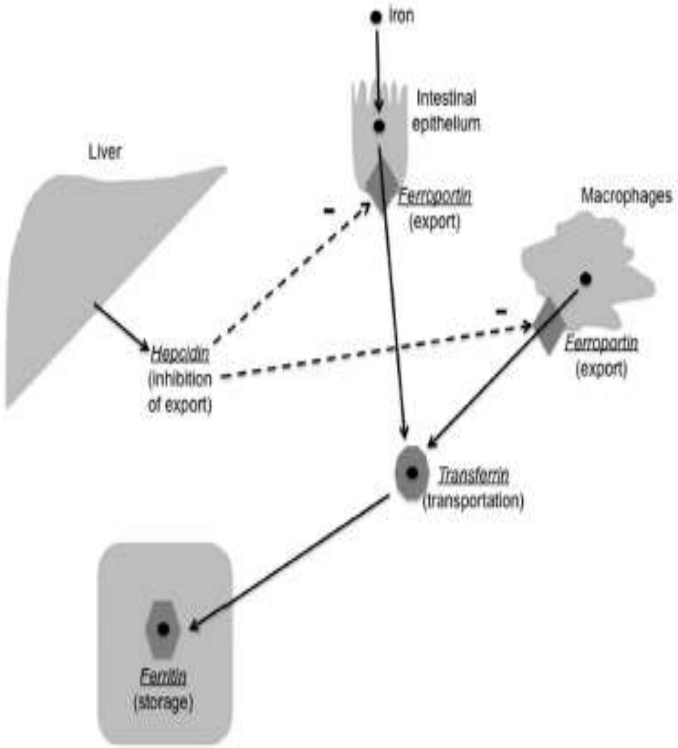


Fig. 2. Summary of interactions between duodenal enterocytes, hepatocytes, and macrophages in iron homeostasis regulated by hepcidin. FPN, ferroportin. (Adapted from Camaschella C. BMP6 orchestrates iron metabolism. Nat Genet 2009;41:386-388. Used with permission from *Nature Genetics*. Copyright © 2009, Nature Publishing Group).

Figure 1. A schematic presentation of the role of the main proteins involved in iron metabolism (see text for details).

Hereditary hemochromatosis genes, inheritance patterns, and clinical features

Gene	Inheritance	Clinical characteristics
HFE	AR	Classical hereditary hemochromatosis (HH) with low penetrance; clinical onset in adulthood
HJV (hemojuvelin) or *HAMP* (hepcidin)	AR	Juvenile hemochromatosis with complete penetrance and early age of iron overload (childhood or young adulthood), along with early onset of hypogonadism and cardiac complications. Liver disease is less prominent.
TFR2 (transferrin receptor 2)	AR	Rare condition described in case reports. Clinically similar to classical HH but with onset in young adults.
SLC40A1 (ferroportin)	AD	Variable dominant disorder: ▪ Families with loss-of-function mutations have ferroportin disease, characterized by high ferritin levels, increased macrophage iron, reduced transferrin saturation, mild anemia, and minimal hepatic iron deposition. ▪ Families with less common gain-of-function mutations have findings similar to classical HH.

Homozygosity for C282Y is **more commonly associated with clinical disease, accounting for over 90 percent of HH cases**

in UpToDate.

low penetrance. This means that biallelic mutations are usually required for clinical disease, but **many individuals with biallelic mutations will not be affected**

of C282Y homozygotes, only 1 in 10 will develop clinical iron overload.

Typical presentations

***Prior to the identification of the HFE* gene**, patients with HH often presented with symptoms attributable **to high levels of tissue iron deposition.**

- Routine availability of iron studies and identification of the *HFE* gene have converted the typical presentation of HH **from an end-stage disease of severe iron overload to a laboratory diagnosis often made in asymptomatic individuals.**

- The severity of presentation depends ***on the extent of iron overload***. Thus, individuals with HH in the modern era are more likely to present with the finding of ***high ferritin levels and/or HFE gene mutations than in the past.***

- Presentations associated with significant iron overload are ***rare in younger individuals. Men typically present at age 40 or older***, **women generally present after menopause** due to slower iron accumulation in the premenopausal years

BRIAN K. CROWNOVER, MD, and CARLTON J. COVEY, MD
American Family Physician Volume 87, Number 3 February 1, 2013

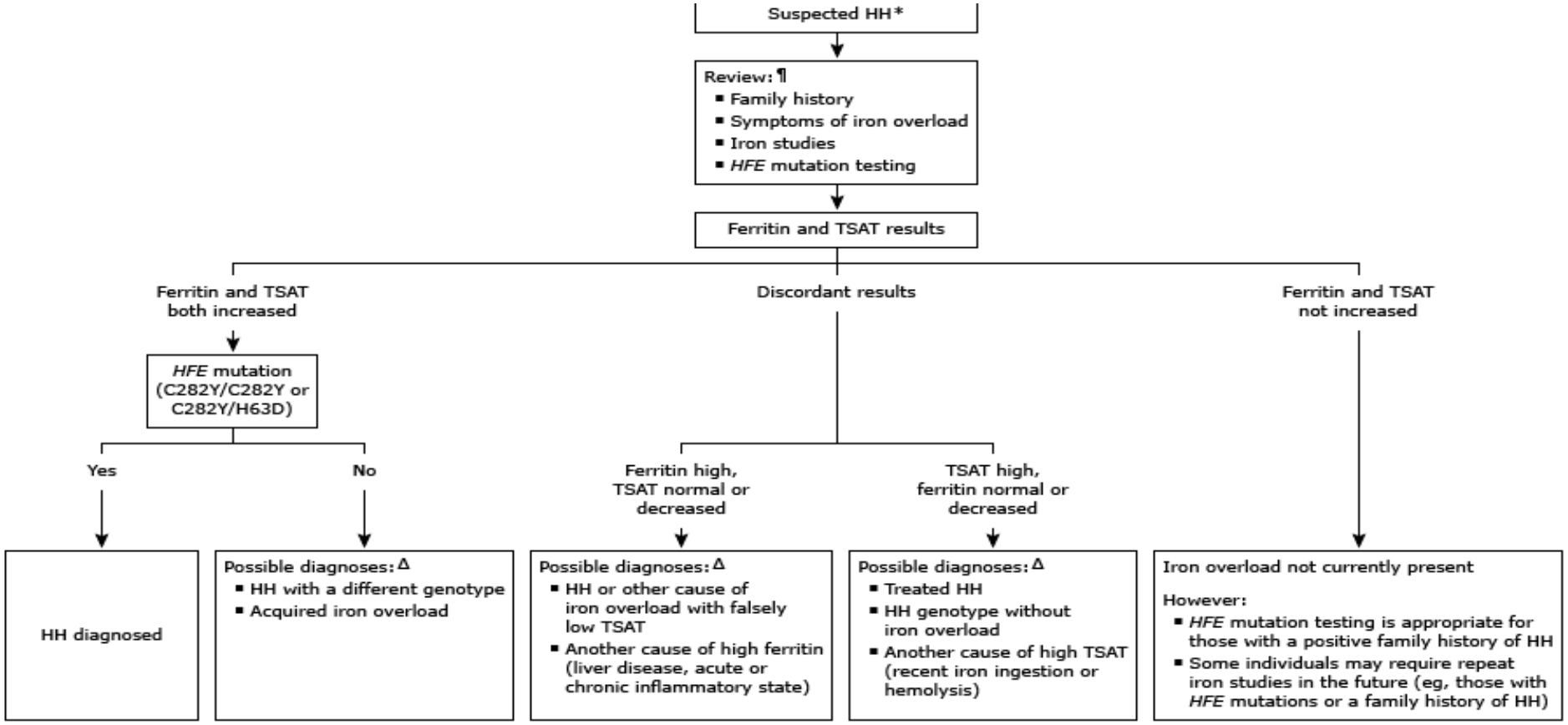
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hemochromatosis and Iron-Overload Screening in a Racially Diverse Population

- In the **Hemochromatosis and Iron Overload Screening (HEIRS) study**, which screened approximately ***100,000*** individuals in the United States and Canada for HH only 72 of 299 ***(24 percent***) had been **diagnosed with iron overload**, suggesting that the other **76 percent were asymptomatic at the time of testing**

- Participants were asked to identify any HH-associated **symptoms before their *HFE* genotype** results were available, and commonly reported symptoms included ***chronic fatigue, skin hyperpigmentation, swelling of the second and third metacarpal phalangeal joints, and generalized joint stiffnes***



An individual may be suspected of having HH based **on signs or symptoms of iron overload** and/or *a* ***positive family history of HH****.* Signs and symptoms of HH include the following:

Unexplained liver disease

Unexplained fatigue

Unexplained heart failure or arrhythmia

Unexplained arthropathy

High serum ferritin or TSAT

Porphyria cutanea tarda (PCT)

Unexplained hypogonadism or low libido

Type 2 diabetes mellitus with atypical presentation (eg, younger age than average or low BMI)

Iron studies and *HFE* genotype interpretation:

High ferritin:

- Women: >150 ng/mL (>337 pmol/L)
- Men: >200 ng/mL (>449 pmol/L)

High TSAT:

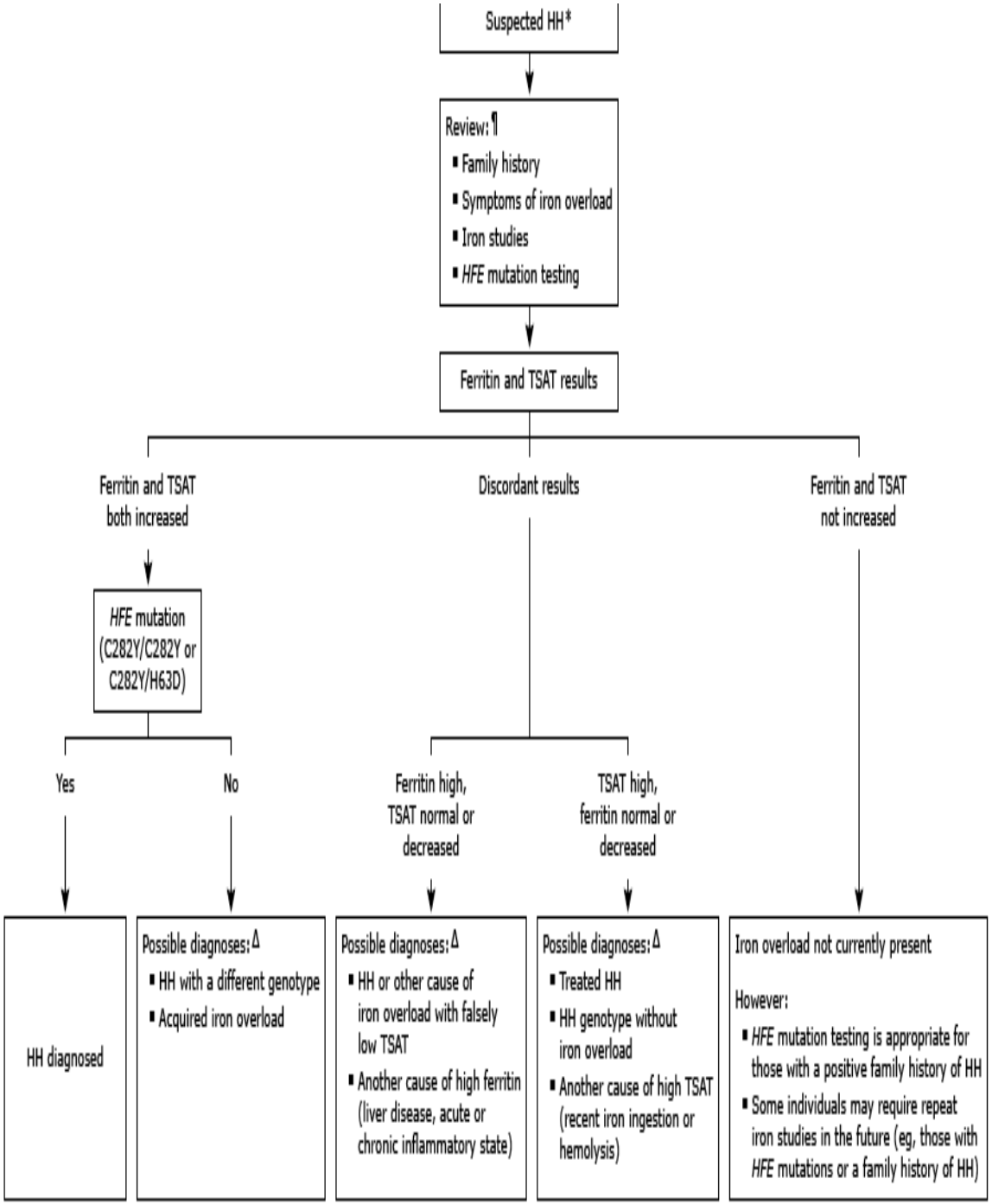
- >45%

HFE genotypes strongly associated with iron overload:

- C282Y/C282Y
- C282Y/H63D

Notes:

- Specific cutoff values used may vary by testing laboratories and professional societies.
- Ferritin is an acute phase reactant and may be elevated in inflammatory states, generally no more than 2 to 3 times increased over the upper limit of normal. Ferritin >1000 ng/mL (>2247 pmol/L) is associated with the greatest risk of organ damage, but some individuals with lower values (eg, 500 to 1000 ng/mL) may have organ damage.
- TSAT is a ratio of iron to transferrin and may be affected by recent iron ingestion or an episode of hemolysis.
- *HFE* genotypes other than those listed above (eg, heterozygous mutation, homozygous H63D/H63D, genotypes involving S65D) are less frequent in patients with HH and do not have as great a risk for iron overload (H63D/H63D, <10%; heterozygotes for any single mutation, similar to the general population). The interpretation of these other genotypes in individuals with significant iron overload is individualized.



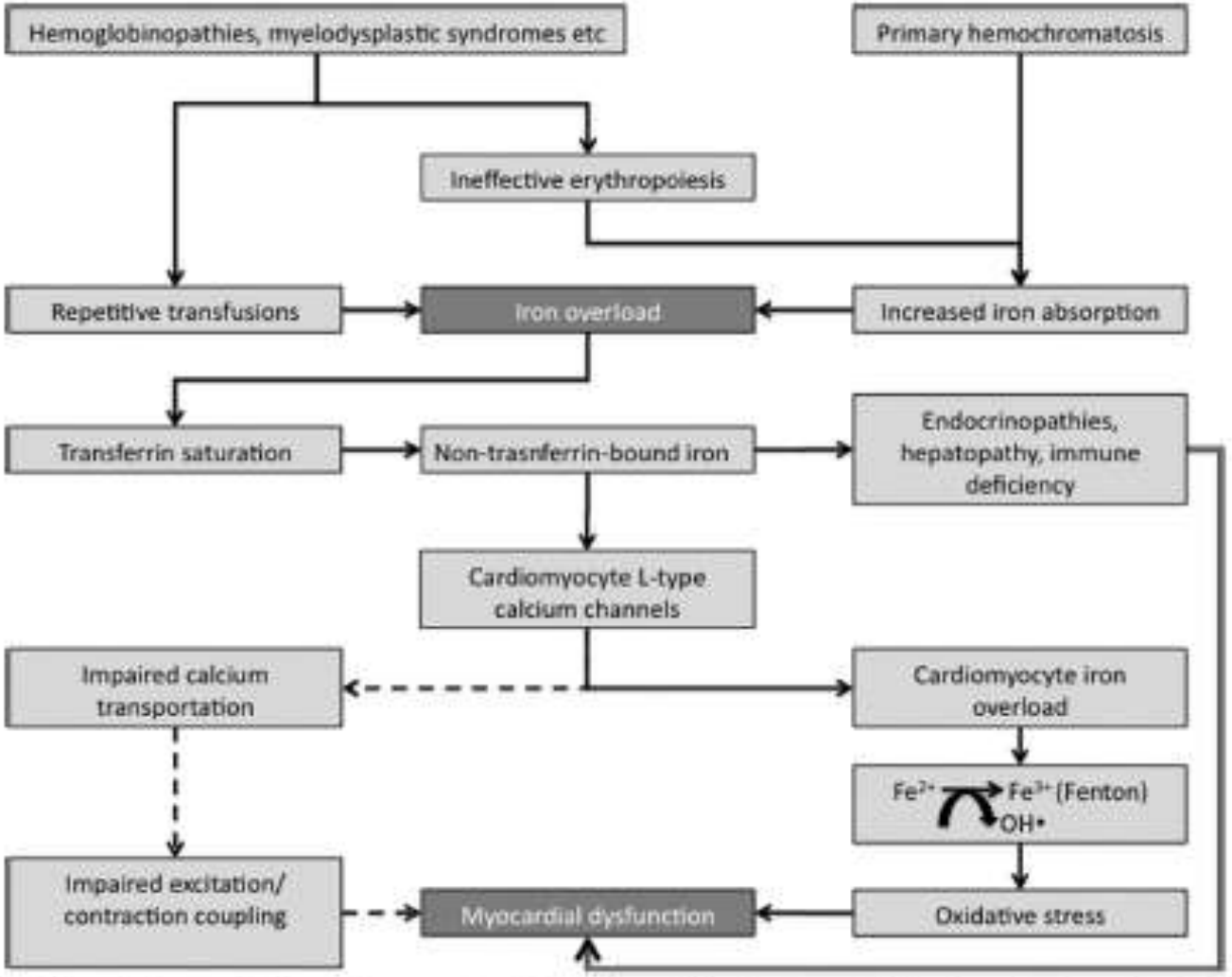


Figure 2. Pathohysiology of iron overload cardiomyopathy. Dotted lines indicate not well-defined mechanisms; double line, indirect effects.

Dimitrios T. Kremastinos. Circulation. Iron Overload Cardiomyopathy in Clinical Practice, Volume: 124, Issue: 20, Pages: 2253-2263, DOI: (10.1161/CIRCULATIONAHA.111.050773)

Phenotypic Expression

- **<u>the Dilated phenotype</u>**,
- characterized by a process of LV remodeling leading to **<u>chamber dilatation and reduced LVEF</u>**

- **<u>Restrictive phenotype</u>**,
- characterized by **diastolic LV dysfunction** with
- **restrictive filling, preserved LVEF, pulmonary** hypertension,
- subsequent **right ventricular dilatation.**

IOC is far more frequent in the secondary forms of iron overload than in primary hemochromatosis

conduction system abnormalities, tachyarrhythmias, and perimyocarditis

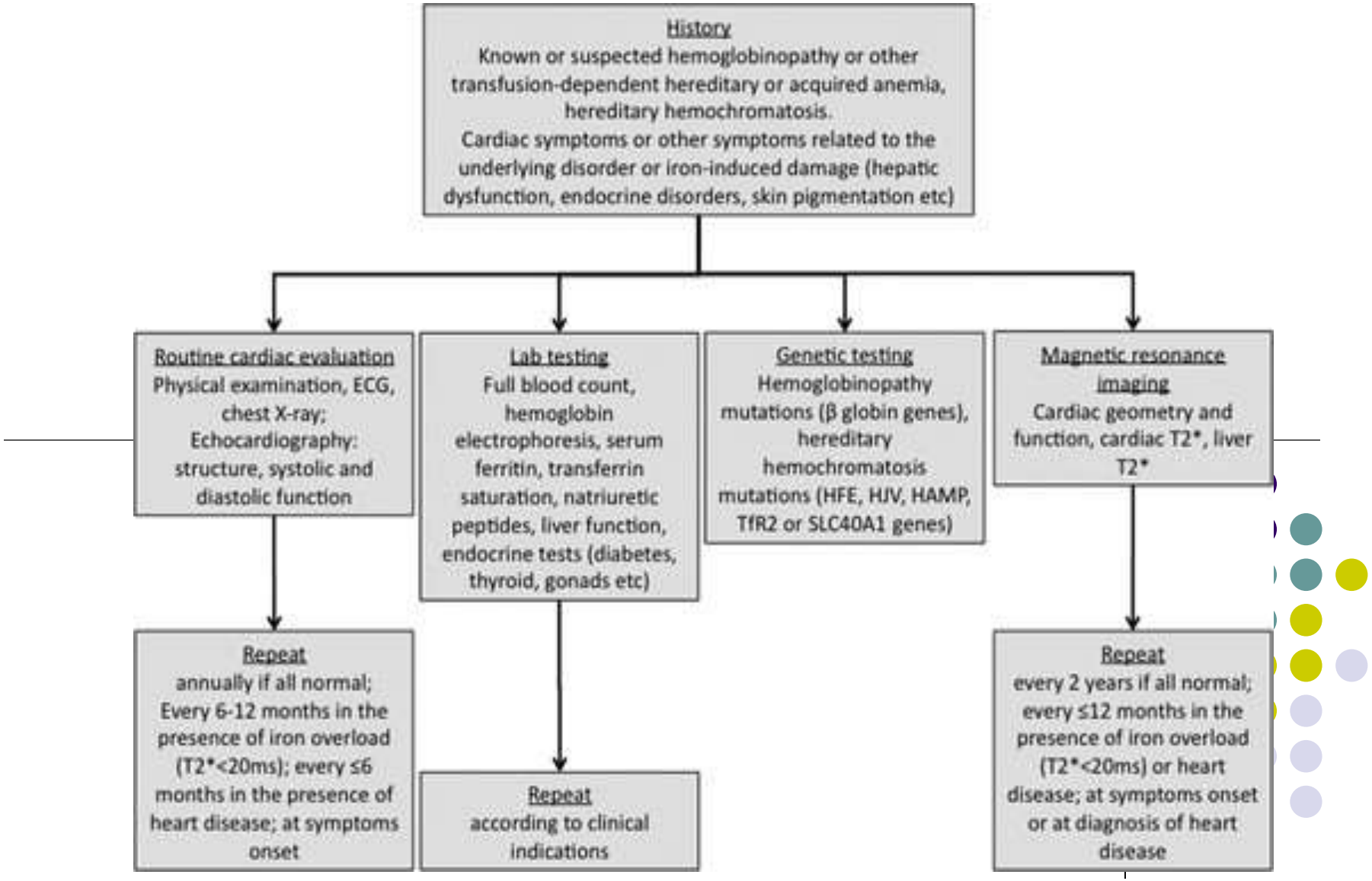
Phenotypic Expression

- Impaired **diastolic LV function featuring pseudonormalization and restrictive filling patterns by Doppler,** with or without left atrial enlargement,constitutes ***early findings***

- In the early stages of disease, **restrictive LV filling** by transmitral and pulmonary vein diastolic Doppler indexes has been reported in **8% to 50% of patients**

- Diastolic dysfunction was more pronounced in patients with advanced age.

- *In a minority of cases(<10%),* restrictive LV dysfunction leads with advancing age to the development of pulmonary hypertension,right ventricular dilation, and right-sided heart failure *without evidence LV remodeling* and continued preservation of LVEF, ***the so-called restrictive phenotype***



Dimitrios T. Kremastinos. Circulation. Iron Overload Cardiomyopathy in Clinical Practice, Volume: 124, Issue: 20, Pages: 2253-2263, DOI: (10.1161/CIRCULATIONAHA.111.050773)

Echocardiography I

- ***Main imaging modality*** used to ***screen*** patients with suspected IOC and for regular ***clinical follow-up.***
- Unlike most infiltrative cardiomyopathies LV wall thickness is not increased in IOC.
- The *time course* for progression from diastolic dysfunction to RCM and then dilated cardiomyopathy is *unknown*
- Identify the consequences of iron overload on the myocardial structure and function but *do not accurately predict myocardial iron content*

Kremastinos DT, Farmakis D, Aessopos A, et al.. Circ.Heart Fail 2010;3

Echocardiography II

- Myocardial ***strain rate imaging*** may be a more sensitive measure of the effects of oxidative stress on LV diastolic dysfunction than a measure of overall iron content

- Palka et al. also reported a decrease in peak systolic and diastolic early filling **mitral annular tissue velocity** as well as prolongation of the duration of atrial reversal wave of pulmonary vein Doppler in early disease

Shizukuda Y, Bolan CD, Tripodi DJ, et al. Does oxidative stress modulate left ventricular diastolic function in asymptomatic subjects with hereditary hemochromatosis? Echocardiography 2009

BIOMARKERS

- The ***amino-terminal pro-B-type natriuretic*** **peptide** may serve as an *early index of diastolic LV dysfunction in patients with iron overload*.
- Amino-terminal pro-B-type natriuretic peptide might be ***elevated*** in thalassemia major patients with preserved LVEF *before conventional Doppler indices of diastolic function became abnormal*

Kremastinos DT, Tsiapras DP, Kostopoulou AG,Hamodraka ES, Chaidaroglou AS, Kapsali ED. NTproBNP levels and diastolic dysfunction in betathalassaemia major patients. **Eur J Heart Fail 2007;9:531–6**.

Kremastinos DT, Hamodraka E, Parissis J,Tsiapras D, Dima K, Maisel A. Predictive value of B-type natriuretic peptides in detecting latent left ventricular diastolic dysfunction in betathalassemia major. **Am Heart J 2010;159:68–74**

FERRITINE

- Increases linearly with the number of blood transfusions.
- Closely correlated with liver iron content.
- **Acute-phase protein** that increases in several other conditions .
- ***Poorly correlated with myocardial iron load***.
- Serum ferritin provides a simple means for the ***monitoring of iron chelation therapy***

Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, Wu D,Taylor J, Westwood MA, Anderson LJ, Pennell DJ. Cardiac T2*magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation*. 2009;

CMR

- The only available noninvasive method with the potential to ***accurately quantitatively assess iron load***

- Iron's paramagnetic effect produces changes in the magnetic resonance signal ***intensity,shortens the T2 weighted relaxation time***

- T2 relaxation time is an **excellent measure of myocardial iron deposition** and is useful for serial assessment of **response to iron chelation therapy.**

Kondur AK, Li T, Vaitkevicius P, Afonso L.Quantification of myocardial iron overload by cardiovascular magnetic resonance imaging T2*and review of the literature. Clin Cardiol 2009

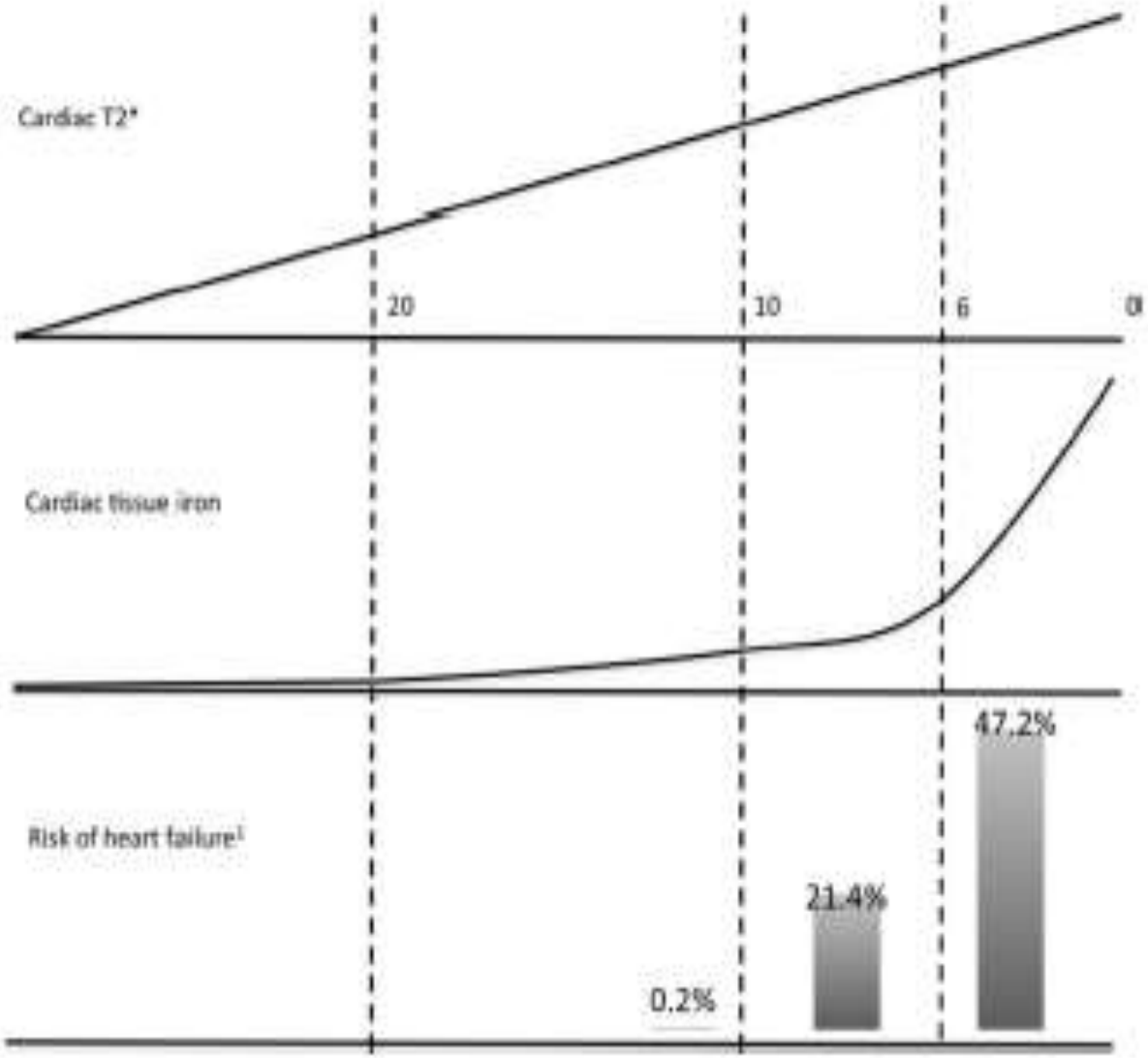
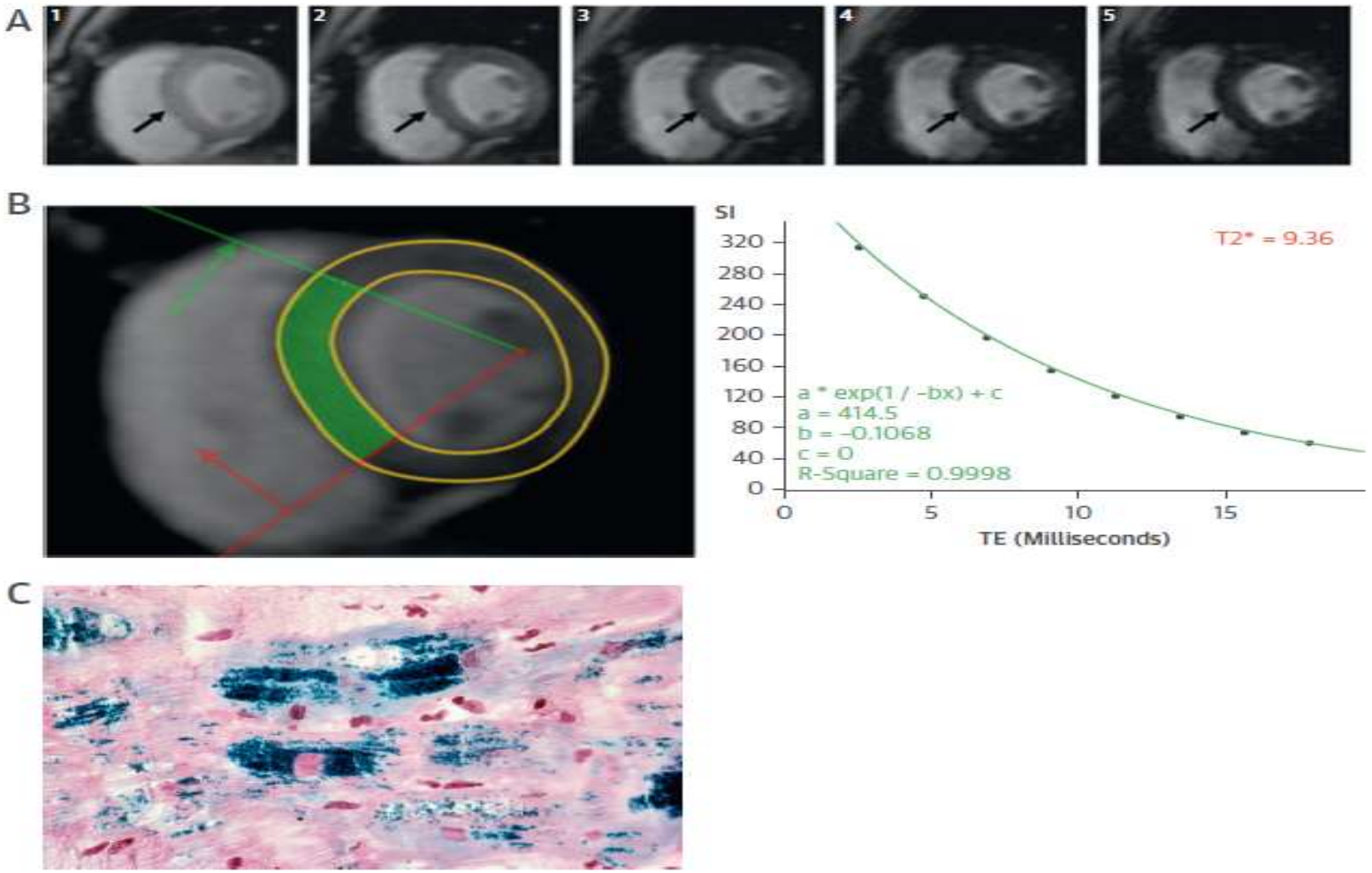


Figure 4. Schematic presentation of the relationship between cardiac T2* values, cardiac tissue iron concentration, and risk for heart failure ([1]data extracted from Kirk et al[20]).

Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, Wu D,Taylor J, Westwood MA, Anderson LJ, Pennell DJ. Cardiac T2*magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation*. 2009;

JACC VOL. 71, NO. 10, 2018
MARCH 13, 2018:1149–66

FIGURE 2 Cardiac Magnetic Resonance Imaging of Iron-Overload Cardiomyopathy



(A) Short-axis imaging demonstrates bright-blood T_2* sequence from a transfusion-dependent thalassemia patient. The myocardium is initially bright **(arrows)**, but the signal delays quickly due to the high myocardial iron content. Reprinted with permission from Gupta A, Gulati GS, Seth S, Sharma S, et al. Cardiac MRI in restrictive cardiomyopathy. Clin Radiol 2012;67:95–105. **(B)** The calculated T_2* value is 9.4 ms, which is indicative of severe iron overload. **(C)** High-power photomicrograph of ventricular myocytes with extensive sarcoplasmic iron accumulation **(blue)** (Prussian blue stain; original magnification ×400). Image courtesy of Dr. Joseph Maleszewski, Mayo Clinic.

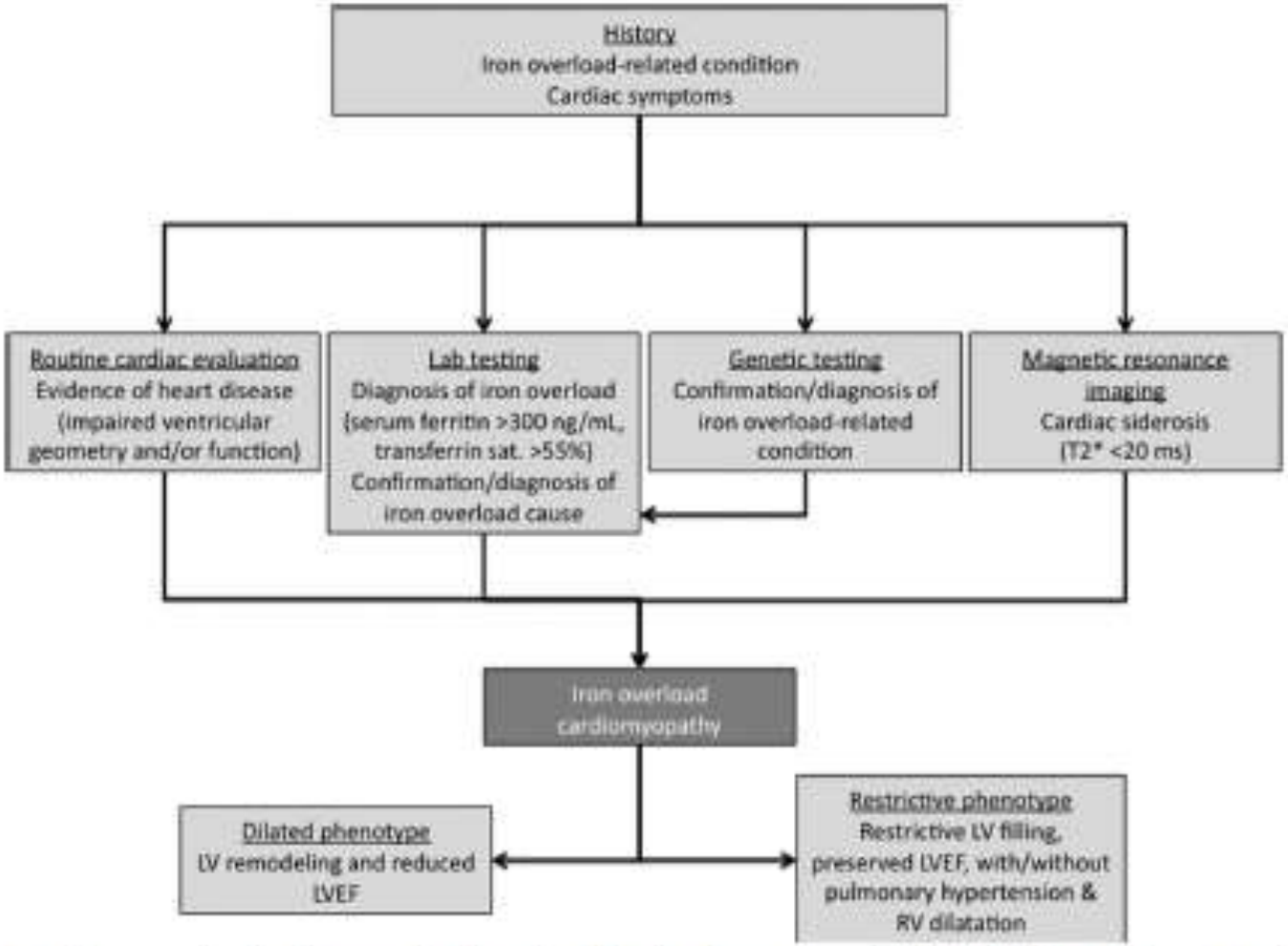


Figure 5. Diagnosis of iron overload cardiomyopathy based on the algorithm proposed in Figure 2. Diagnosis requires the presence of (1) iron overload (serum ferritin >300 ng/mL, transferrin saturation >55%), (2) cardiac siderosis (cardiac iron <20 ms), and (3) evidence of heart disease. LV indicates left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular.

Prevention and Therapy

- **The mainstay of treatment** for excessive iron deposition in patients with **hemochromatosis** is **phlebotomy**
- **All 4 types of hereditary hemochromatosis respond to therapeutic phlebotomy**
- ***Phlebotomy*** is an **easily applicable,safe, and inexpensive** procedure that ***prevents*** the development of iron-induced organ damage
- **prolongs survival** when initiated early
- cannot reverse the established severe complications

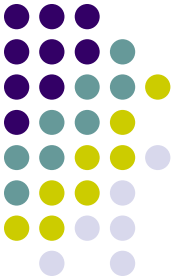
Pietrangelo A. Hereditary hemochromatosis–a new look at an old disease. *N Engl J Med*. 2004;350:2383–2397

Phlebotomy I

- **Individuals with iron overload (or at risk for iron overload) are treated with phlebotomy**. Those who cannot tolerate phlebotomy (eg, due to concomitant anemia) may be treated with an iron chelator instead if iron overload is significant

- Individuals ***without iron overload*** who have a HH genotype (homozygosity for *HFE* C282Y or compound heterozygosity for two *HFE* mutations) can be **monitored regularly**
- ***Heterozygotes generally do not require phlebotomy***. All individuals (including heterozygotes) should have attention paid to *other contributing factors such as alcohol use if relevant*

People with organ injury from excess iron



- **Significant liver iron** (eg, >3 mg [>3000 mcg] per gram of dry weight) by magnetic resonance imaging (MRI), transient elastography , liver biopsy, or increased liver function tests without another cause.
- **Cardiac iron <20 msec on MRI, reduced ejection fraction on echocardiography**, or cardiac iron on endomyocardial biopsy

- **Ferritin >1000 ng/mL (>2247 pmol/L), often ≥500 ng/mL (≥1124 pmol/L)and biallelic *HFE* mutations** (or mutations in other genes strongly associated with HH).

Phlebotomy II

- In patients with hereditary hemochromatosis when serum **ferritin exceeds 1000 ng/Ml or in the presence of symptoms**
- Consists of an induction phase with **weekly removal of 1 to 2 blood units to reduce serum ferritin 50 ng/mL and transferrin saturation 30%,**
- Followed by a **life-long maintenance phase** aiming at **serum ferritin 100 ng/mL and transferrin saturation 50% .**

Pietrangelo A. Hereditary hemochromatosis–a new look at an old disease. *N Engl J Med*. 2004;350:2383–2397

Results of therapeutic phlebotomy in patients with hemochromatosis

Complications of iron overload	Expected treatment outcome
None	Prevention of complications of iron overload; normal life expectancy
Weakness, fatigue, lethargy	Improvement in majority of patients
Elevated serum concentrations of hepatic enzymes	Resolution or marked improvement
Hepatomegaly	Resolution often occurs
Hepatic cirrhosis	No change
Increased risk for primary liver cancer	No change*
Right upper quadrant pain	Resolution or marked improvement¶
Arthropathy	Improvement in arthralgias sometimes occurs; change in joint deformity is rare; progression is sometimes seen
Hypogonadotrophic hypogonadism	Resolution is rare
Diabetes mellitus	Occasional improvement, often temporary
Hypothyroidism, hypogonadism	Resolution is rare
Cardiomyopathy	Resolution sometimes occurs
Hyperpigmentation	Resolution usually occurs
Hyperferritinemia	Resolution
Excess absorption and storage of nonferrous metals△	
Infection with *Vibrio vulnificus* or other bacteria	Little or no change

* Increased risk occurs only in persons with cirrhosis.
¶ Right upper quadrant pain in persons with hemochromatosis is often related to hepatic iron overload. In these cases, therapeutic phlebotomy usually results in marked improvement or resolution. However, right upper quadrant pain may also be caused by primary liver cancer, portal vein thrombosis, gallbladder disease, lesions in the hepatic flexure, or nephrolithiasis. Iron depletion alone will not alleviate right upper quadrant pain due to these causes.
△ Cobalt, manganese, zinc, and lead.

Adapted from: Barton JC, McDonnell SM, Adams PC, et al. Management of hemochromatosis. Hemochromatosis Management Working Group. Ann Intern Med 1998; 129:932.

CHELATION THERAPY I

- Three chelators are currently available: parenteral **deferoxamine, and oral deferiprone and deferasirox**

- Management of ***secondary iron overload*** also became possible

- **Early initiation** of iron chelation treatment, particularly **guided by serial CMR-T2*** imaging, has dramatically **improved prognosis and survival**, **prevent the development of iron overload cardiomyopathy, heart failure,** and other complications

Modell B, Khan M, et all Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J CardiovascMagn Reson 2008;10:42.

CHELATION THERAPY II

- Patients with **low to moderate cardiac iron deposition (T2* values:10 to 19 ms and without evidence for RCM)** are generally treated with a **single-drug chelation regimen to** increase T2* >20 ms

- **Combination therapy** could be considered for patients with T2*values of **10 to 15 ms**

- Patients with **marked cardiac iron deposition (T2* <10 ms** or **documented either restrictive or dilated phenotypes) require intensive therapy, employing a combination of deferoxamine and deferiprone**.

- In **clinically unstable cases**, **continuous deferoxamine infusion** to increase T2*>20 ms should be administered and can improve cardiac performance

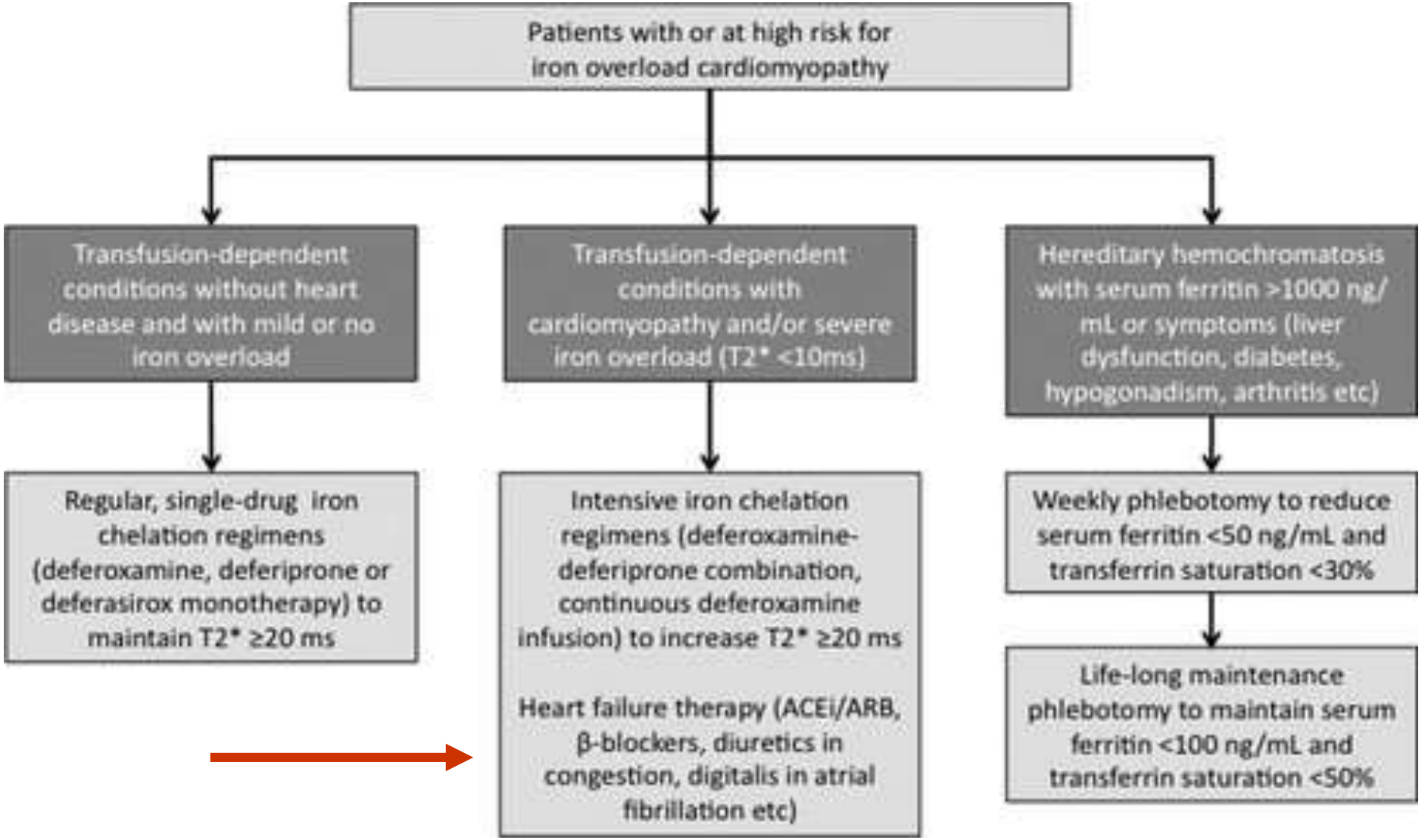
Aessopos A, Kati M, Farmakis D, Polonifi E, Deftereos S, Tsironi M. Intensive chelation therapy in beta-thalassemia and possible adverse cardiaceffects of desferrioxamine. Int J Hematol 2007;

CHELATION THERAPY III

- In patients with **thalassemia** major, chelation therapy is usually started **2 to 3 years after the initiation of transfusions**

- In transfusion-dependent patients with **MDS** or other acquired hematologic conditions, iron chelation therapy is generally **initiated after 10 to 20 transfusions** to prevent clinically significant tissue iron accumulation.

Bennett JM. Consensus statement on iron overload in myelodysplastic syndromes. *Am J Hematol*. 2008;83:858–8
The management of the cardiac complications of thalassaemia major. In: *Guidelines for the Clinical Management of Thalassaemia*. 2nd revised ed.Nicosia, Cyprus: Thalassaemia International Federation; 2008:83–91.



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PROGNOSIS

- **Untreated, HH can lead to early death**. Common causes of mortality in the **pre-phlebotomy era** included ***heart failure,*** *cirrhosis, diabetes mellitus, and hepatocellular cancer (HCC)*
- **In the era of active treatment**, prognosis depends on the **extent of organ injury at the time treatment** is initiated and the extent of iron removal.

- **Survival appears to be normal in those with a serum ferritin <2000 ng/mL at the time of diagnosis**

Bardou-Jacquet E, Morcet J, Manet G, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. J Hepatol 2015; 62:682.

CONCLUSIONS I

- Hereditary hemochromatosis (HH) is an inherited disorder in which **mutations in the HH gene (*HFE*)** or other genes cause lifelong **increased intestinal iron absorption, with resultant iron overload and tissue damage**

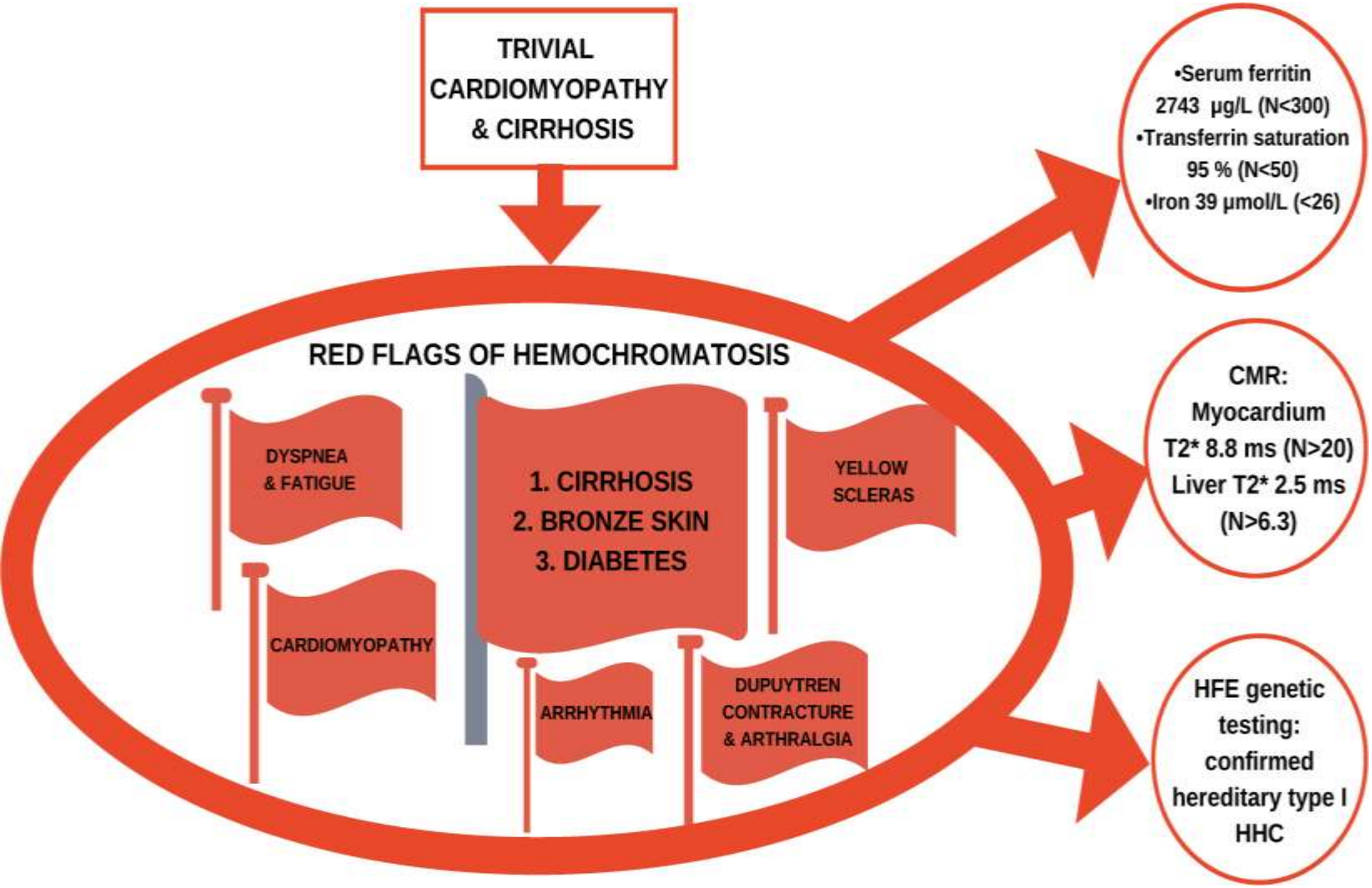
- ***Identifying HH*** is important because treatment is highly ***effective and safe*** and can prevent virtually all of the disease complications if instituted at an early stage of the disease.

- **Phlebotomy** is the main intervention to remove excess iron

CONCLUSIONS II

- **Iron-induced heart disease** is mainly caused by secondary iron overload and involves a particular *type of cardiomyopathy* with **2 main LV phenotypes, a more frequent dilated one and a less frequent restrictive one.**

The scheme of diagnostic workup and the red flags of haemochromatosis.



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