# Systemic complications and management for thalassaemias

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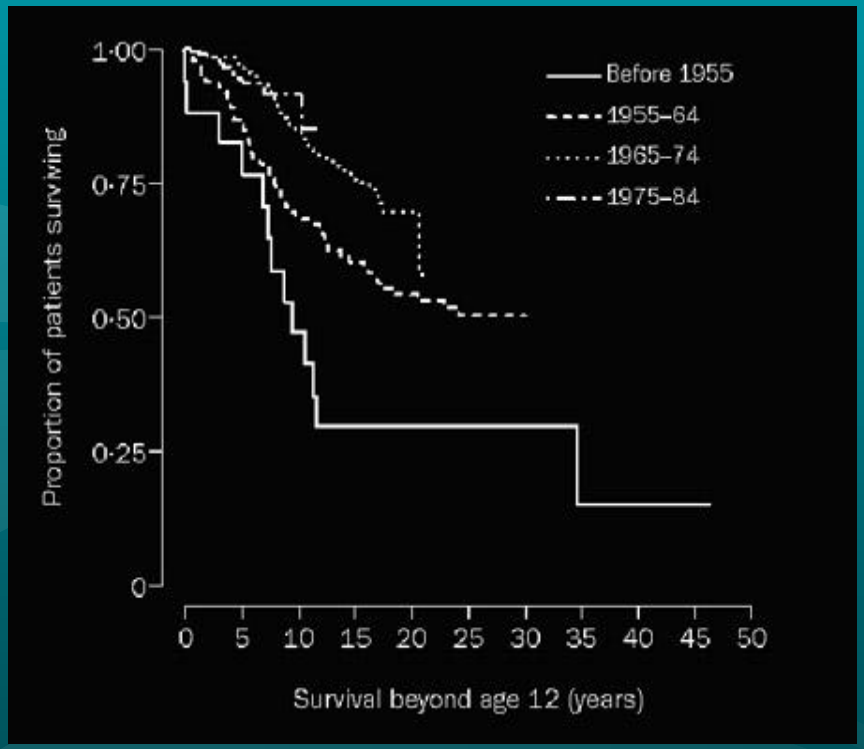
# หัวข้อในการบรรยาย

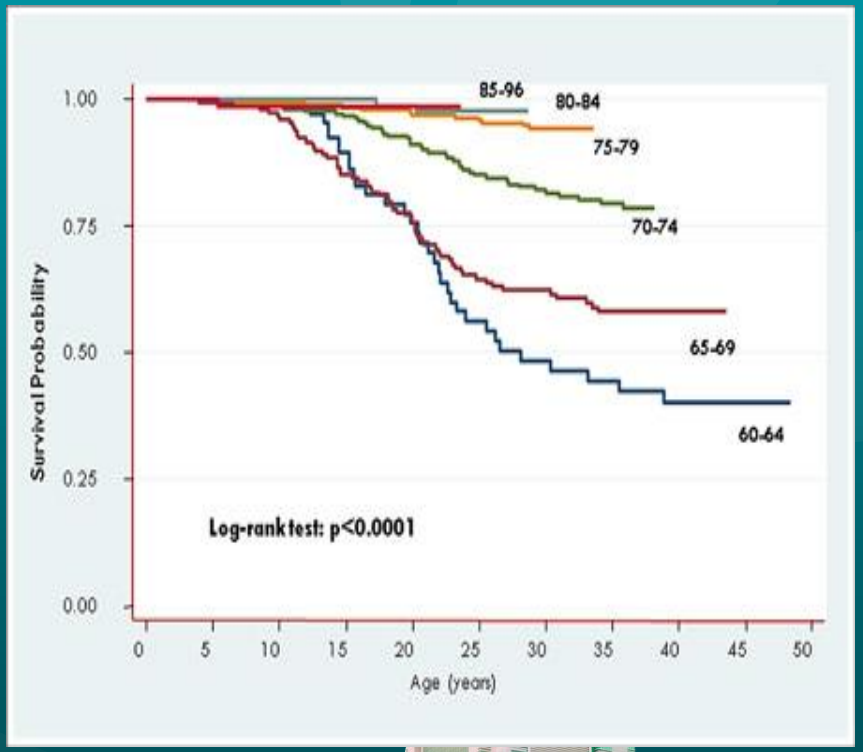
- Overview of systemic complications
- ภาวะแทรกซ้อนที่เกิดจากตัวโรคธาลัสซีเมีย
- ภาวะแทรกซ้อนที่เกิดจากภาวะธาตุเหล็กเกิน จากการได้รับเลือด
- ภาวะแทรกซ้อนที่เกิดจากการรักษา
- ภาวะแทรกซ้อนอื่น ๆ ที่พบได้บ่อย

# Improving life expectancy in thalassemia paitents

**UK**




**Italy**




Most common cause of death is cardiac complication

# ภาวะแทรกซ้อนที่เป็นปัญหาสำคัญ

## OPTIMAL Study

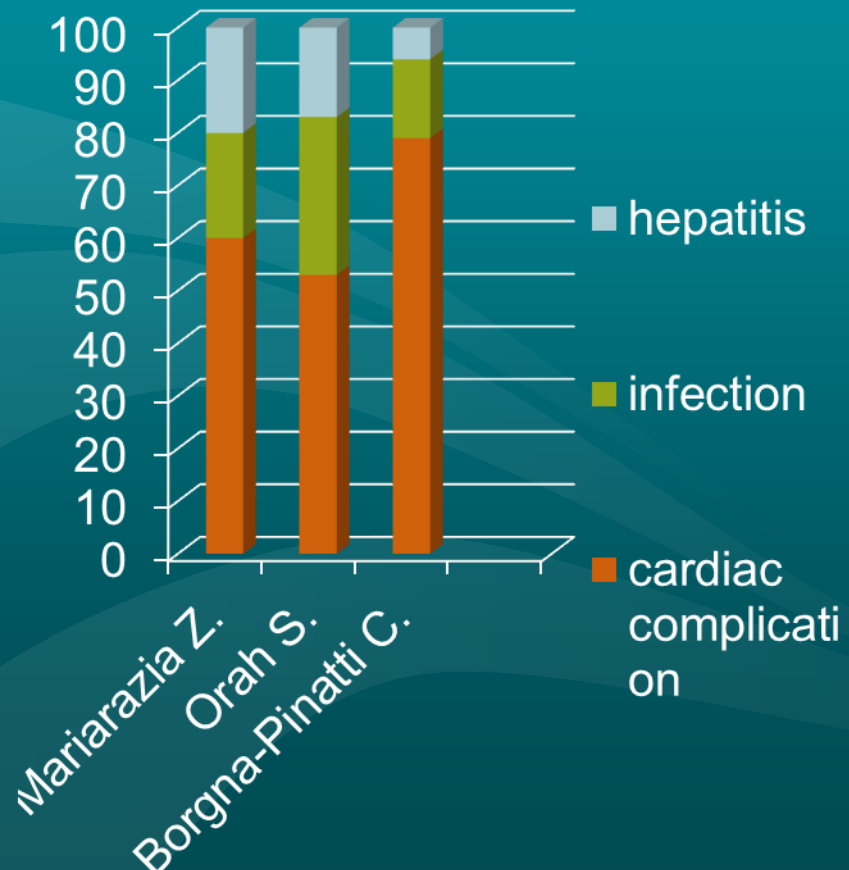
| Complications | |
|---|---|
| Osteoporosis | 134 (22.9) |
| EMH | 124 (21.2) |
| Hypogonadism | 101 (17.3) |
| Cholelithiasis | 100 (17.1) |
| Thrombosis | 82 (14) |
| PHT | 64 (11) |
| Abnormal liver function | 57 (9.8) |
| Leg ulcers | 46 (7.9) |
| Hypothyroidisim | 33 (5.7) |
| HF | 25 (4.3) |
| Diabetes mellitus | 10 (1.7) |

## Thai study (data available)

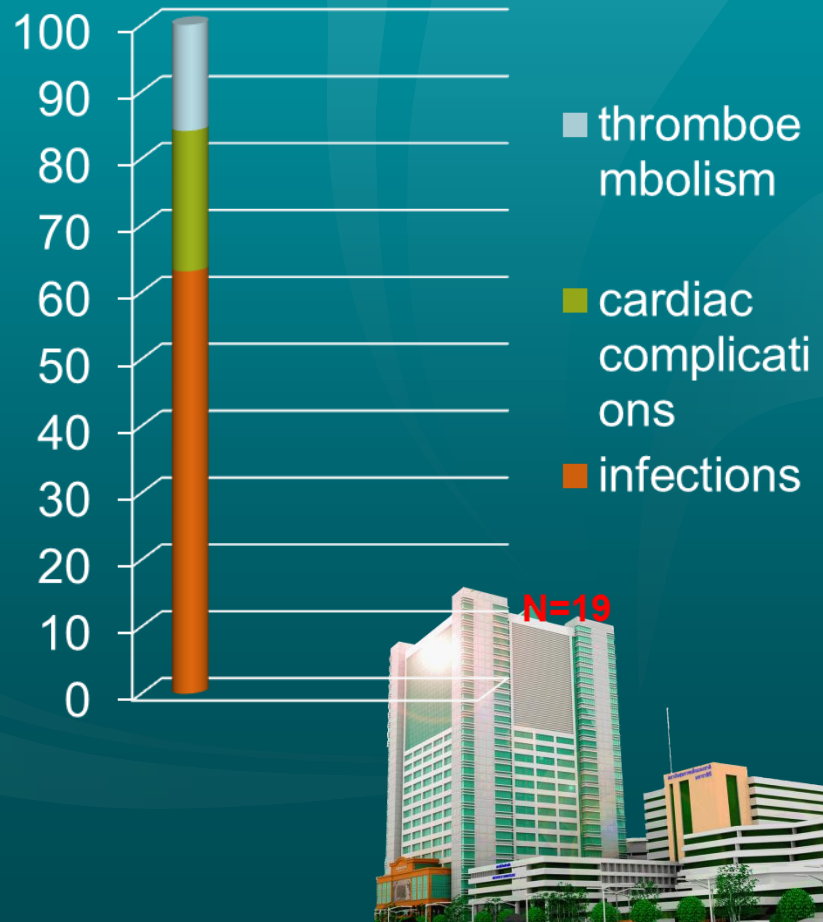
- No exact data
  - Osteoporosis 11.6%(n=190)
  - EMH (no actual data)
  - Hypogonadism(50% -thal major; 21% adult)
  - Subclincal hypothyroidism(26.5%)
  - Heart failure
  - Thrombosis and PHT (4%)

# สาเหตุการตาย (mortality rate)

**West countries and Middle east**




**Thailand (Siriraj hospital n=585)**



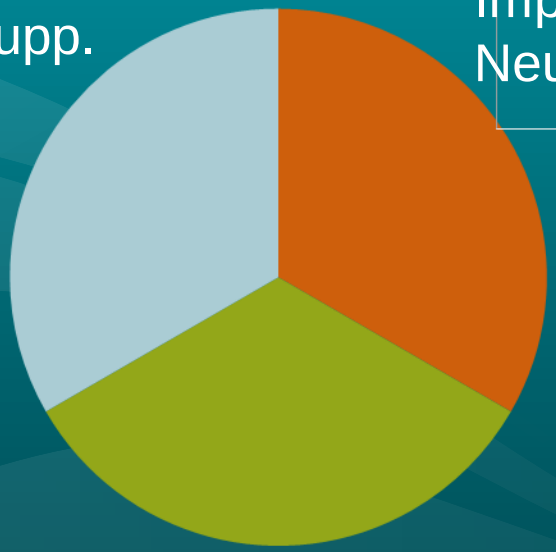
# Systemic complications

- Infections
  - Thailand most common causes of death

# Pathogenesis of immune dysfunction in thalassemias

-Splenectomy
-Constant Ag stimulation
-transmission of immunosupp. Viruses

Quantitavie and functional defect of T,B lymphocytes
Impaired Ig production
Neutrophils and macrophage dysfunctions




Chelation therapy: low level of Zn
Susceptible to Bacteria that need iron:Yersinia spp.

# Bacterial infections

- *Yersinia enterocolitica* : normally low virulence
  - In thalassemia patients: esp. iron chelation *with Deferrioxamine*
  - Rarely transmitted by contaminated blood
- อาการและอาการแสดง ไข้สูง ปวดท้อง ร่วมกับท้องเสีย คลื่นไส้ อาเจียน จำเป็นต้องแยกโรคที่มีข้อบ่งชี้ทางศัลยกรรม อันได้แก่ acute appendicitis, acute secondary peritonitis
- ไม่มีการวินิจฉัยทางห้องปฏิบัติการที่จำเพาะ
- ดังนั้นหากสงสัยพิจารณา empirical antibioticsก่อนและจำเป็นต้องหยุดiron chelation therapy

# Other bacterial infections

- Incidence of infection with Klebsiella spp. Higher than normal population-acute sinusitis, intracranial infection, meningitis,septicemia and visceral organ abscesses: liver, lung, kidney
- Important risk factor: iron overload
- Splenectomized patients: proned to encapsulated bacterial infection-streptococcus pneumoniae, H. influenzae, N. meningitidis
- Management: Vaccination -2 weeks before splenectomy(pneumococcal vaccine, H influenzae type b)
- Prophylaxis antibiotic :Penicillin V for first 2 years after splenectomy*( controversy dueto penicillin resistant organisms)*

# Viral infections

- Parvovirus B19: most common infected by multiple transfusion
- Clincal S&S: transient aplastic crisis
- Laboratory findings: low reticulocyte count, parvovirus B19 viremia
- Management: no specific therapy –spontaneous resolution within 2-3 weeks, need supportive care with blood transfusion as needed
- In case of immunocompromised patients: IVIg
- Need surveillance in patients with frequent blood transfusions

# HIV infection

- Prevalence in thalassaemias : <1% to >20%
- Upto quality of screening donor and test for blood components and endemic area
- Guideline for using ARV in thalassaemias : the same as general population
- Patients wth iron overload-clinical outcome deteriorates fater thant those of no iron overload
- Adequate iron chelation is a must!!!
- Which agents is the best?: no evidences – caution for Deferipone – risk of neutropenia ,even agranulocytosis

# HIV infection

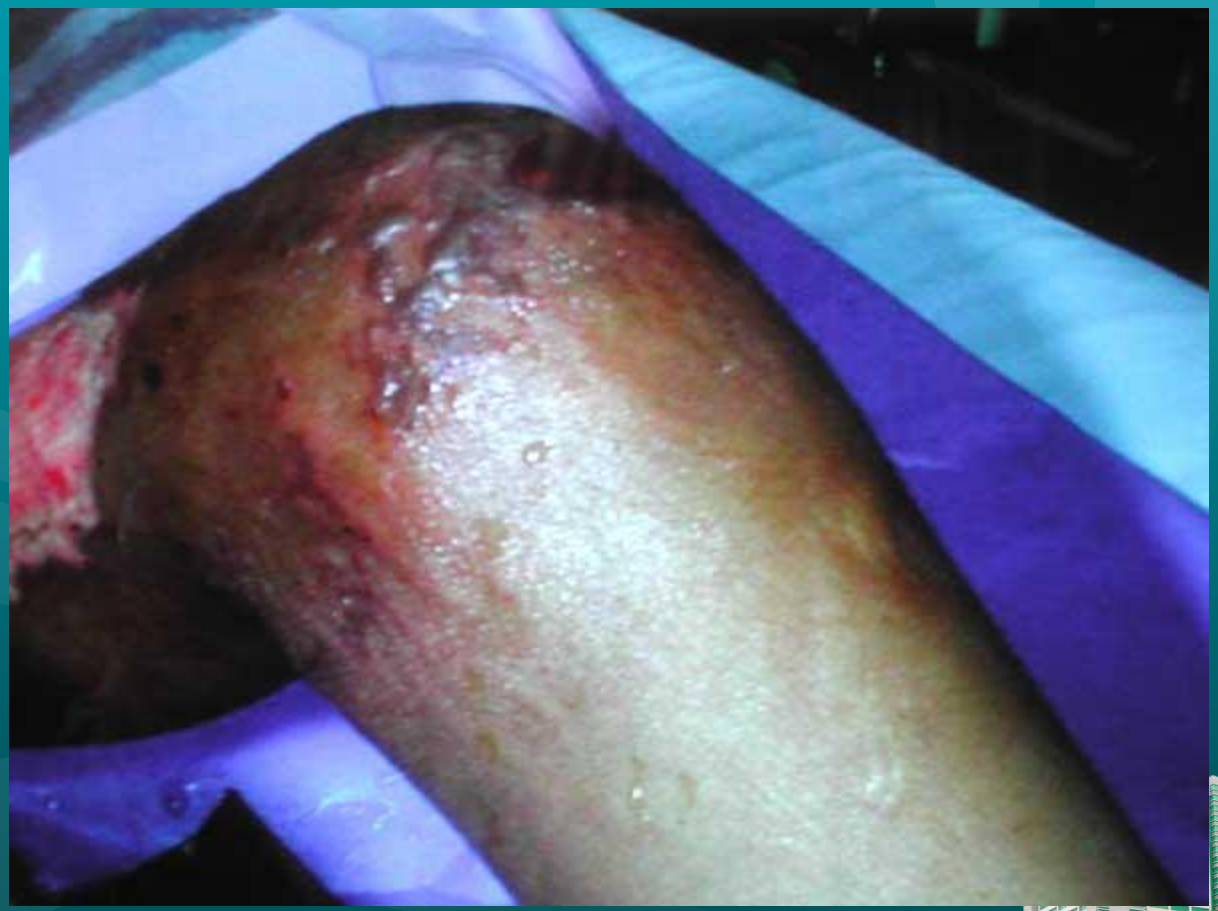
- Splenectomy: theoretically impaired immune function,esp. T cell – no evidences  that this procedure make progression of HIV infection

# fungal infection

- Iron overload: risk factors for infection with fungus : Mucor spp. , also in patients chelated by Deferrioxamine , BMT patients
- Pythisosum insidiosum(Pythiosis)
  - Human infection (3 forms)
  - 1.Cutaneous or Subcutaneous pythiosis: orbit , periorbital soft tissue, face, extremities: lesion granulomatous ulcer or abscess or cellulitis
  - 2.Ophthamlic pythiosis: corneal ulcer or keratits
  - 3.systmic pythiosis: -vascular infection→ arterial occlusion→gangrene severe form: high mortality rate

Treatment : need surgery; antifungal agents-not work

# Vascular pythiosis



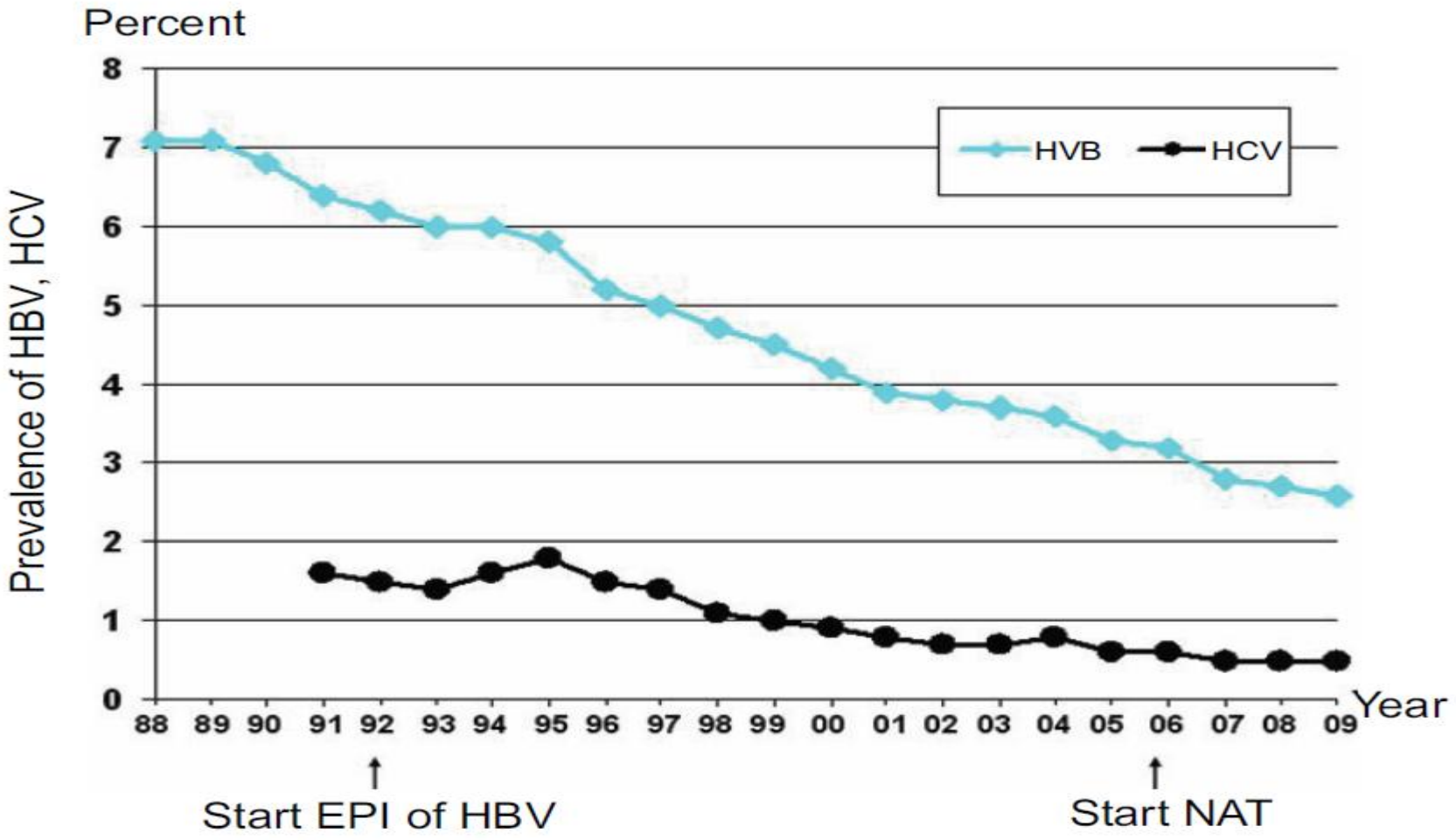
# malarial infection

- In Thalassaemia trait: small Red cell is tolerated to malarial parasite infection
- However; β thal major ,intermedia-high risk of severe malaria infection→treat as normal population

# Hepatitis infection

- Risk of hepatitis infection : most come from blood transfusion(hepatitis B, C)
- Application of NAT for all blood components in Thailand for Hepatitis B(2006)and Hepatitis C(2006)
- Prevalence still higher than in Western countries: HBsAg +ve 2% vs(0.3-5.7%), antiHCV+ve 21.2% vs (4.4-85.4%)
- All newly diagnosed thalassemia patients should be screened for antibody to HBS (even EPI for all thais since 1995- 20% of already immunized subjects are still seronegative)
- If negative recommend to have immunization

# Prevalence of HBV,HCV in blood donors in thailand



# HCV infection

- All new diagnosed thalassemia patients  should be screened for anti HCV , esp. those who have received blood components before 2006
- If positive for Anti HCV ,need further clarification of hepatitis from Hepatitis C by using HCV RNA and liver enzyme ,SGPT(ALT)
- High risk of thalassemias with hepatitis C infection: iron overload with inadequate chelation therapy→cirrhosis, Hepatocellular carcinoma
- Thalassemias with cirrhosis : Risk of hepatocellular carcinoma 6 times as normal

# HBV infection

- Who need further investigation and therapy?
- Asymptomatic- need  check ALT(SGPT), HBV DNA copies in serum
- All patients with hepatitis need to evaluate iron overload status and  initiation of Rx along with hepatitis Rx
- Cirrhotic patients : by clincal and imaging(ultrasound)+ HBV DNA viral load >2000 copies/ml even normal liver enzyme
- Chronic hepatitis B: HBsAg +ve more than 6 months+ HBV DNA>2000 copies/ml+ALT >2XUNL or liver biopsy shows severe inflammation or fibroscan-severe fibrosis

# HCV infection

- If anti HCV+ve, need confirmation infection with HCV RNA → indication for treatment
- Genotype of HCV predicts prognosis and response to treatment with IFN + ribavirin
- Goal: decrease hepatitis, cirrhosis, Hepatocellular carcinoma
- Caution: Interferon suppresses BM function and also ribavirin induces red blood cell hemolysis → treatment with these agents in thalassemia→ increase blood transfusion(upto 30%)
- Treated Paitents who are on chelation with Deferipone need more frequent monitoring about neutropenia

# HCV infection

- Who need treatment ?
  - Age ≥ 18 years old
  - Liver biopsy shows severe fibrosis
  - Child Pugh score >9

# recommendation

- Abstinence from alcoholic drinking
- Have a hygienic meal
- Avoid food with suspected aflatoxin contamination
- Avoid herbal and unnecessary food supplement
- No blood organ, sperm donation
- Avoid using toothbrush, razor, nail cutter with others

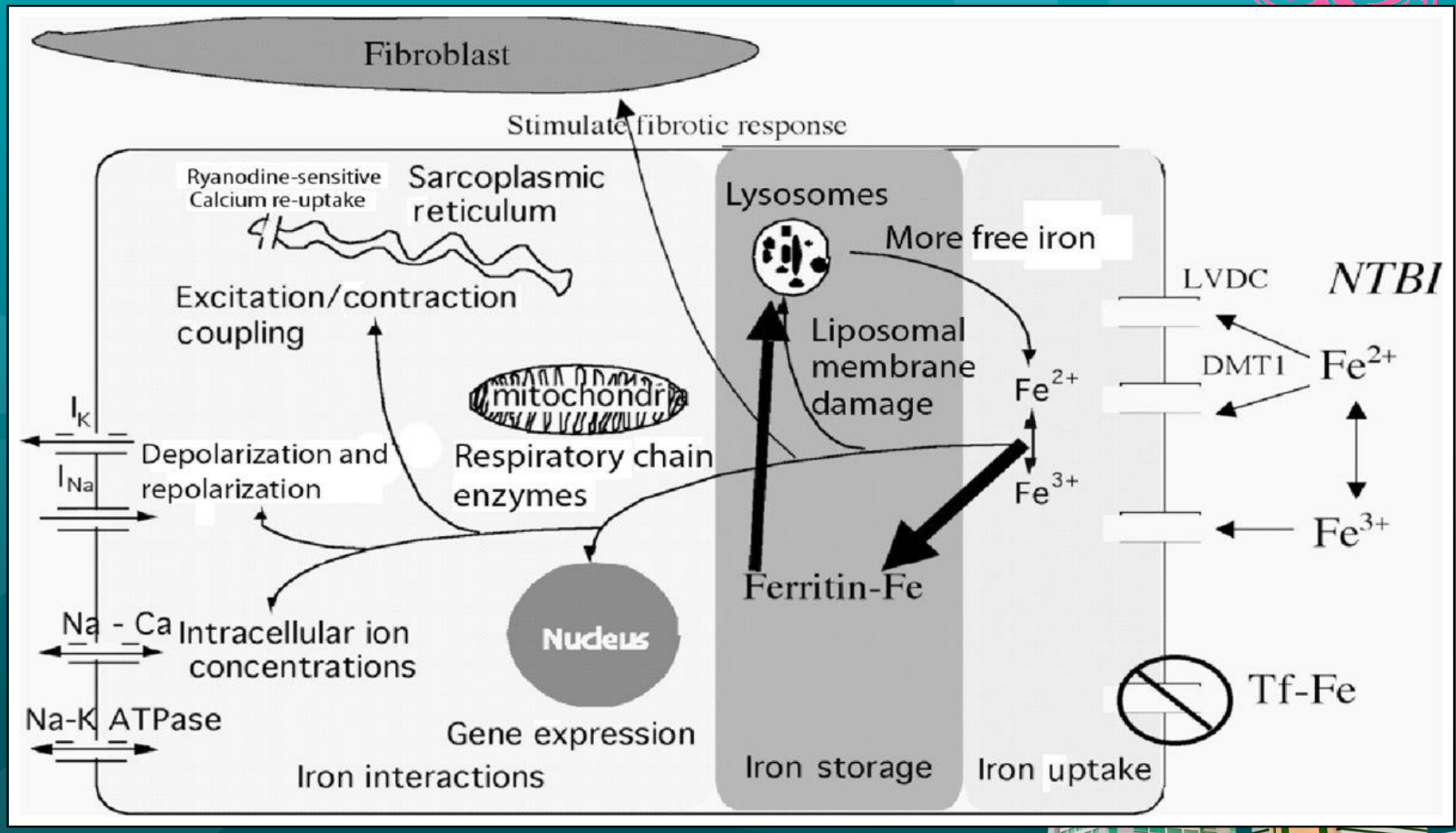
# ภาวะแทรกซ้อนทางด้านหัวใจและหลอดเลือด

# Cardiac and vascular complications

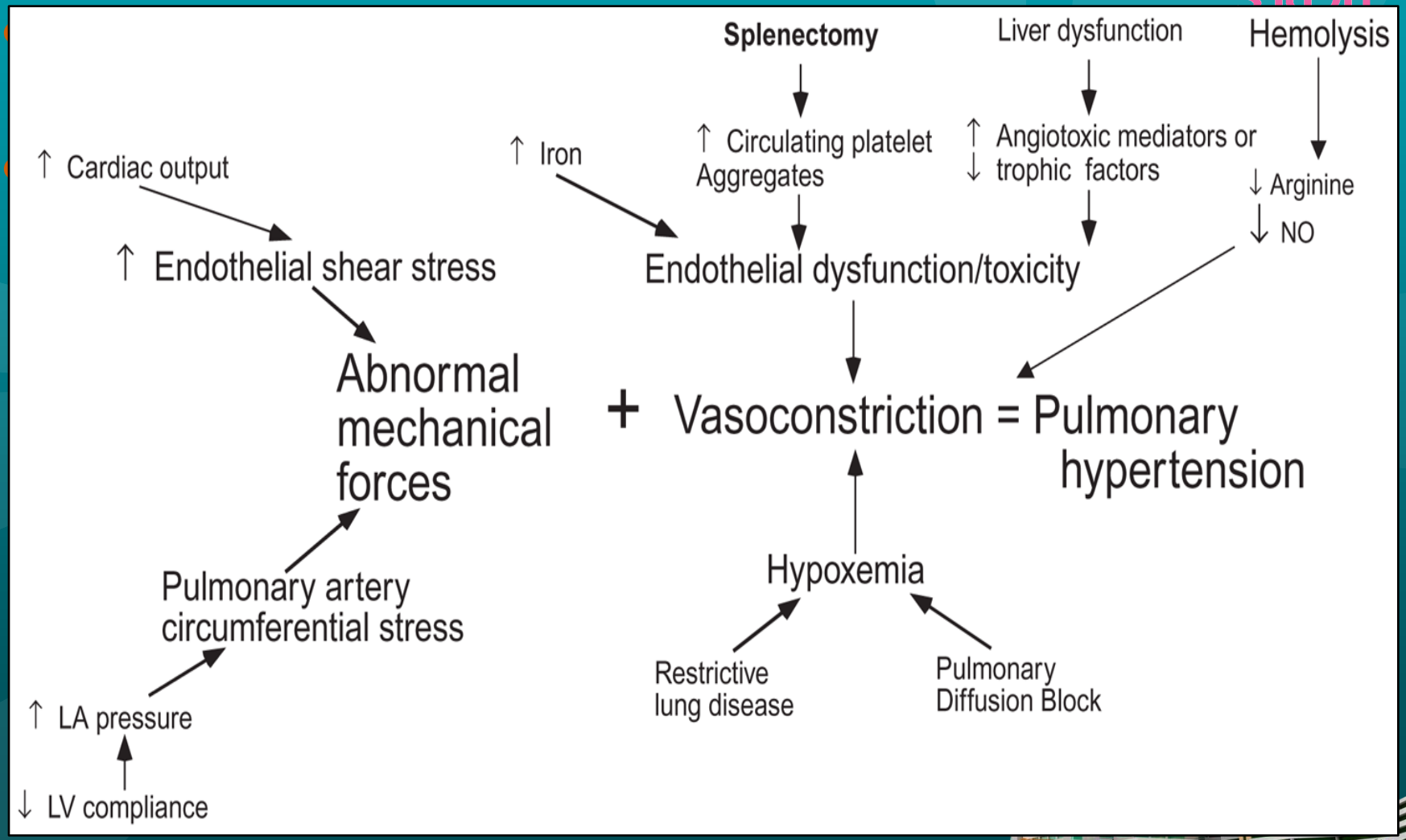
# Cardiac complictions

- 1st most common cause of death in thalassemia patients worldwide , 2nd for thai thalassemias
- Important risk factors: iron overload, chronic anemia ,hypoxia

# Pathogenesis cardiac complication



# Pathogenesis vascular complication



# Cardiac complictions

- Signs and symptoms: early manifestation-asymptomatic
- Late manifestation: heart failure, arrhythmia
- Early detection: need investigation
  - EKG: nonspecific findings
  - Echocardiography: evaluate LVEF
  - Cardiac MRI fro evaluation iron content in myocardium
- Late manifestation
  - Have to be discriminate heart failure condition from anemia or iron toxicity to myocardium

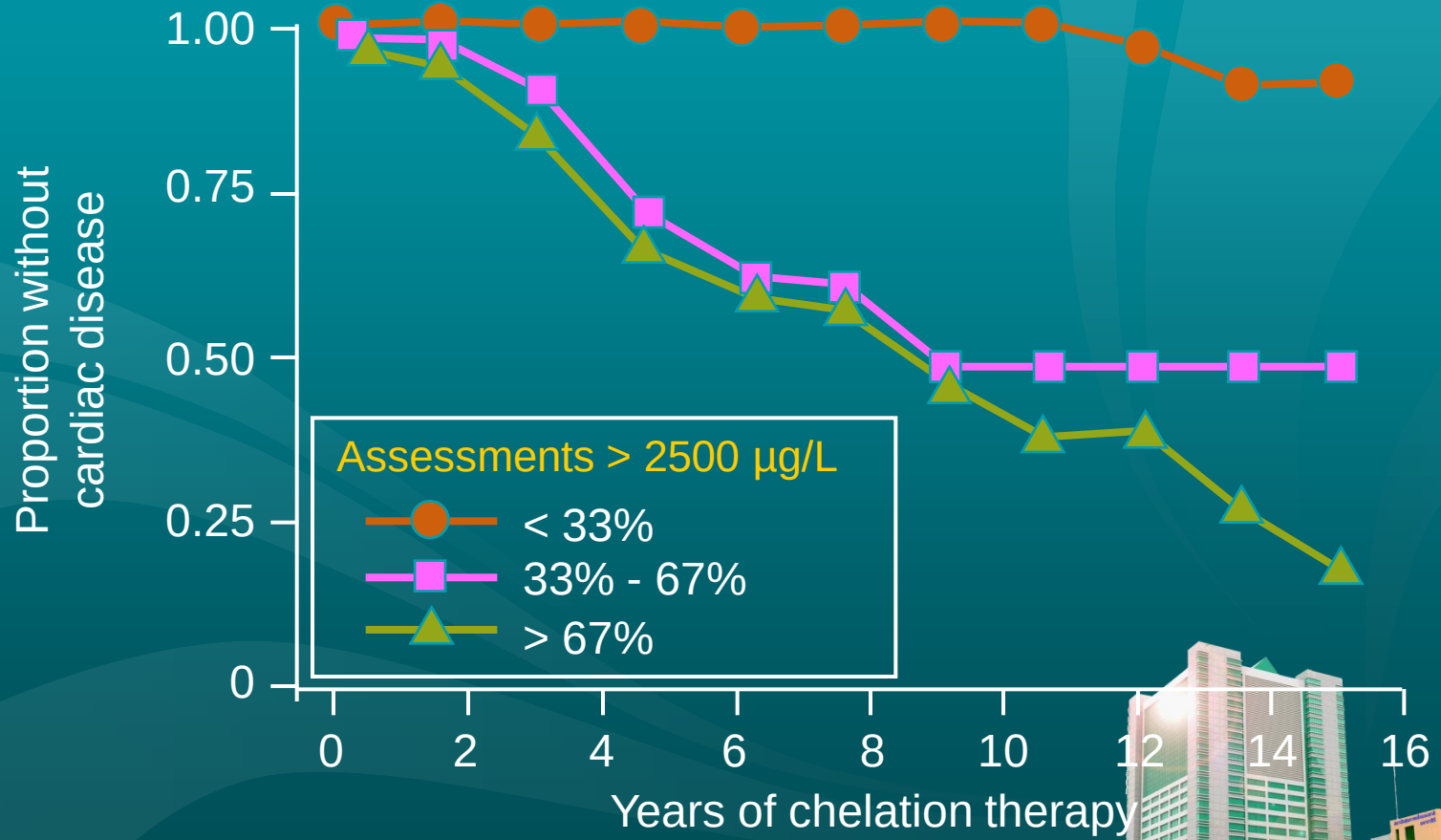
# Cardiac MRI

- ค่าปกติ คือ >20 miliseconds
- ค่าผิดปกติน้อยถึงปานกลาง คือ 10-20 miliseconds
- ค่าผิดปกติรุนแรง คือ <10 miliseconds
- ค่าที่น้อยกว่า 6 miliseconds: โอกาสเกิดภาวะ heart failure ในระยะเวลา 1 ปี 50%
- **Limitation: not available , high cost**

# Cardiac complictions

- Anemia –need to keep higher Hb level 7-8g/dl
- Iron toxicity- effective adequate iron chelation therapy( deferipone-more effective than DFO in chelation iron from myocardium, deferasirox also have this efficacy

# Cardiac Disease and % of Time With Serum Ferritin > 2500 µg/L




Olivieri, et al. *N Engl J Med.* 1994;331:574.

# Can serum ferritin reflect cardiac iron load as in liver?

- **No**

***Serum ferritin***

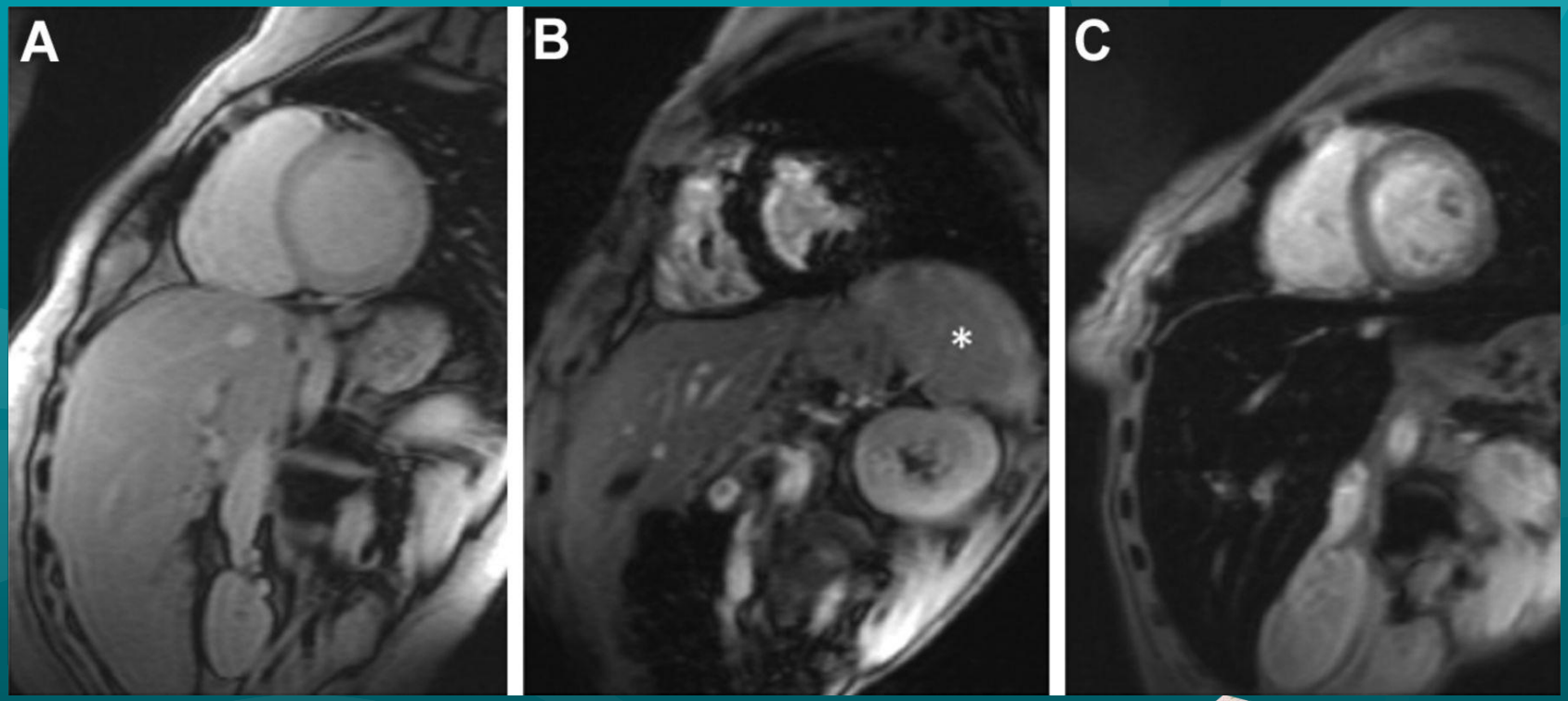
Serum ferritin was not significantly correlated with cardiac T2*, r= 0.25 (95%CI -0.17 to 0.59), *p*=0.24.

***Relationship between cardiac and hepatic iron***

No correlation was found between cardiac and hepatic iron [r= 0.4 (95%CI -0.06 to 0.70, *p*=0.09)] *Di Tucci et al,aematologica 2008*,

- Cardiac MRI , T2*

**Cardiovascular magnetic resonance T2* images showing the heart and liver from 3 different patients at the same echo time (10.68 ms).**




Hoffbrand A V et al. Blood 2012;120:3657-3669

# Cardiac complications

- Thalassemia patients who should be benefit from cardiac evaluation
  - Serum ferritin >2,500 mg/ml
  - Cardiac problem from iron overload: arrhythmias, LVEF decrease(<55%), Cardia T2* <20ms
  - Patients planning for pregnancy
  - Iron content in liver >15 g/1 gDry weight liver

# Other vascular complications

- Thalassemia patient : higher incidence of VTE 14% (585 thal intermedia), 2.2% (83 pregnancies)
- Risk factors : Hx of previous venous thromboembolism, Splenectomy, pregnancies, indequate Hb level
  - Patients with splenectomy have higher incidence of Pulmonary hypertension
- Clinical evaluation and investigation: symptoms and sign of pulmonary hypertension
- Noninvasive procedure: Tricuspid valve regurgitant jet velocity ≥3.2 m/sec vs gold standard Rt cardiac Cath. , Positive predictive value 95%

# vascular complications

- Who will be benefit from evaluation?
  - Thalassemia paitents with Hx of splenectomy(esp more than 5 years)
  - Hx or evidence of Thrombosis
  - High risk for VTE
  - Clinical signs and symptoms suspected pulmonary hypertension(dyspnea on exertion, loud P2)

# Management

- As normal population
- Anticoagulants: Aspirin, warfarin
- Oxygen therapy
- Blood transfusion

# endocrinopathies

# Hypogonadism/delayed growth

- Main:anemia-tissue hypoxia, iron overload
- Clinical clue: no or delayed secondary sex development: male:13 years old ; female: 14 years old
- Evaluation and investigation: BW and height ,upper segment to lower segment ratio, pubertal stage
- Plain film for bone age, lateral spine
- Ca,P, 25-hydroxyvitamin D,intact PTH, Free $T_4$,TSH,LH,FSH, testosterone, Estradiol, IGF-1,IGFBP-3,GH provocative test and ferritin
- Irreversible process: so early detection and treatment is benefit most for patients

# Management

- Prepubertal: adequate Hb level preventing chronic tissue hypoxia→maintain hypothalamic pituitary-gonadal axis normal function
- Adequate iron chelation therapy
- Early detection : hormonal supplement: male-testosterone, female-estrogen

# diabetes

- Main cause: iron overload in liver and pancreas
- Evaluation and investigation: same as DM patients- clinical symptom, FPG≥126 mg/dl, OGTT
- Esp. patients with high serum ferritis(>2500ng/ml) –fasting plasma glucose annually
- Irreversible process: so early detection and treatment is benefit most for patients

# hypothyroidism

- Prevalence in India :higher to 35%, in thailand: subclinical hypothyroidism (n=190) 26.5% (high TSH ,normal $FT_4$)
- Cause: iron overload
- Symptoms: not clear
- Screening in patient with high ferritin:Free $T_4$,TSH
- Irreversible process: so early detection and treatment is benefit most for patients
- Management : thyroid hormone supplement

# Skeletal related complications

- **Osteoporosis: thal intermedia** prevalence in mediterranean and middle east: 23%, thailand: 11.6% ( 2 times as compared with postmenopause thai women(5.9%))
- Skeletal related events : fracture at OPD orthopedics among thalassemia patients 30%
- Patients with high risk for osteoporosis: low BMI, female, inadequate iron chelation, splenectomy, hypogonadism, inadequate calcium intake, vitamin D deficiency(25OH vitD)
- Clinical evaluation : BW,Ht record , BMD for T score at neck of femur and spine, additional calcium intake, vitamin D level

# Management

- Prepubertal: adequate Hb level preventing expansion of erythropoietic activity in BM → maintain normal bone and skeletal
- Adequate iron chelation therapy
- Modification of risk factors: adequate Calcium intake (800 mg/day) , thai study: >80% of thal intermedia patients : inadequate daily calcium intake(<800mg/day), vitamin D level: about 35% of thai thalassemia patients have defined as vitamin D deficiency(<25ng/ml)

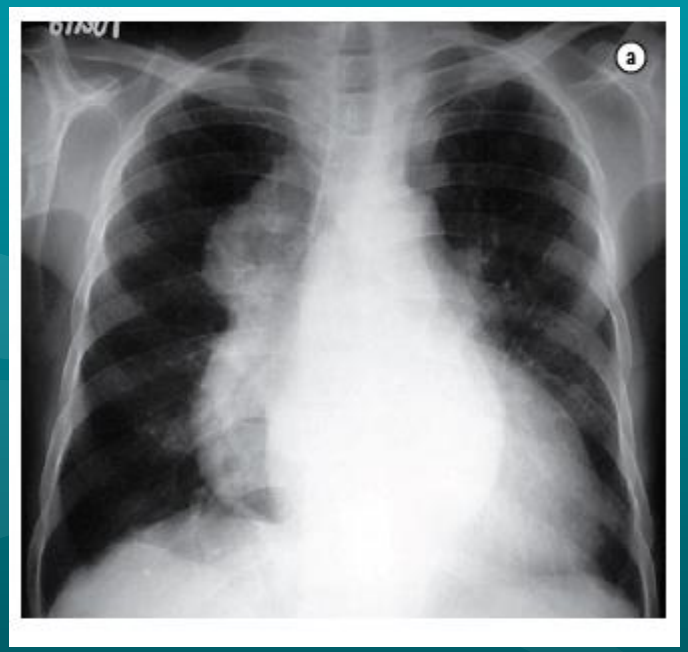
# Management

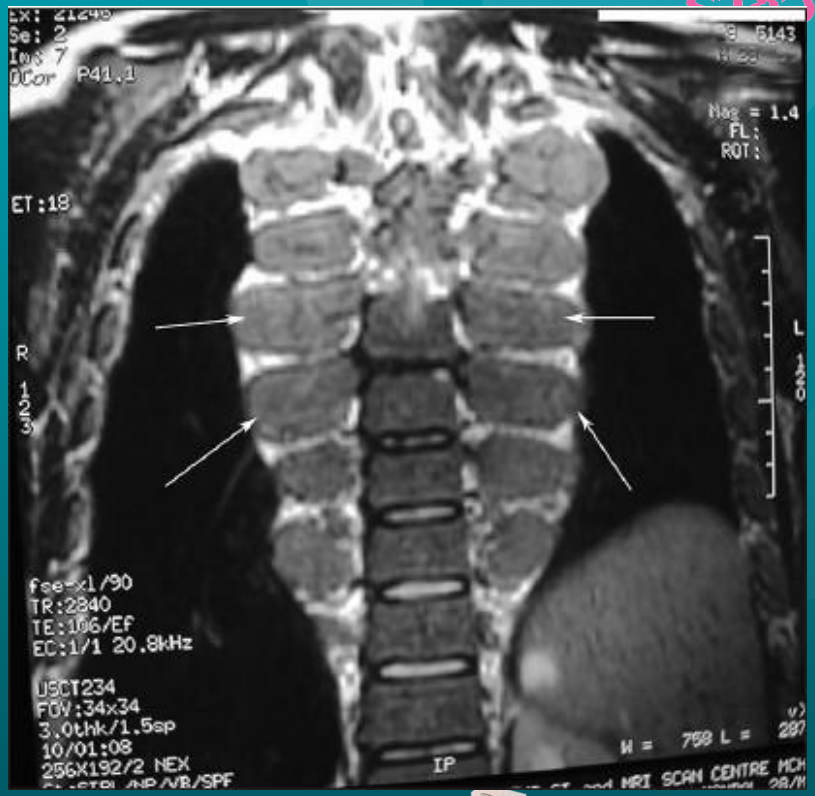
- In case of suspected low vitamin D: total vitamin D level
- Calcium supplement: 800-1000mg/day( 3 cartons of pasturizied 250 ml milk)
- Vitamin D supplement D2 ,D3
- Monitor about Height and weight
- Bisphosphonates : increase BMD Z score in thalassemias but no evidences supporting wheter decrease long-term skeletal related events or not

# Other complications

- Extramedullary Hematopoiesis(EMH)
  - Most common area: Liver , Spleen, Vertebral body of spine
  - Compressive symptoms: esp. spinal cord-paraparesis , paraplegia
  - Dx: Imaging CT,MRI
- Thai data(Siriraj) most common area Lower thoracic spine, M:F 5:1

# Imaging in EMH



# Management

- Surgery is treatment of choice: get tissue diagnosis
- Blood transfusion is adjunctive treatment
- Radiation therapy : effect within 3-5 days and prevent recurrence but can not get tissue diagnosis
- Hydroxyurea may help in decrease erythropoieitic activity and increase Hb F

# Chronic Leg Ulcers

- Common in thalassemia intermedia
- Ever high Hb F, still occur in lower leg
- Cause: chronic tissue hypoxia

# Management

- Elevated leg with lesion higher than heart level for 1-2 hours every day
- Zn supplement, Rheological property of red cell modifier: Pentoxyfylline
- Hydroxyurea
- Oxygen Chamber
- Intralesional G-CSF  as combination therapy with other methods mentioned above

# Take home messages for health care providers

- Systemic complications in thalassemia : common
- Early detection of cases
- Adequate treatment : early , effective
- Frequent monitoring
- Concerns about possible complications
  - → **good quality of life of our thalassaemia patients**

# Thank you very much for your attention