AN UPDATE ON ACUTE PANCREATITIS

Riaz Chowdhury, M.D, PhD, AGAF, FACG
Director
Division of Gastroenterology, Hepatology and Endoscopy
Wakemed Hospital, Raleigh
Clinical Associate Professor, UNC @ Chapelhill

- Certain facts need to be reviewed in day to day practice regarding etiology, pathogenesis, clinical features
- Drug induced pancreatitis:GLP-1 agonists
- Post ERCP pancreatitis
- Role of rectal indomethacin
- Management of Acute Pancreatitis
- IVF
- Autoimmune pancreatitis
- Role of antibiotics
- Pancreatic Necrosis
- Nutrition

Etiology

- Gall stones (40-70%)
- Alcohol (25-35%)
- Idiopathic
- Drugs
- Hyperlipidemia
- Hypercalcemia
- Infection
- Trauma/ERCP
- Hereditary
- Obstruction
- Postoperative, hypotension, scorpion venom

Gall Stones

- 40-70% of cases
- Stone size < 5 mm, microlithiasis
- Abdominal ultrasound to evaluate for cholelithiasis should be performed on all patients with AP
- Meta-analysis:
- ALT>150 IU/L had PPV of 95 %

Tanner et al, Am J Gastro 1994;89:1863

ETOH induced AP

- Abstinence from alcohol and tobacco. Recently, it has been recognized that smoking is worse that alcohol, and the 2 together are a very toxic brew
  - *Arch Intern Med* . 2009;169:1035–1045

- The repeated visits at 6-month intervals appear to be better than the single standardized intervention alone during hospitalization in reducing the development of recurrent AP during a 2-year period.
- **The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial .** *Gastroenterology* . 2009;136:848–855

RISK FACTORS FOR POST ERCP PANCREATITIS

- Prior H/O Post ERCP pancreatitis
- Suspected sphincter of Oddi dysfunction
- Females
- Normal serum bilirubin
- Absence of chronic pancreatitis
- Biliary sphincter balloon dilation
- Difficult cannulation
- Pancreatic sphincterotomy 1 or more injections of contrast into the pancreatic duct

- Freeman et al 2001

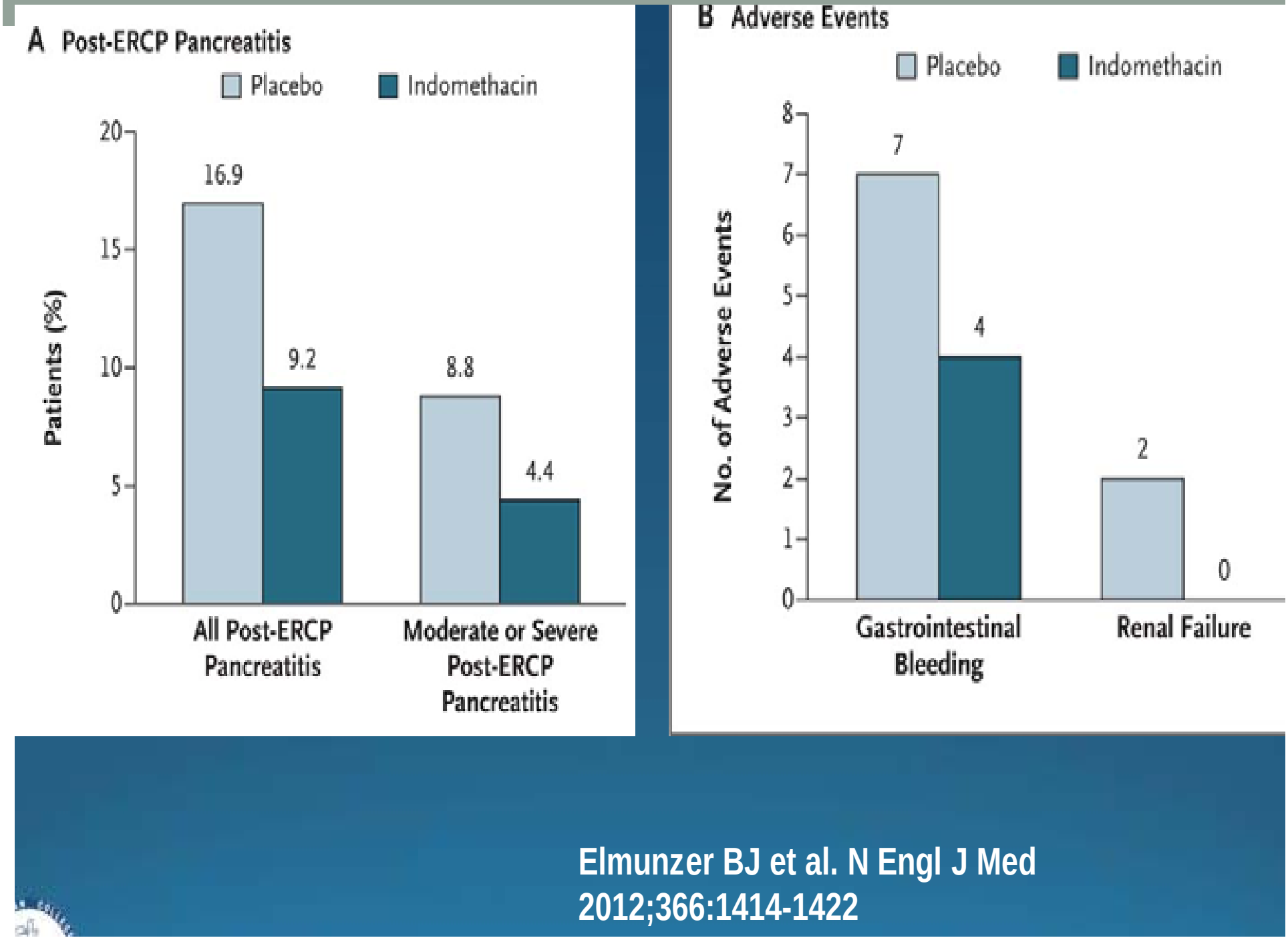
POST ERCP PANCREATITIS

Avoidance of ERCP if alternative diagnostic tool available like EUS, MRCP, IOC

POST ERCP PANCREATITIS

- Proven therapy for the prevention of post ERCP pancreatitis is:

A. Gabexate
B. Corticosteroid
C. Indomethacin
D. Ulinastatin
E. Unfractionated heparin

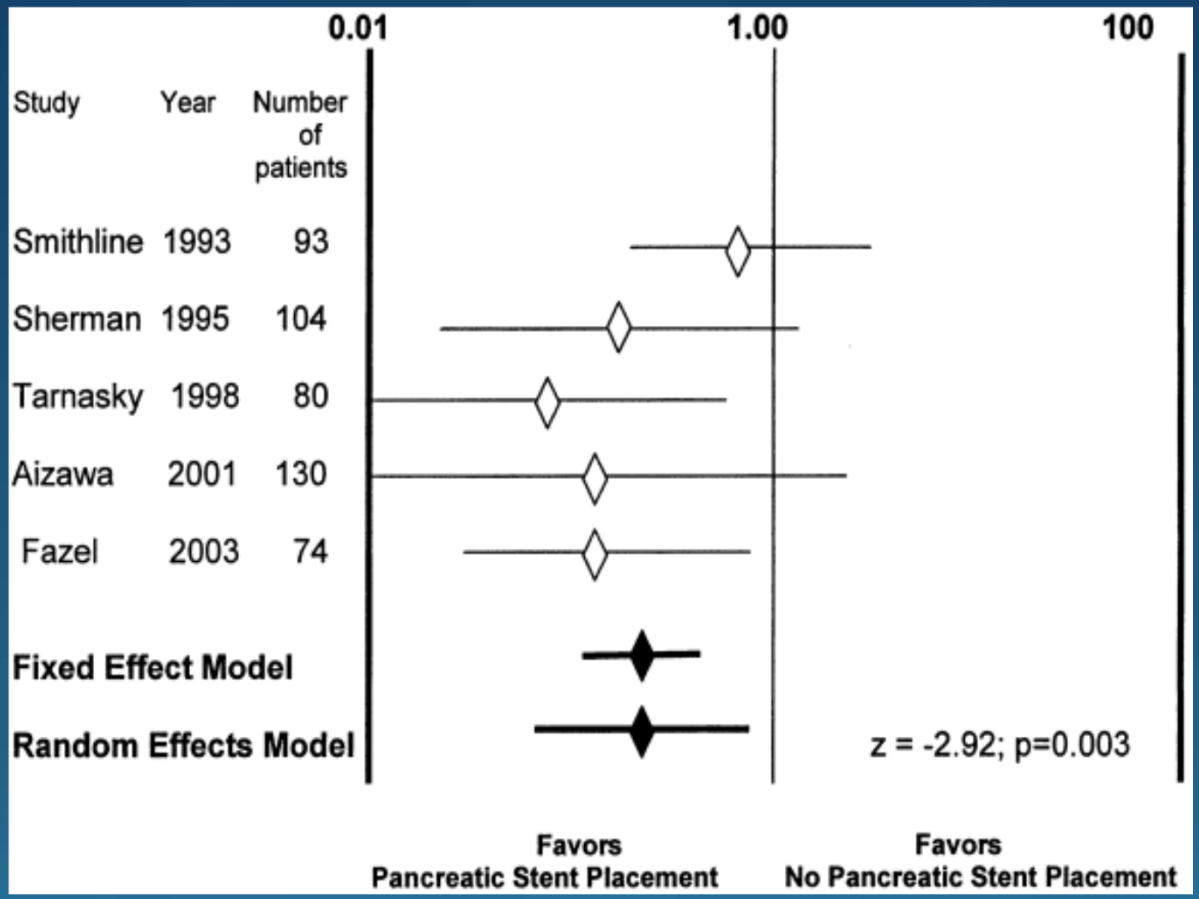


Elmunzer BJ et al. N Engl J Med 2012;366:1414-1422

Post-ERCP pancreatitis

- **Rectal NSAIDs are effective tool in reducing post ERCP pancreatitis**
- **Indomethacin suppository 100mg immediately after ERCP**
- **Can be formulated by your pharmacy**
- **Use is recommended in high risk pts *without contraindications***

PANCREATIC STENTING *to reduce pancreatitis risk after ERCP:meta-analysis*



Singh P, Gastrointest Endosc 2004

Hypertriglyceridemia and Pancreatitis

- Accounts for 1.3 -3.8 % of cases of AP.
- > 1000 mg%
- Pathogenesis is unclear.
- The serum amylase and lipase **may not be elevated** in 50% of cases.

Caution with: Vitamin A, Thiazide, Beta-blocker, Estrogen and Alcohol.

Toskes PP . Gastroenterol Clin North Am 1990 Dec;19(4):783-91

Pancreatitis and drugs

- 2-4% of all cases of AP
- Definite:
- Azathioprine/6 MP
- Estrogens
- Valproic acid
- Pentamidine/DDI
- Thiazides
- Furosemide
- Sulfonamides
- NSAIDS

- Possible:
- Asparaginase
- ACE inhibitor
- 5 ASA
- GLP-1 agonist:
  - exenatide, liraglutide, sitagliptin

Hereditary Pancreatitis

- Mutation in exon 2(N291) and exon 3 (R122H) of the cationic trypsinogen gene
- Autosomal dominant hereditary pancreatitis
- The mutant trypsin is resistant to lysis and remain active
- Causes recurrent Acute Pancreatitis= Chronic pancreatitis
- Life time risk for pancreatic Cancer is > 40 %

Whitcomb D et . Al. Gastroenterology 1996 Jun;110(6):1975-80

Autoimmune Pancreatitis

- Great deal of attention recently
- Reported in Japan and Europe
- Presence of auto antibodies against pancreatic exocrine and endocrine cells
- Elevated serum IgG 4, Anti-PBP
- Diffuse enlargement of pancreas, HOP Mass, Biliary pancreatic ductal stricture
- Irregular narrowing of MPD
- Symptoms usually mild
- Steroids may be beneficial
    - Finkelberg DL et.al.N Engl J Med. 2006 Dec 21;355(25):2670-6

IDIOPATHIC PANCREATITIS

- Varies from 10-18%
- Depends on how extensive the search would be
- Some found to have microlithiasis, genetic abnormalities (CFTR mutation
- No patient should be allowed to have >1 attack of AP without having an Imaging study
- Age > 50, should be cautious about carcinoma
  - Toskes PP . Gastroenterol Clin North Am 1990 Dec;19(4):783-91

- Which of the following therapy has been demonstrated to be effective in acute pancreatitis

1. Lexipafant
2. Octreotide
3. Glucagon
4. H2 receptor antagonist
5. None of the above

Errors in management

- Failing to identify and monitor severity of the disease
- Monitor the patient closely
- Failing to prevent necrosis
- Aggressive intravenous hydration
- Failing to establish the DX and Rx biliary sepsis and pancreatitis
- Specificity of LFTS
- The importance of urgent ERCP
- Role of antibiotics
- Maintenance of the nutrition

Revised Atlanta Criteria (2013)

Mild acute pancreatitis

Absence of organ failure

Absence of local complications

Moderately severe acute pancreatitis

Local complications **AND/OR**

Transient organ failure (< 48 h)

Severe acute pancreatitis

Persistent organ failure > 48 h

Risk factors for severe disease at admission: Bedside BISAP criteria

- B=BUN> 25
- I=Impaired mental status
- S= systemic inflammatory response syndrome(SIRS)

  (Pulse >90/min, Res >20/min, or PaCO2<32 mm hg, T max >100.4 F or < 96.8 F, WBC > 12 K or < 4Kor > 10% bands)
- A= Age >60
- P=Pleural effusion

- Conwell D et all. Clinical gastro and hepatology . May 2010, Vol 8, No 5, p: 410425

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Hematocrit and Severity

- Hemoconcentration with an admission Hematocrit 47% or failure of admission Hematocrit to decrease at approximately 24 h were strong risk factors for the development of pancreatic necrosis.

- Extravasations of fluid to peritoneum- decreased intravascular volume- Hematocrit rises-decreased pancreatic perfusion- increased pancreatic necrosis

Break the cycle with IVF

Baillargeon JD et al. Am J Gastroenterol 1998;93:2130-34

How much fluid should we give

- Aggressive hydration, defined as 250–500 ml per hour, unless cardiovascular, renal, or other related comorbid factors exist.
- Most beneficial during the first 12–24 h
- In a patient with severe volume depletion, manifest as hypotension and tachycardia, more rapid repletion (bolus) may be needed
- Lactated Ringer's solution may be the preferred isotonic crystalloid replacement fluid
- Fluid requirements should be reassessed at frequent intervals within 6 h of admission and for the next 24–48 h.
- The goal of aggressive hydration should be to decrease the BUN and HCT

- *Am J Gastroenterol* 2013; 108:1400–1415

Errors in management

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Role of early ERCP and Biliary Sphincterotomy

- Biliary pancreatitis
- Transaminases > 3 times of normal value
- Stone in CBD
- Biliary sepsis
- Perform urgently (< 24 hrs better than 72 hrs)
- Fortunately, most gallstones that cause AP readily pass to the duodenum and are lost in the stool

Fan et al NEJM 1993;328: 228-232
Neoptolemos et al. Lancet 1988;2:979-983

Errors in management

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Role of Antibiotics in Acute Pancreatitis

- No Longer Controversial.
- Double blinded placebo controlled study
- 100 patients from 32 centers
- Meropenem vs. Placebo
- No statistically significant benefit in preventing infection, sepsis, mortality
- **Prophylactic antibiotics are not recommended in acute pancreatitis**

Dellinger T et al. annals of Surgery 2007;435:222-231

Isenmann R et al.Gastroenterology2004;126:997-1004

Management of Sterile Necrosis

- Organ failure seen in almost 50% of patients
- The use of antibiotics in patients with sterile necrosis to prevent the development of infected necrosis is not recommended
- Sterile necrosis- best managed medically for the first 2-3 weeks.

- After that , if pain persists or unable to eat

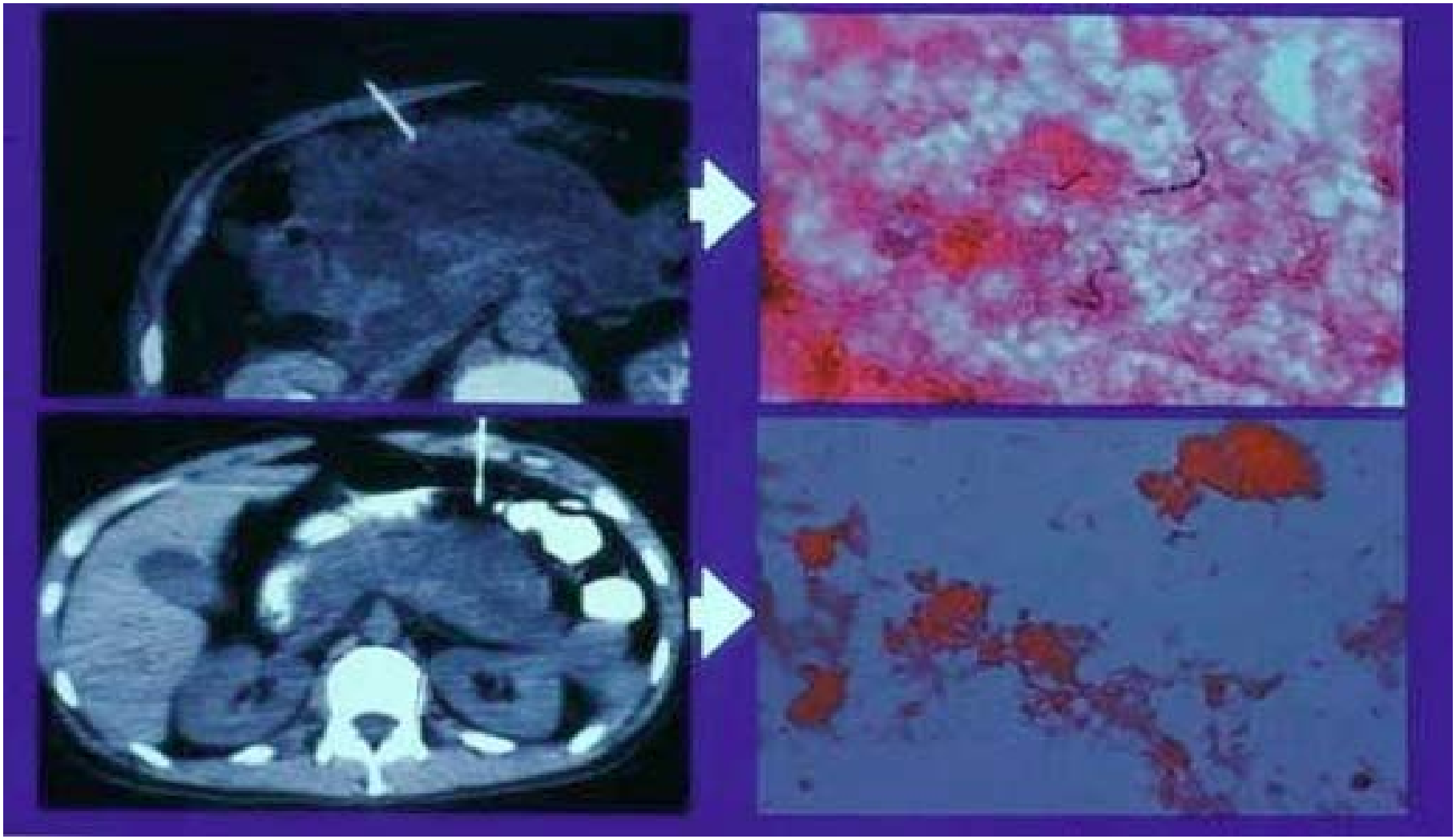
  Debridement
- Surgical, Endoscopic Necrosectomy or Percutaneous drainage
- Be cautious about early intervention, may increase mortality, introduction of infection with re-surgery

Bank and Freeman Am J Gastroenterol.2006;101:23792400

Management of Infected Necrosis

- Patients with pancreatic necrosis who deteriorate or fail to improve after 7–10 days of hospitalization.
- CT FNA for Gram stain and culture to guide use of appropriate antibiotics or empiric use of antibiotics without CT FNA should be given.
- In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed by preferably 4 weeks to allow the development of a wall around the necrosis (walled-off pancreatic necrosis).
- 64% of the patients managed by conservative antibiotic treatment with 12% mortality, and only 26% underwent surgery.
  - *Am J Gastroenterol* 2013; 108:1400–1415

Diagnosis of Pancreatic Infection



Which Antibiotic?

- Penicillin has no role in pancreatic infection
- Carbinepenem group is the antibiotic of choice
- Ciprofloxacin and Metronidagole are good alternative

Errors in management

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Nutrition in Acute Pancreatitis

- Historically, despite the absence of clinical data, patients with AP were kept NPO (nothing by mouth) to rest the pancreas

- Bowel rest is associated with intestinal mucosal atrophy and increased infectious complications because of bacterial translocation from the gut.

- Oral feeding early in the course of AP have a shorter hospital stay, decreased infectious complications, decreased morbidity, and decreased mortality

  - *Am J Gastroenterol* 2013; 108:1400–1415

Nutrition in Mild Acute Pancreatitis

- In mild AP, oral feedings can be started immediately if there is no nausea and vomiting, and the abdominal pain has resolved
- In mild AP, initiation of feeding with a low-fat solid diet appears as safe as a clear liquid diet
  - *Am J Gastroenterol* 2013; 108:1400–1415

Nutrition in Severe Acute Pancreatitis

- Enteral nutrition.
- EN vs. TPN
- Maintains gut integrity and decreases intestinal permeability
- Less hyperglycemia
- Fewer septic complication
- Fewer days in hospital
- Decreased costs
- Decrease in morbidity and mortality

Tanner S et al.AGA post graduate course syllabus2009;393-407

Nutrition in Severe Acute Pancreatitis

- No statically significant difference has been shown in RCT comparing NG over NJ feeding in severe AP
- **NG or NJ feeding should be started early within 36-48 hours in patients with severe acute pancreatitis**

- A large multicenter trial sponsored by the National Institutes of Health (NIH) is ongoing

Eatock et al. Am J gastro 2005;100:432-439

When to take Gallbladder out?

- Mild biliary AP cholecystectomy should be performed before discharge to prevent a recurrence of attacks
- Necrotizing biliary AP, in order to prevent infection, cholecystectomy is to be deferred until active inflammation subsides and fluid collections resolve or
- Asymptomatic pseudocysts and pancreatic and/or extrapancreatic necrosis do not warrant intervention regardless of size, location, and/or extension

Mortality in Acute Pancreatitis

- Overall 6%
- Interstitial Pancreatitis 3%
- Necrotizing Pancreatitis 17%
- Infected Necrosis 30%
- Single Organ failure 3%
- MOF 47%

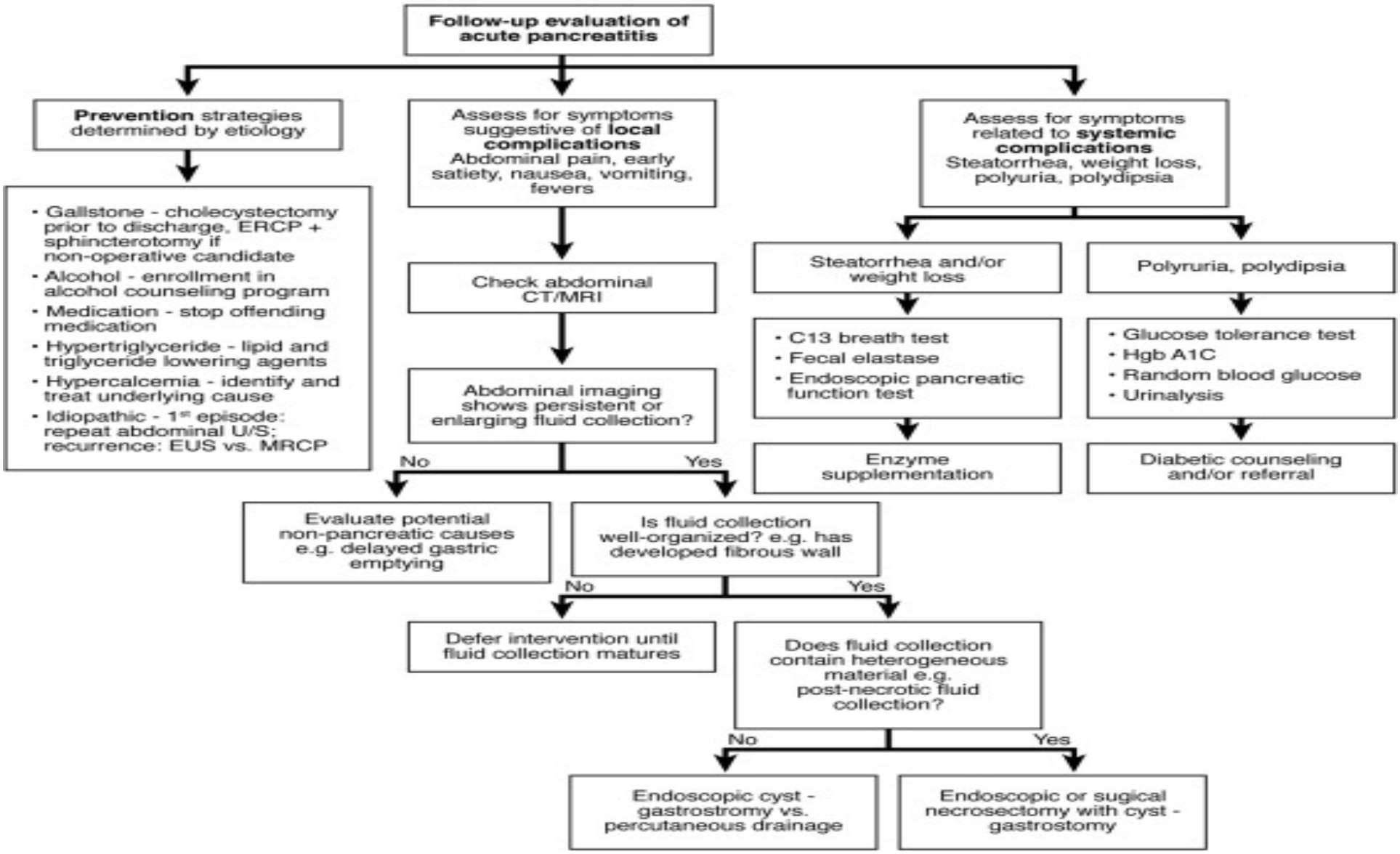
Bank and Freeman Am J Gastroenterol.2006;101:23792400

Do’s and Don’t

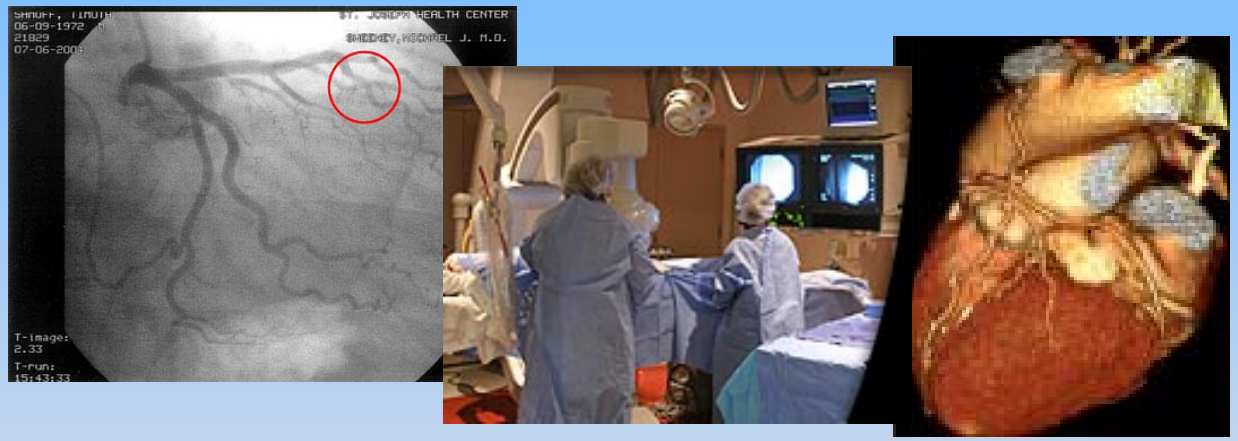
- Avoid labeling patients with “mild” during the first 48 hrs
- Beware of organ failure- maximize supportive care
- Prevent necrosis -- aggressive hydration
- Remove retained stone: early ERCP, if indicated
- Prevent infection of necrosis(if present)
- Do not use prophylactic antibiotic
- Avoid TPN
- Enteral feeding
- Sterile necrosis- conservative approach- supportive care> 3 wks, if persistent pain, unable to eat– surgical debridement
- Infected necrosis- begin antibiotic, debridement

Most Deaths In Patients With Acute Pancreatitis Are Avoidable.

Follow up of Acute Pancreatitis



Coronary Artery Disease: Risk Assessment and Therapy



Chowdhury H Ahsan,
MRCP, MD, Ph.D., FACC, FSCAI
Clinical Professor of Medicine, University of Nevada School of Medicine
Program Director, Cardiology Fellowship at University of Nevada School of Medicine
Director, Marlon Cardiac Catheterization Laboratories, UMC, Las Vegas, Nevada

CONFLICT OF INTEREST

Speaker/consultant/Grants:

Boehringer Ingelheim
Astra Zeneca
Amgen
Gilead
NOVARTIS
Biotronik

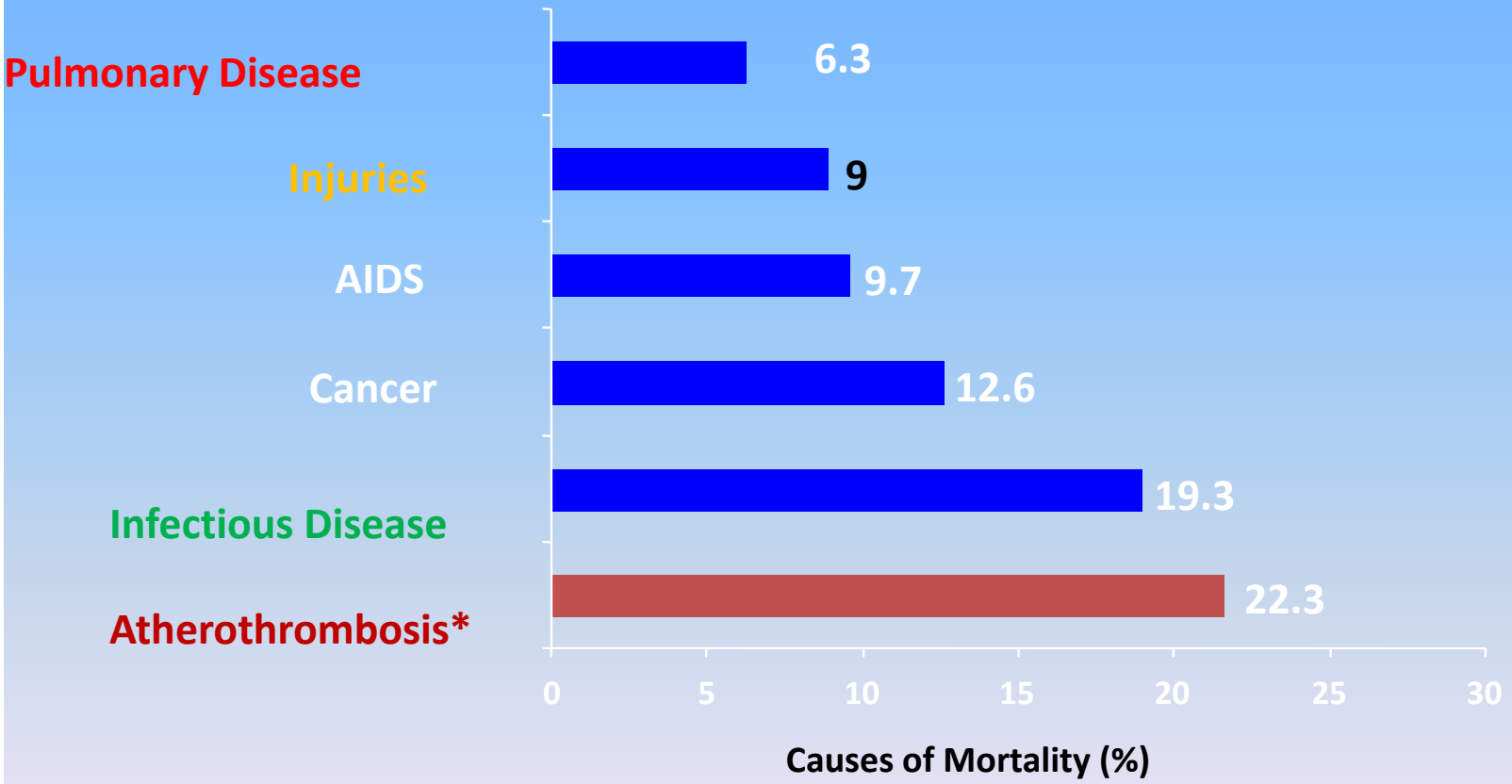
Dr J Jollis, Faculty at Duke
Duke Clinical Research Institute

RACE Registry : North Carolina STEMI Care

American Heart Assoc : Mission Lifeline

Collaborative work: Across the globe

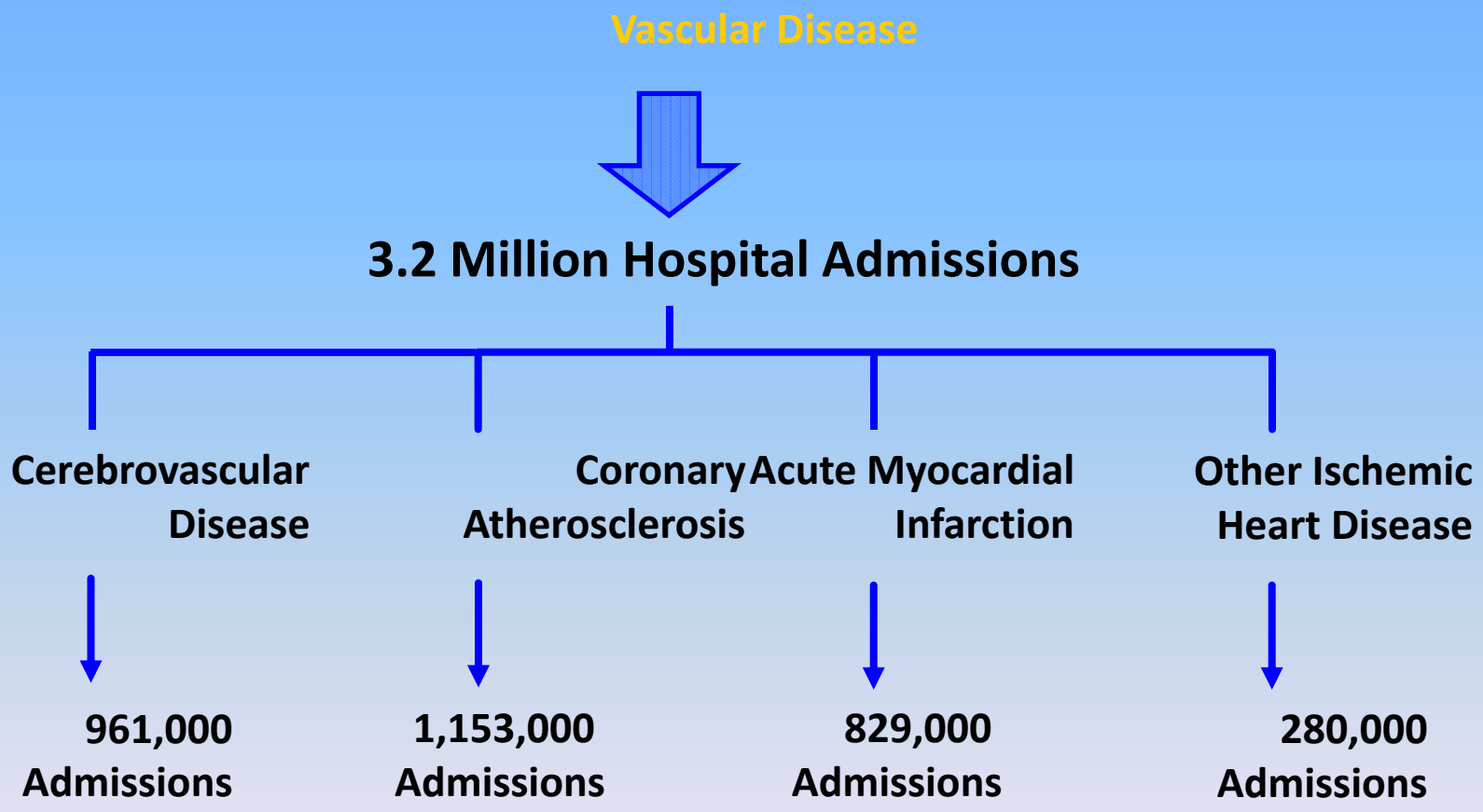
Atherothrombosis* is the Leading Cause of Death Worldwide[1]



*Atherothrombosis defined as ischemic heart disease and cerebrovascular disease.

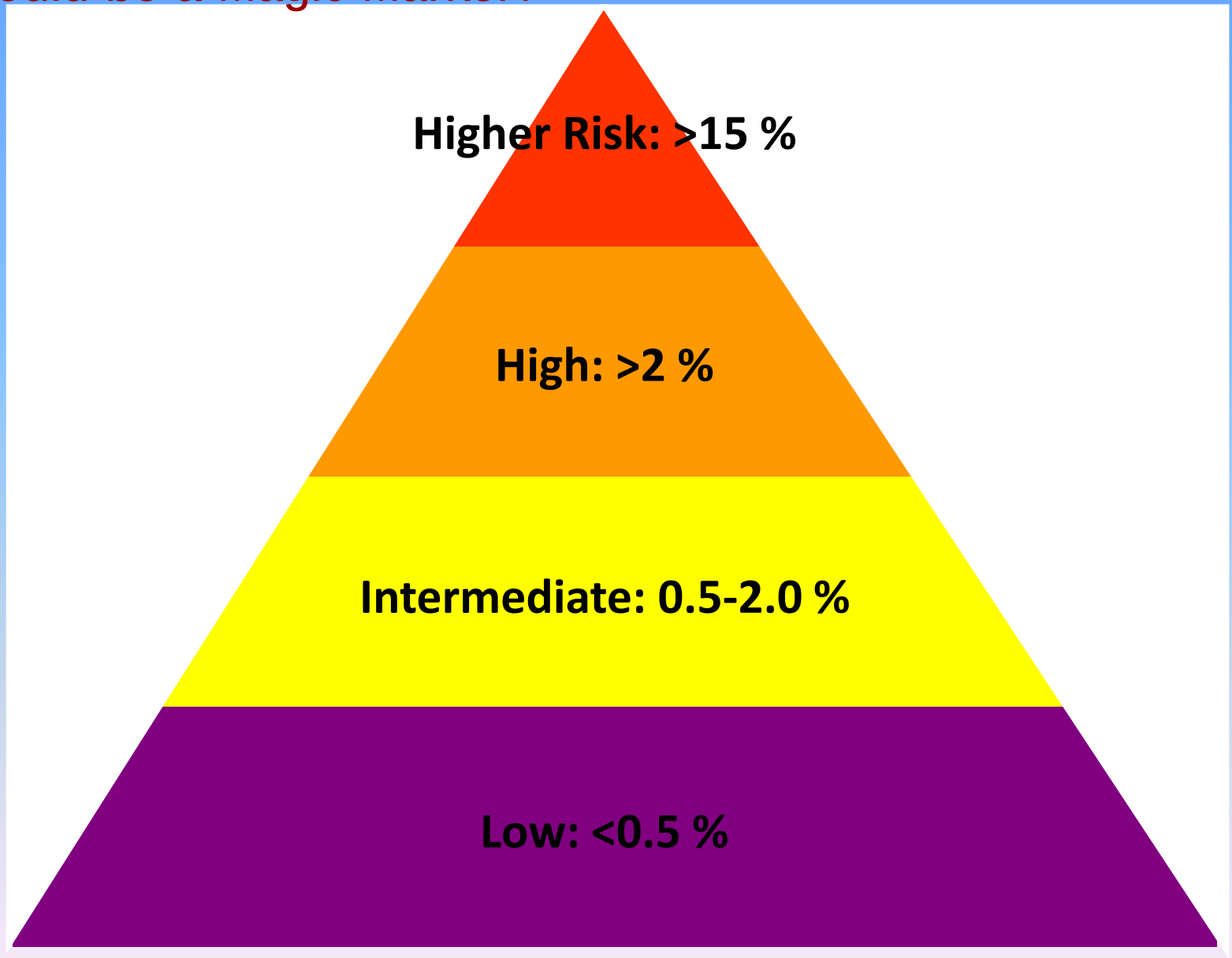
[1]*The World Health Report 2001*. Geneva: WHO; 2001.

Hospitalizations in the US Due to Atherosclerotic Disease



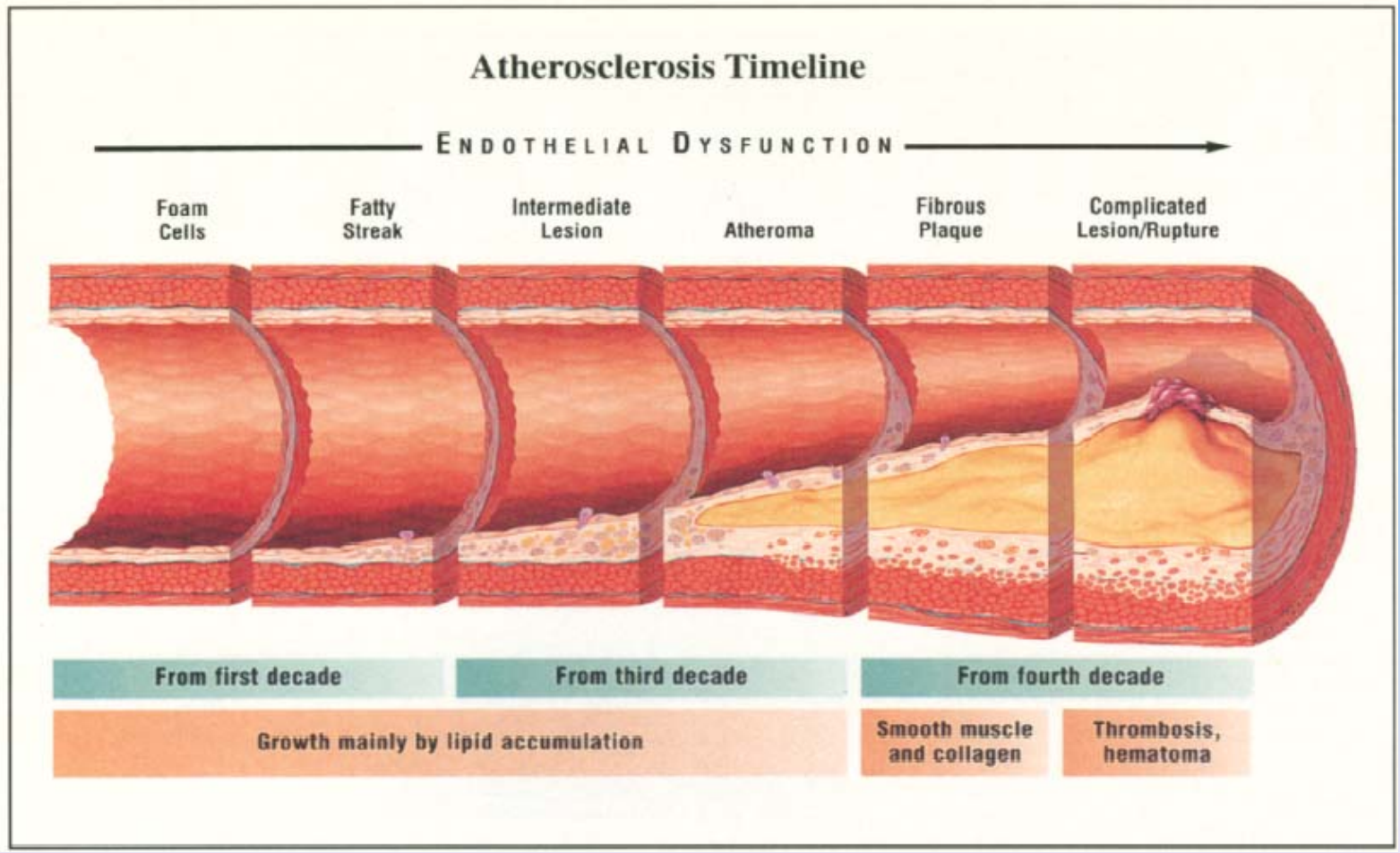
From Popovic JR, Hall MJ. *Advance Data*. 2001;319:1-20. Slide reproduced with permission from Cannon CP. Atherothrombosis slide compendium. Available at: www.theheart.org.

Should We Expect a Magic Marker?
What Would be a Magic Marker?

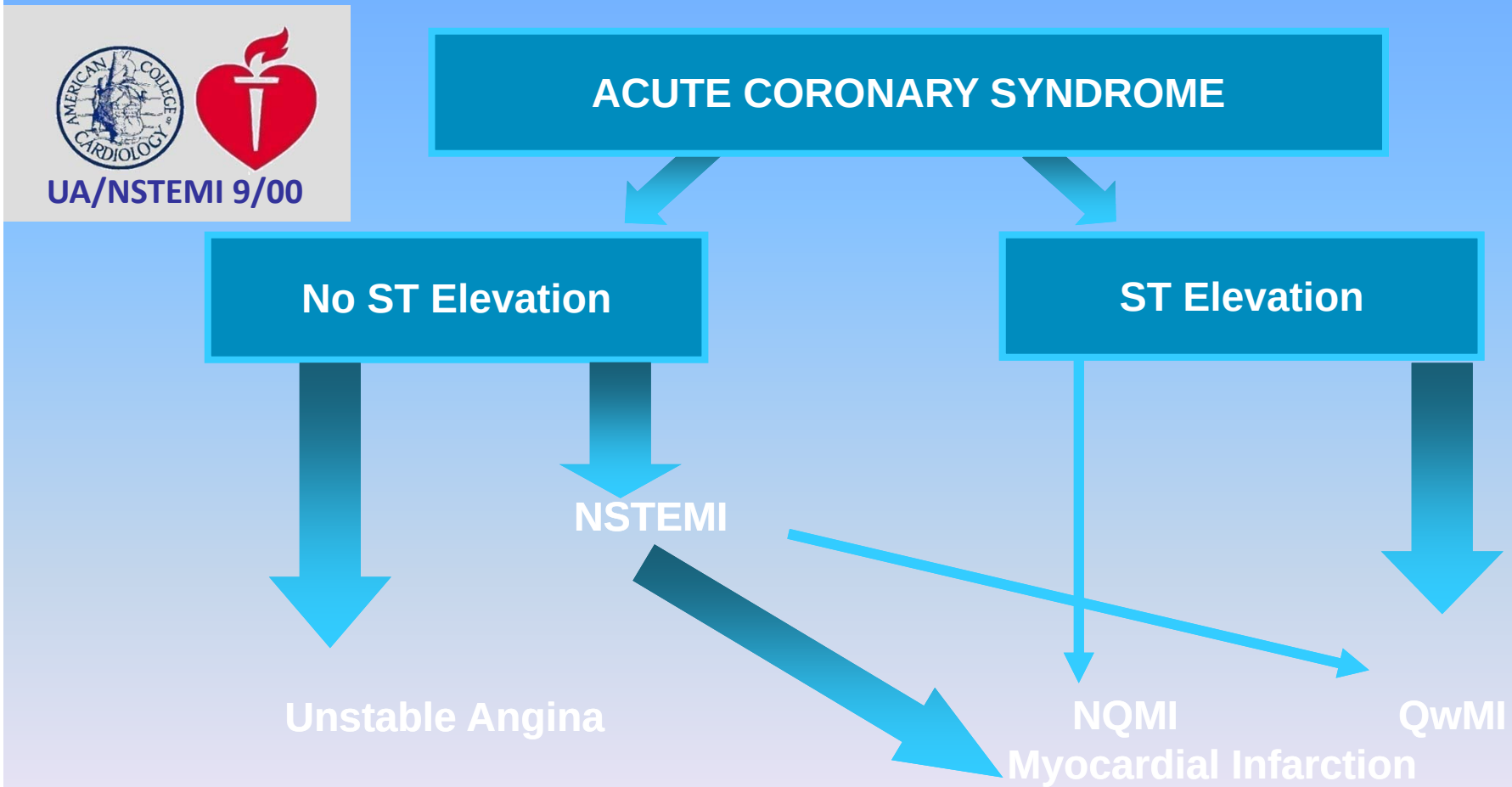


Braunwald, JACC 2006

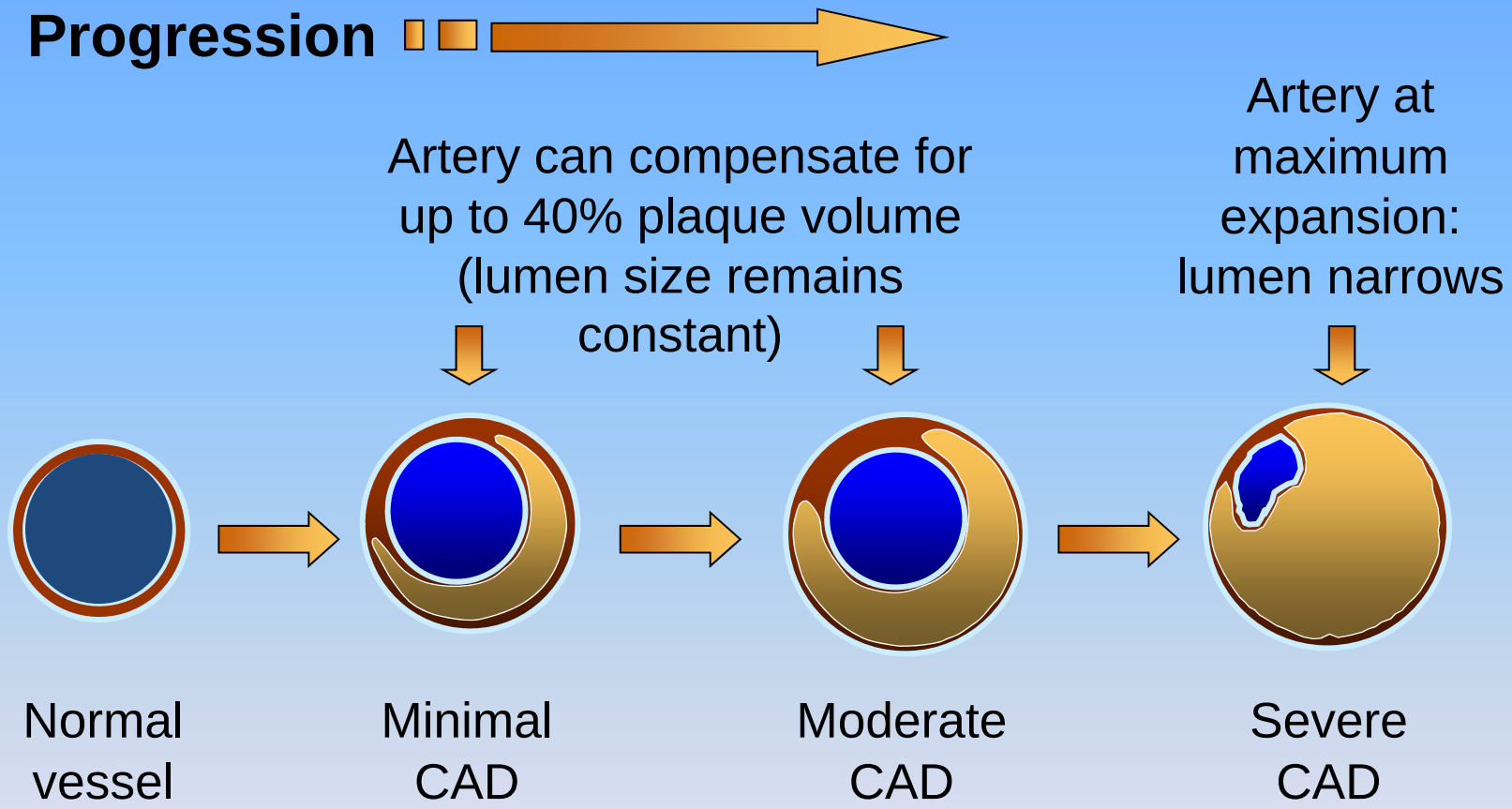
Newer Understanding of Atherosclerosis



Pathogenesis



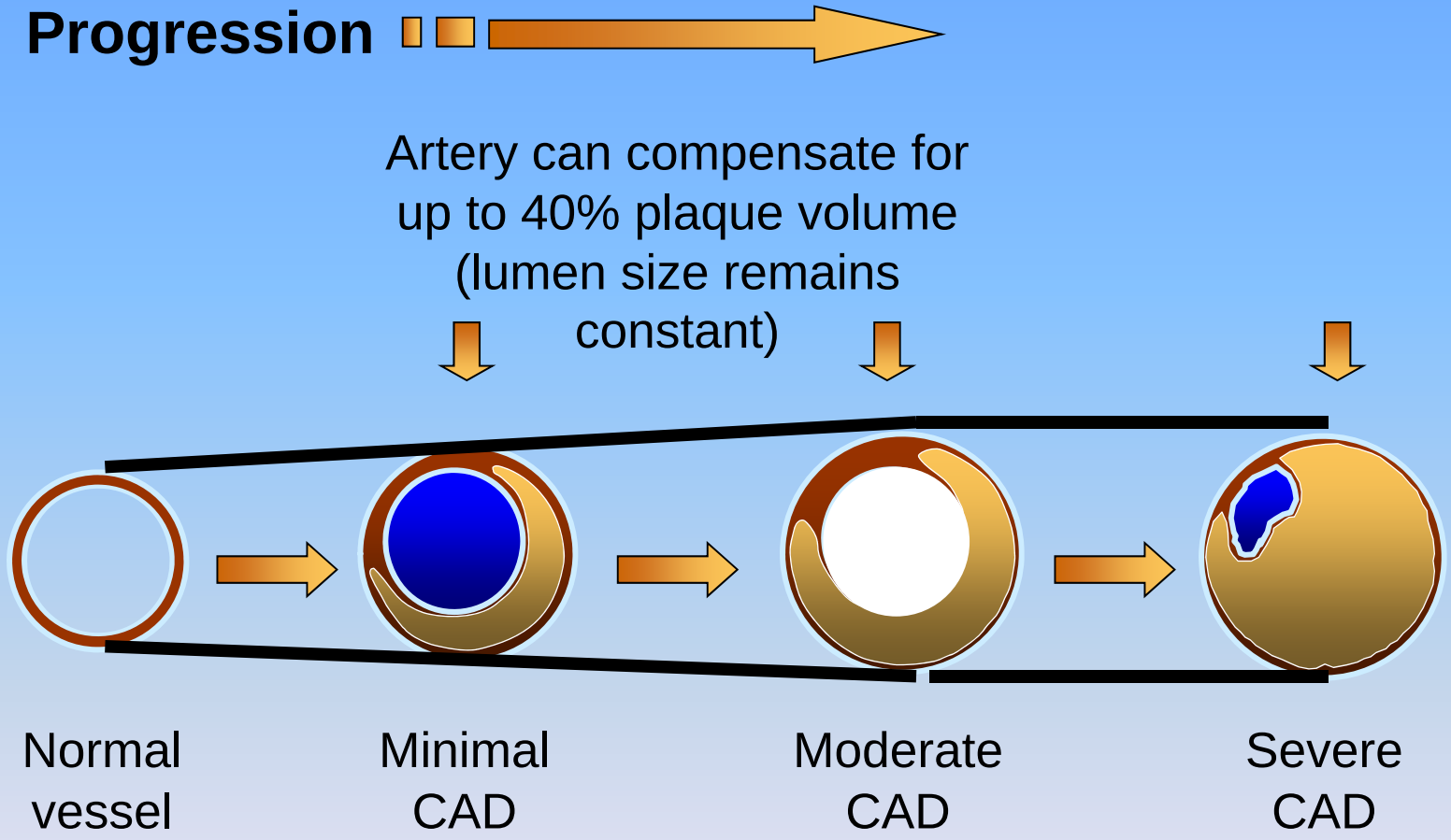
Glagov Hypothesis: Coronary Remodeling



Glagov S et al, *N Engl J Med*, 1987.

Glagov Hypothesis: Outward Remodeling

Progression



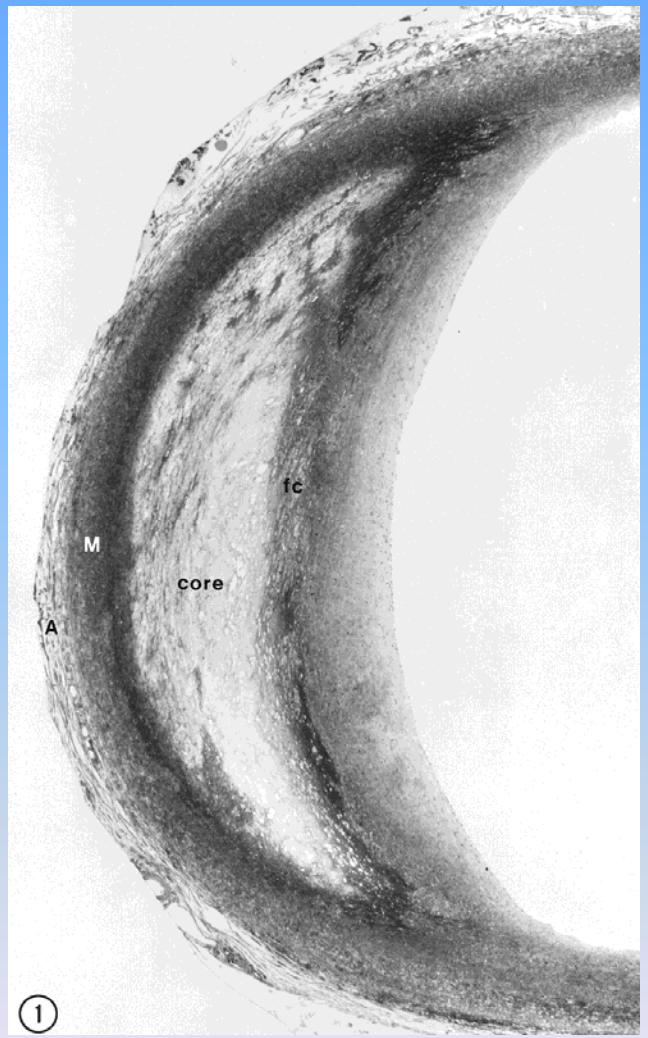
Glagov S et al, *N Engl J Med*, 1987.

A Definition of Advanced Types of Atherosclerotic Lesions and a Histological Classification of Atherosclerosis

by Herbert C. Stary, A. Bleakley Chandler, Robert E. Dinsmore, Valentin Fuster, Seymour Glagov, William Insull, Michael E. Rosenfeld, Colin J. Schwartz, William D. Wagner, and Robert W. Wissler

Circulation
Volume 92(5):1355-1374
September 1, 1995

Photomicrograph of atheroma (type IV lesion) in proximal left anterior descending coronary artery.



Stary H C et al. Circulation. 1995;92:1355-1374

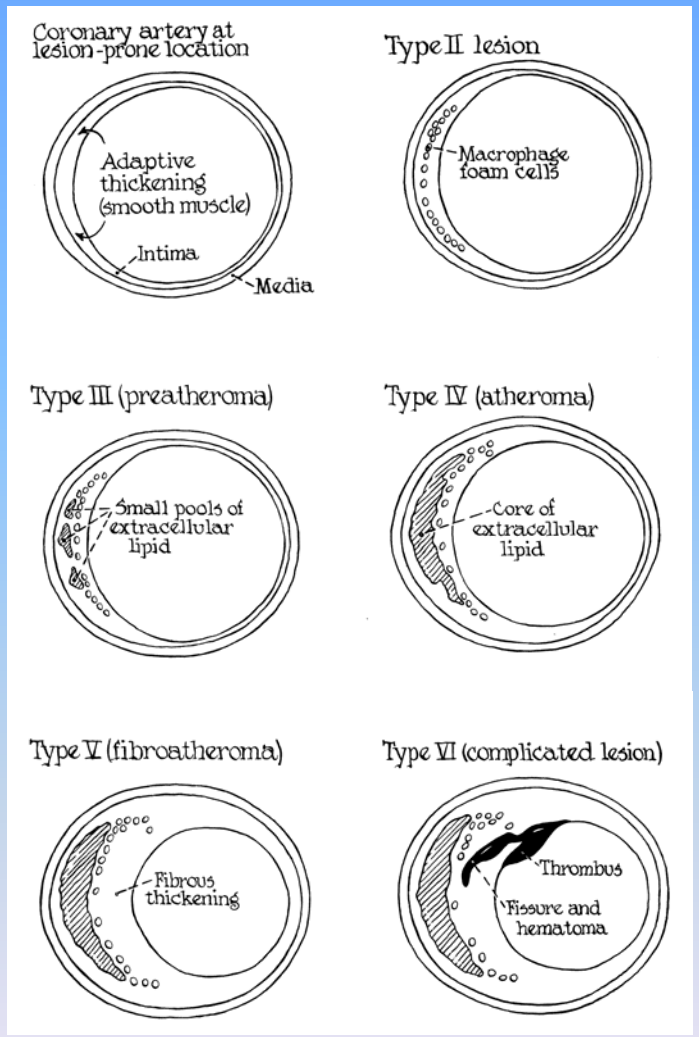
American Heart Association.

Table 2 Major types of lesions of atherosclerosis

Lesion Name	Lesion Description by Histopathology	Thrombosis
Nonatherosclerotic intimal lesions		
1. Intimal thickening	The normal accumulation of SMCs in the intima with the absence of lipid or macrophage foam cells	Thrombus is absent
2. Intimal xanthoma or fatty streaks	Subendothelial accumulation of foam cells in intima without necrotic core or fibrous cap; animal and human data show that such lesions usually regress	Thrombus is absent
Progressive atherosclerotic lesions		
1a. Pathologic intimal thickening	SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrosis	Thrombus is absent
1b. With erosion	Luminal thrombosis, plaque same as above	Thrombus most often mural and infrequently occlusive
2a. Fibrous cap atheroma	Well-formed necrotic core with overlying fibrous cap	Thrombus is absent
2b. With erosion	Luminal thrombosis; plaque same as above, no communication of thrombus with necrotic core	Thrombus most often mural and infrequently occlusive
3. TCFA	A thin fibrous cap infiltrated with macrophages and lymphocytes, rare SMCs, and an underlying necrotic core	Absent, with intraplaque hemorrhage/fibrin
a. With rupture	Fibroatheroma with cap disruption; luminal thrombus communicates with underlying necrotic core	Thrombus usually occlusive
4. Calcified nodule	Eruptive nodular calcification with underlying fibrocalcific plaque	Thrombus usually nonocclusive
5. Fibrocalcific plaque	Collagen-rich plaque usually with significant stenosis; contains large areas of calcification with few inflammatory cells; necrotic core may be present	Thrombus is absent

SMC = smooth muscle cell; TCFA = thin-cap fibroatheroma. Reprinted with permission from *Arterioscler Thromb Vasc Biol.*[12]

Drawing of cross-sections of identical, most proximal part of six left anterior descending coronary arteries.



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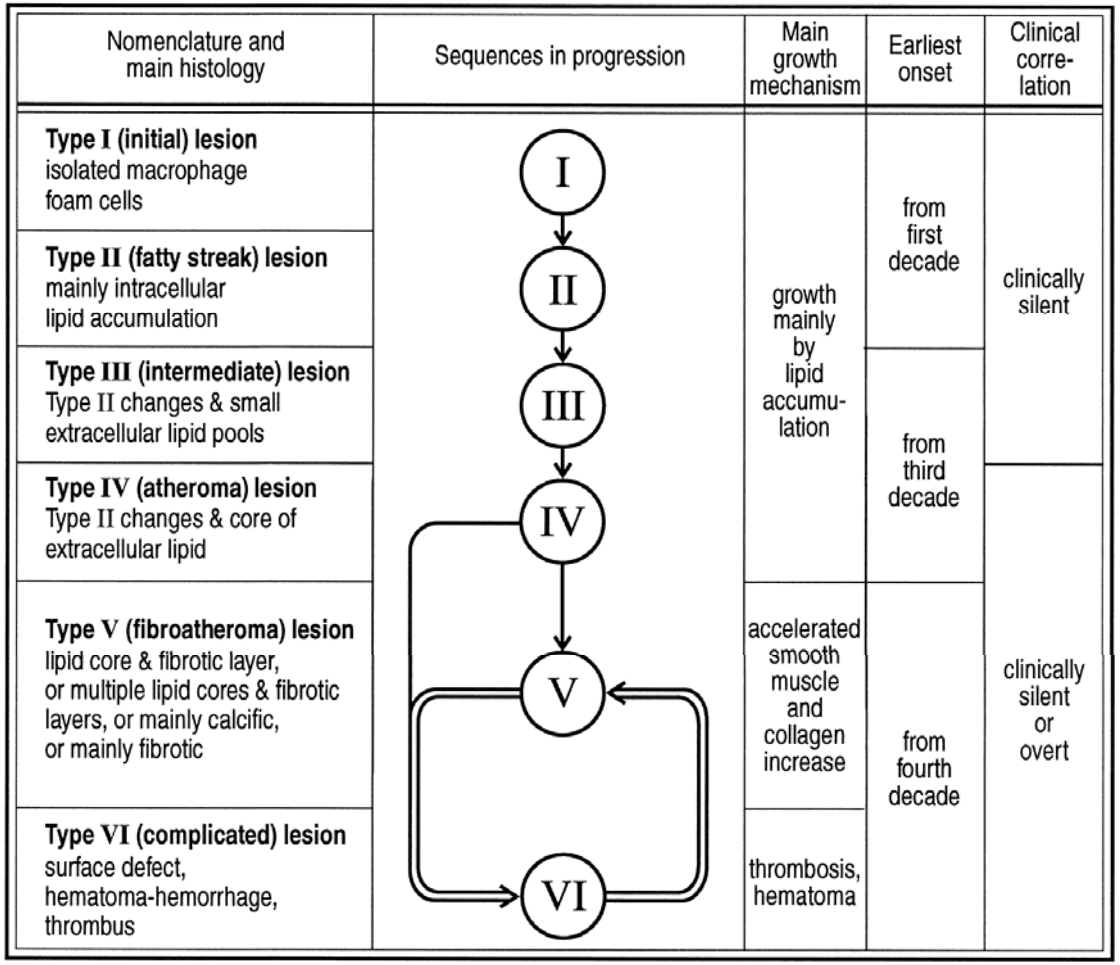
American Heart Association.

Flow diagram in center column indicates pathways in evolution and progression of human atherosclerotic lesions.



Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical correlation
Type I (initial) lesion isolated macrophage foam cells	I	growth mainly by lipid accumulation	from first decade	clinically silent
Type II (fatty streak) lesion mainly intracellular lipid accumulation	II			
Type III (intermediate) lesion Type II changes & small extracellular lipid pools	III		from third decade	
Type IV (atheroma) lesion Type II changes & core of extracellular lipid	IV			clinically silent or overt
Type V (fibroatheroma) lesion lipid core & fibrotic layer, or multiple lipid cores & fibrotic layers, or mainly calcific, or mainly fibrotic	V	accelerated smooth muscle and collagen increase	from fourth decade	
Type VI (complicated) lesion surface defect, hematoma-hemorrhage, thrombus	VI	thrombosis, hematoma		

Stary H C et al. Circulation. 1995;92:1355-1374

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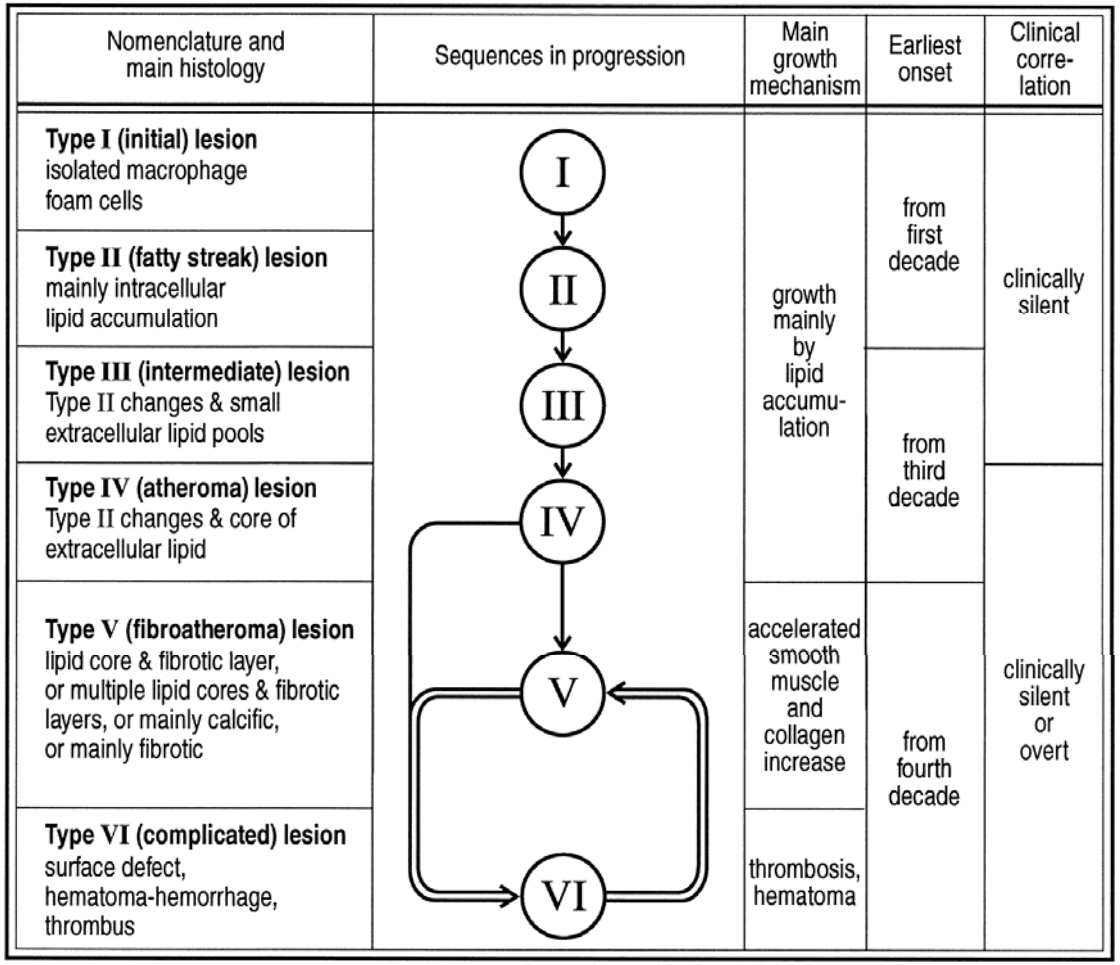

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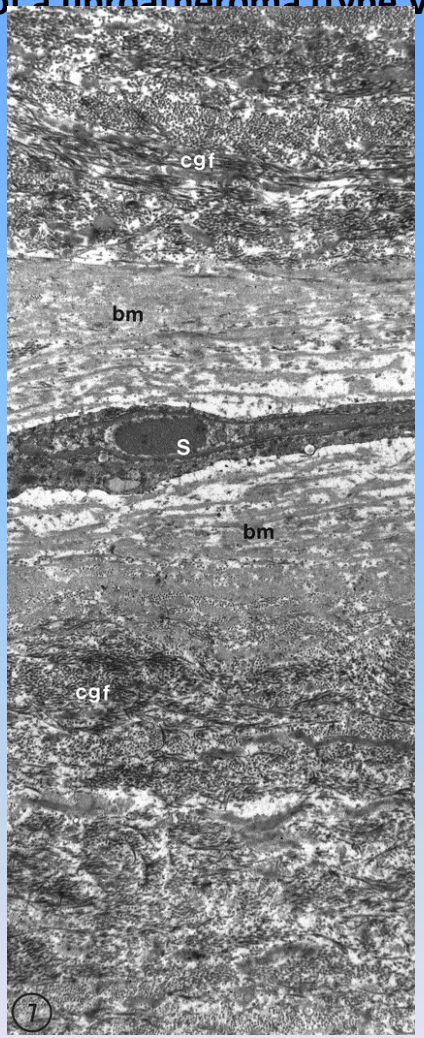
American Heart Association.

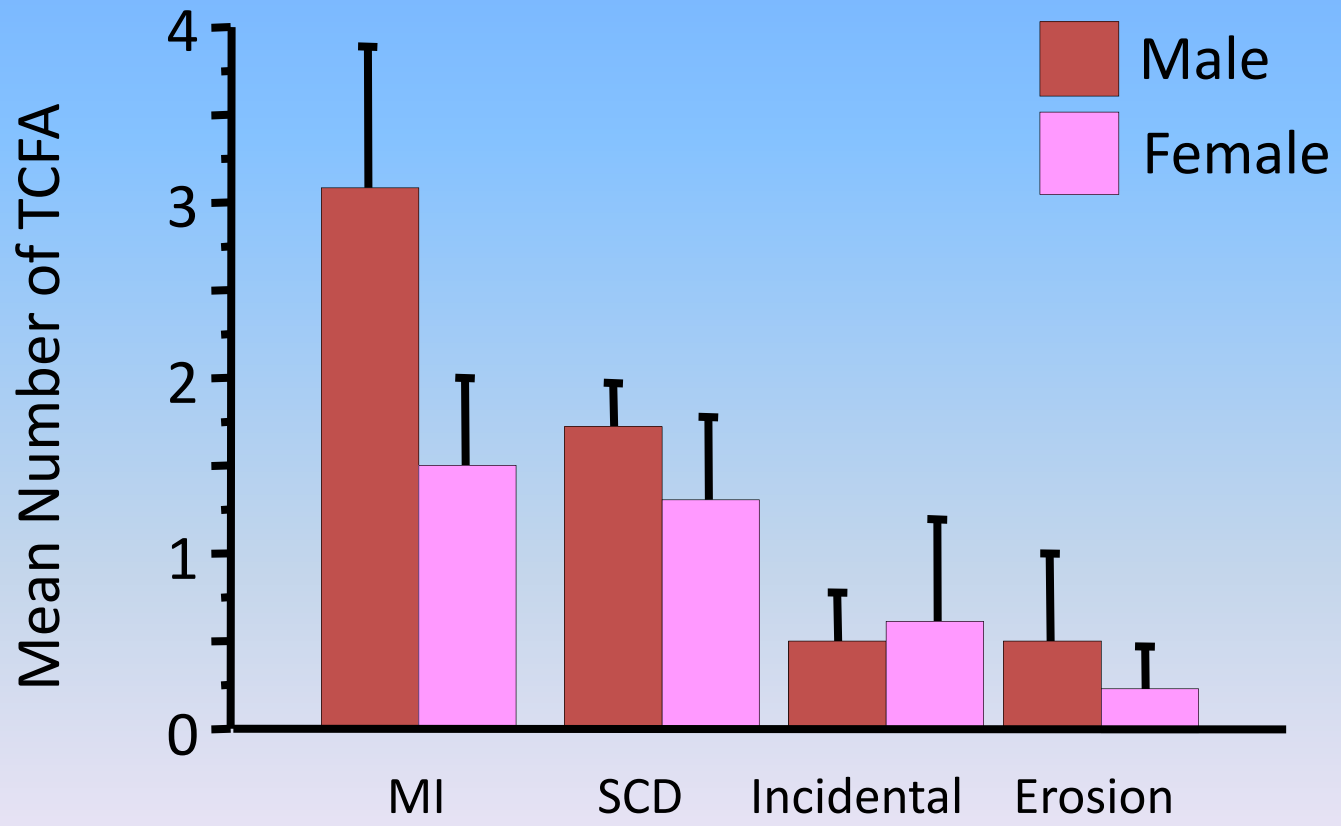
Electron photomicrograph of basement membrane (bm)–rich smooth muscle cell (S) and intercellular matrix of collagen fibers (cgf) in the region between lipid core (not visible) and endothelial surface (not visible) of a fibroatheroma (type V lesion).



Stary H C et al. Circulation. 1995;92:1355-1374

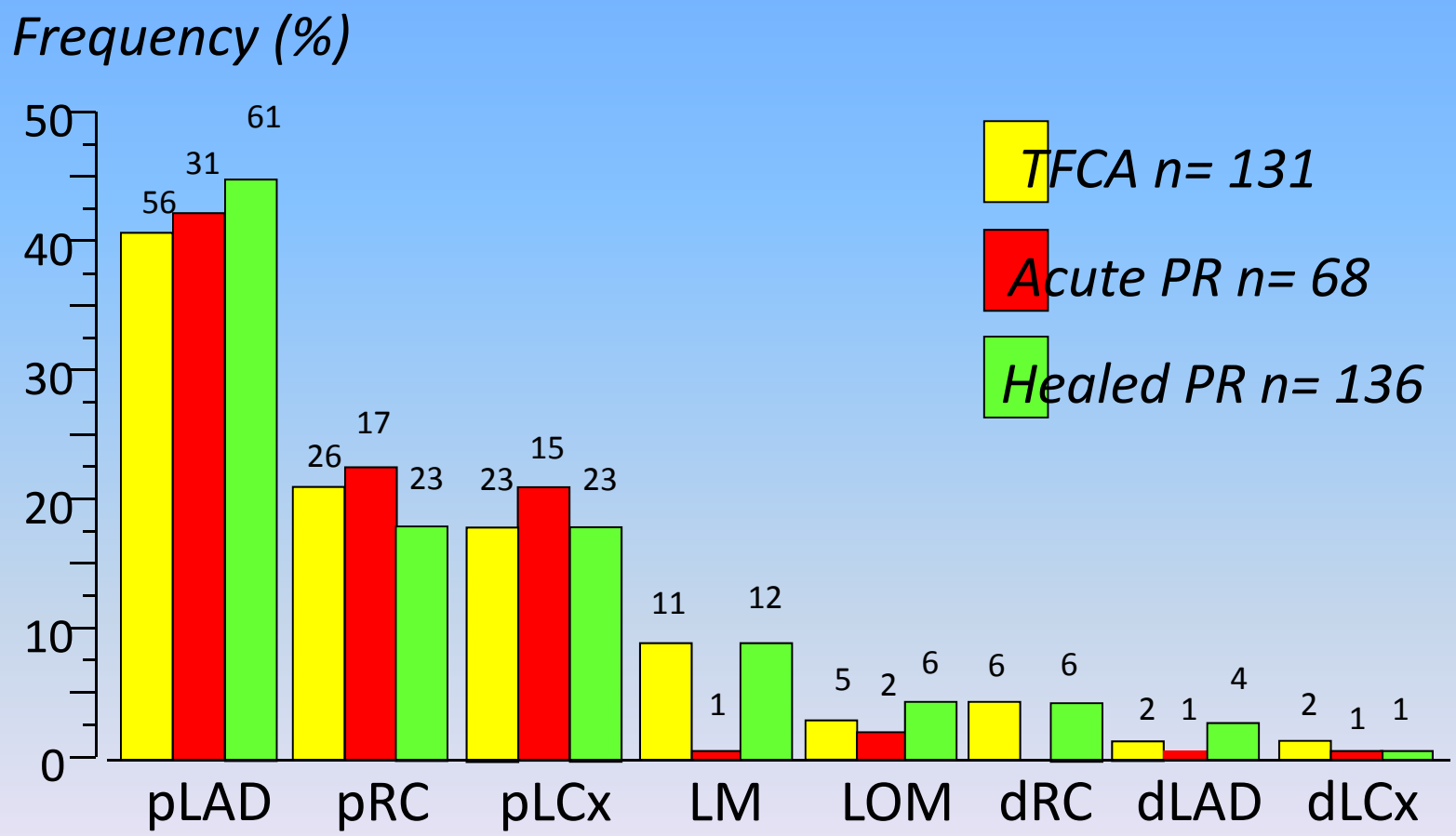
American Heart Association

TCFA in ACS are Usually Not Many



Narula, Virmani, Shapiro: Braunwald's Atlas of CV CT (2007)

Unstable Lesions are Located Proximally



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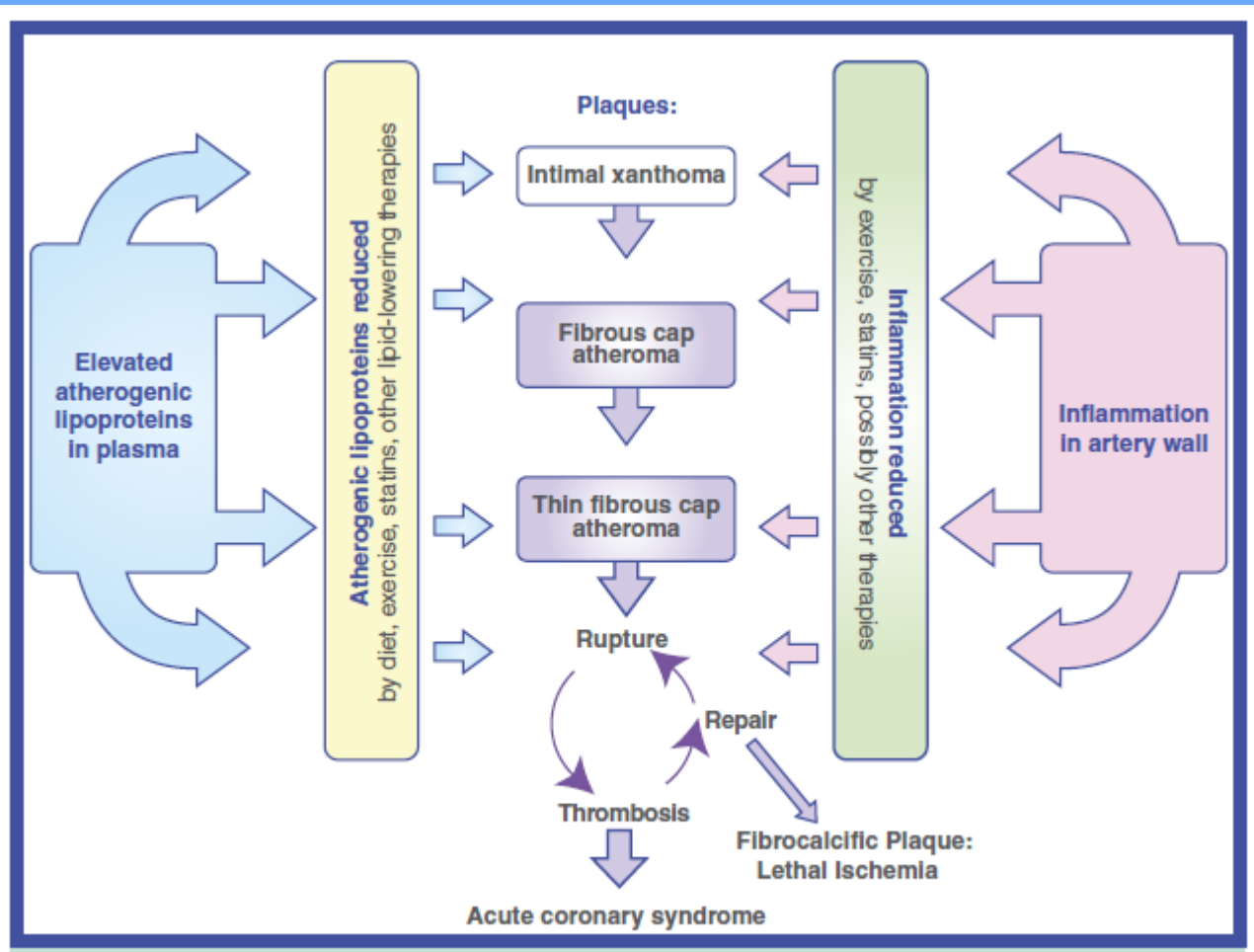


Figure 4 Influence of therapeutic intervention on the atherosclerotic process.

On Clinton, Cholesterol & Coronary Concepts…

http://story.news.yahoo.com/news?g=events/pl/080601billclinton&a=&tmpl=sl&ns=&l=o&e=69&a=o&print

er=

1996

1992	
Weight	226 #
Height	6-2
BMI	29.1
BP	130/70
HR	75
Glucose	104
Bruce V	91%
No EKG Δ	
1999	
TC	196
TG	80
HDL	46
LDL	134
2001	
TC	**233**
LDL	**177**

Sept 3, 2004

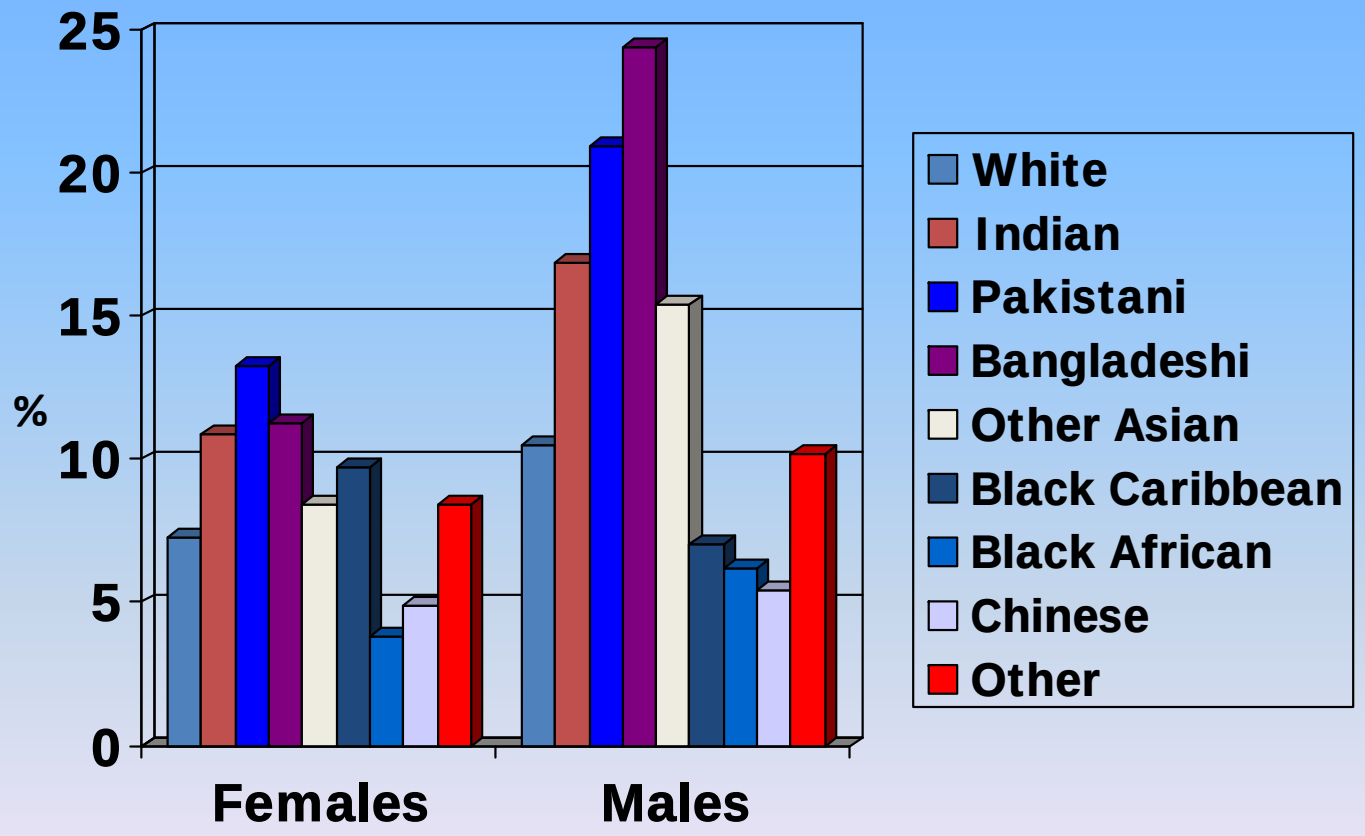
UA → CABG × 4

HOW WE ASSESS RISKS

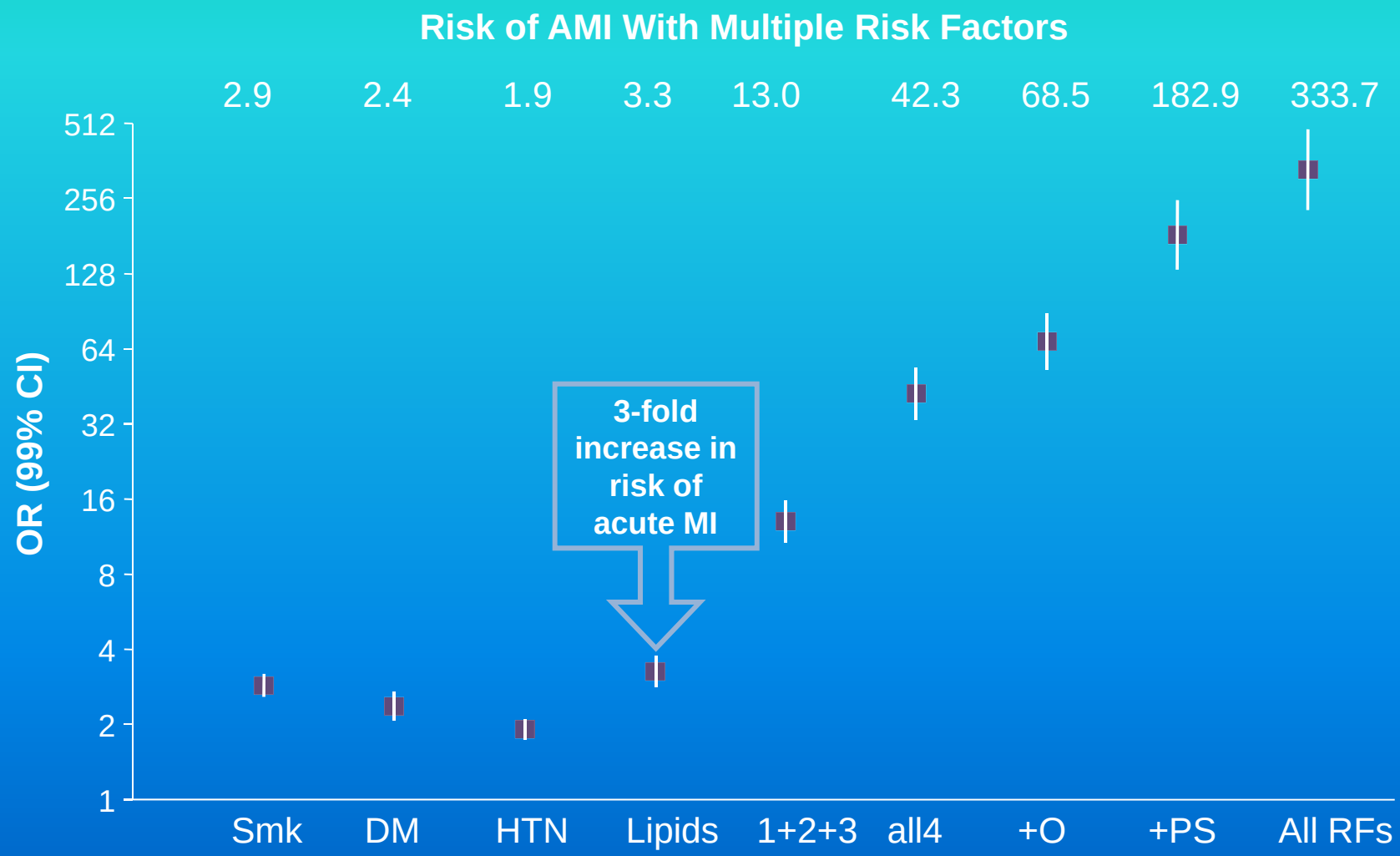
Table 1. *10-year cardiovascular risk score prediction models in individuals without known cardiovascular disease.*

Name	Variables	Advantages
Framingham (Sayin et al., 2014) [19]	Gender, Age, HDL Cholesterol, Total Cholesterol, Treatment for Hypertension status, Systolic Blood Pressure, Smoking Status, Diabetes Status	Easy to calculate risk assessment tool that uses information from the classic Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years.
Reynolds (Móczár, 2013) [20]	Gender, Age, HDL Cholesterol, Total Cholesterol, Treatment for Hypertension status, Systolic Blood Pressure, Smoking Status, Family history of premature CAD, high sensitivity C-Reactive Protein (hs-CRP)	By adding hs-CRP and family history, Reynolds risk score add predictive value especially for women, young individuals, and those with metabolic syndrome
ASSIGN (Van Staa et al., 2014) [21]	Gender, Age, HDL Cholesterol, Total Cholesterol, Treatment for Hypertension status, Systolic Blood Pressure, Family history of premature CAD, Number of cigarettes smoked per day, Scottish Index of Multiple Deprivation (SIMD)	This risk score takes into account social status according to the area the person lives in. Also, smoking status is considered dependent on how many cigarettes the person smokes.
QRISK2 (Van Staa et al., 2014) [21]	Gender, Age, Ethnicity, Cholesterol/HDL ratio, Diabetes Status, Treatment for Hypertension status, Systolic Blood Pressure, Smoking Status, Area of residence, Chronic Kidney Disease status, Atrial fibrillation status, Rheumatoid Arthritis status, BMI (height and weight)	Despite the challenges of coordination, development, and implementation, eight sessions in 4 European universities demonstrated the efficacy of PBL and can be useful in a cross-cultural context.
ASCVD (Loprinzi & Davis, 2015) [22]	Gender, Age, Ethnicity, HDL Cholesterol, Total Cholesterol, Diabetes Status, Treatment for Hypertension status, Systolic Blood Pressure, Smoking Status	These are pooled Cohort Risk Assessment Equations which include the risk of stroke. There was some concern about accuracy.
Joint British Society (JBS-3) (Deanfield, 2014) [23]	Gender, Age, Ethnicity, HDL Cholesterol, Total Cholesterol, Diabetes Status, Treatment for Hypertension status, Systolic Blood Pressure, Smoking Status, Area of residence, Chronic Kidney Disease status, Atrial fibrillation status, Rheumatoid Arthritis status, BMI (height and weight)	The JBS calculator allows for the estimated impact of lifestyle modifications like smoking cessation and on future risk.

Age-standardised incidence of CVD by Ethnicity per 1000 pyrs



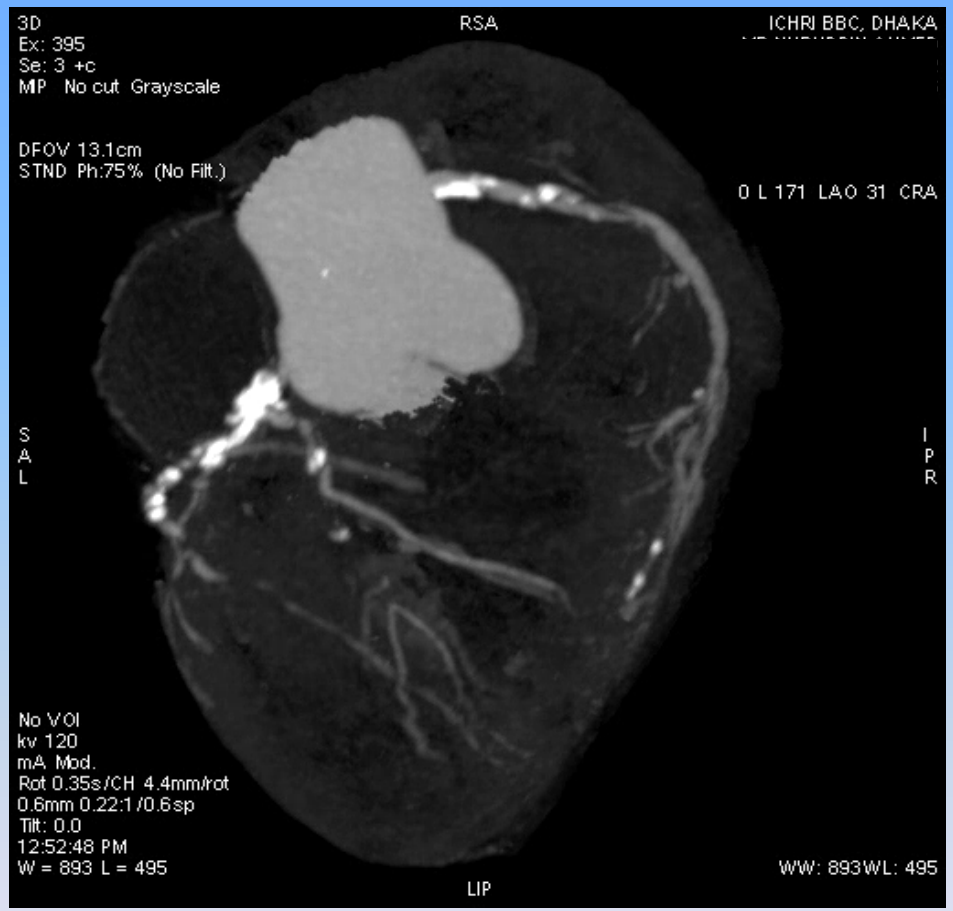
Association of Dyslipidemia and myocardial Infarction Risk: INTERHEART



AMI, acute myocardial infarction; Smk, smoking; DM, diabetes mellitus; HTN, hypertension; O, obesity; PS, psychosocial; RF, risk factors; OR; odds ratio.

Yusuf S et al. *Lancet.* 2004;364:937-952.

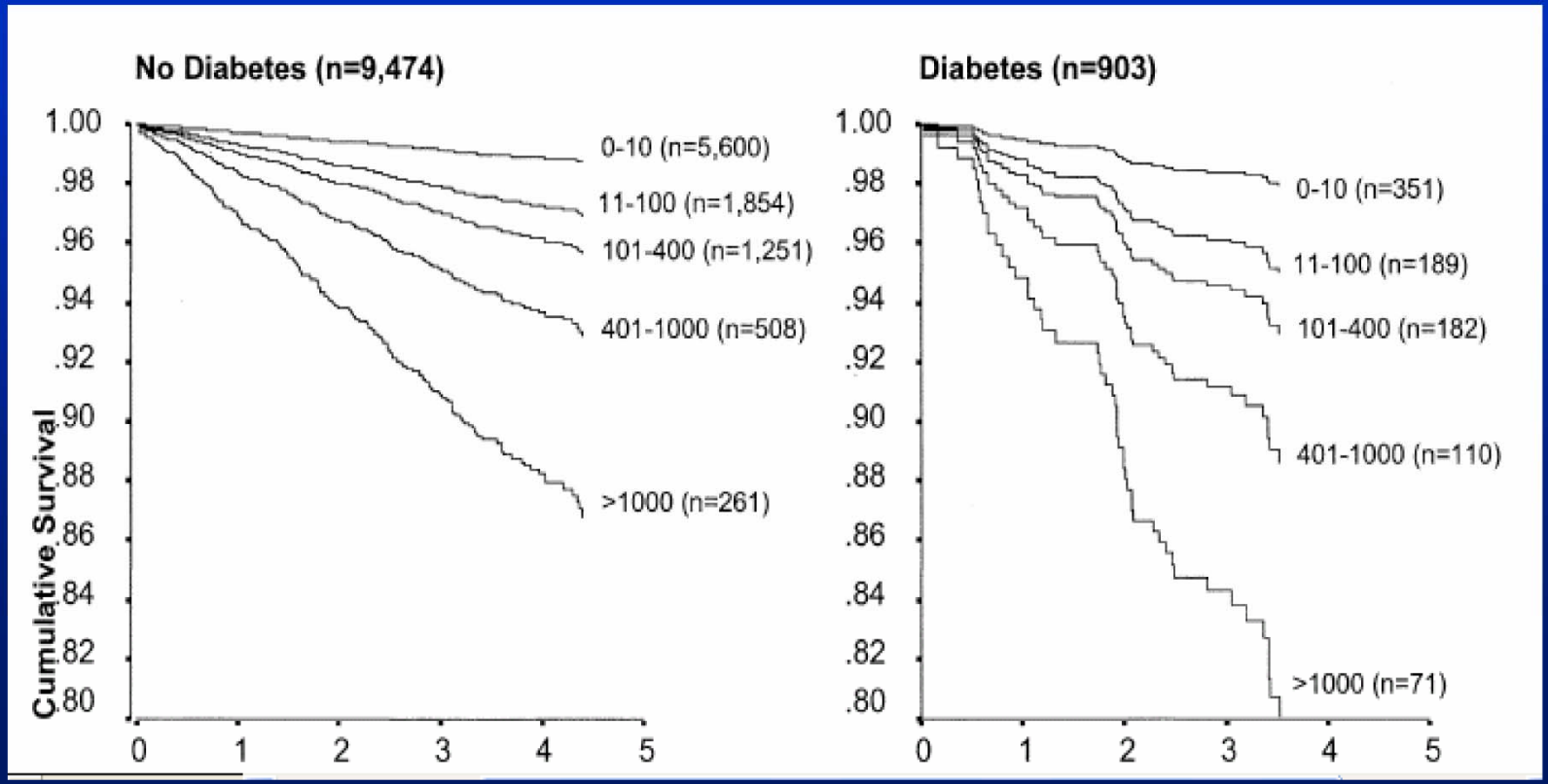
Atherosclerosis : Asymptomatic patient



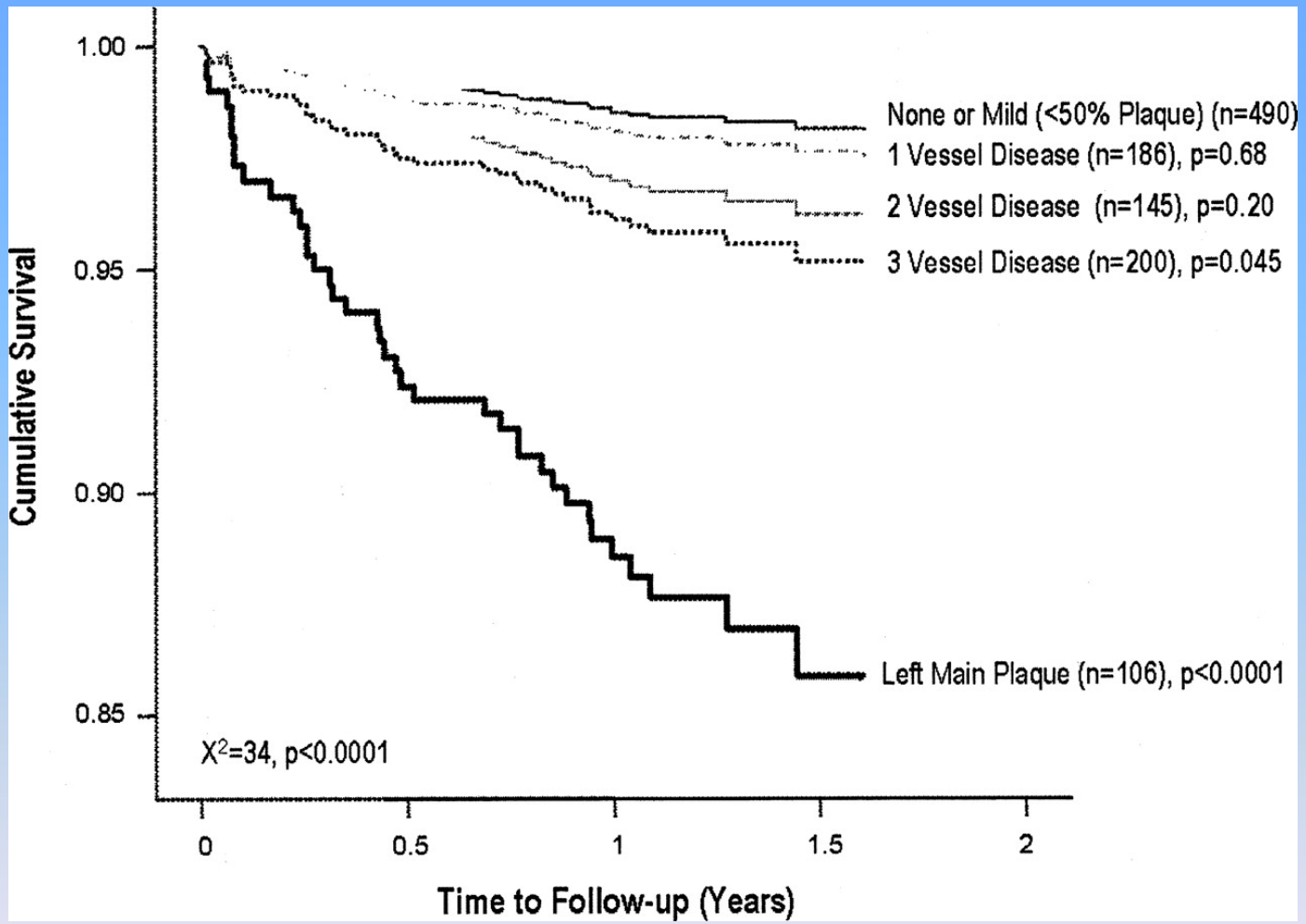
45 year old South Asian Male HTN --asymptomatic; new DM LDL 126 HDL 33 ; HbA1c 6.4

- Calcification in the vessel wall is an indicator of degree of damage that has occurred to the vessels.
- A high calcium score is consistent with a moderate to high risk of coronary artery disease.
- A negative calcium score is predictive of a comparatively very low incidence of coronary artery disease.
- The coronary arteries are seen similar to as seen on a regular catheter angiogram.

EBT 5 year All-Cause Mortality



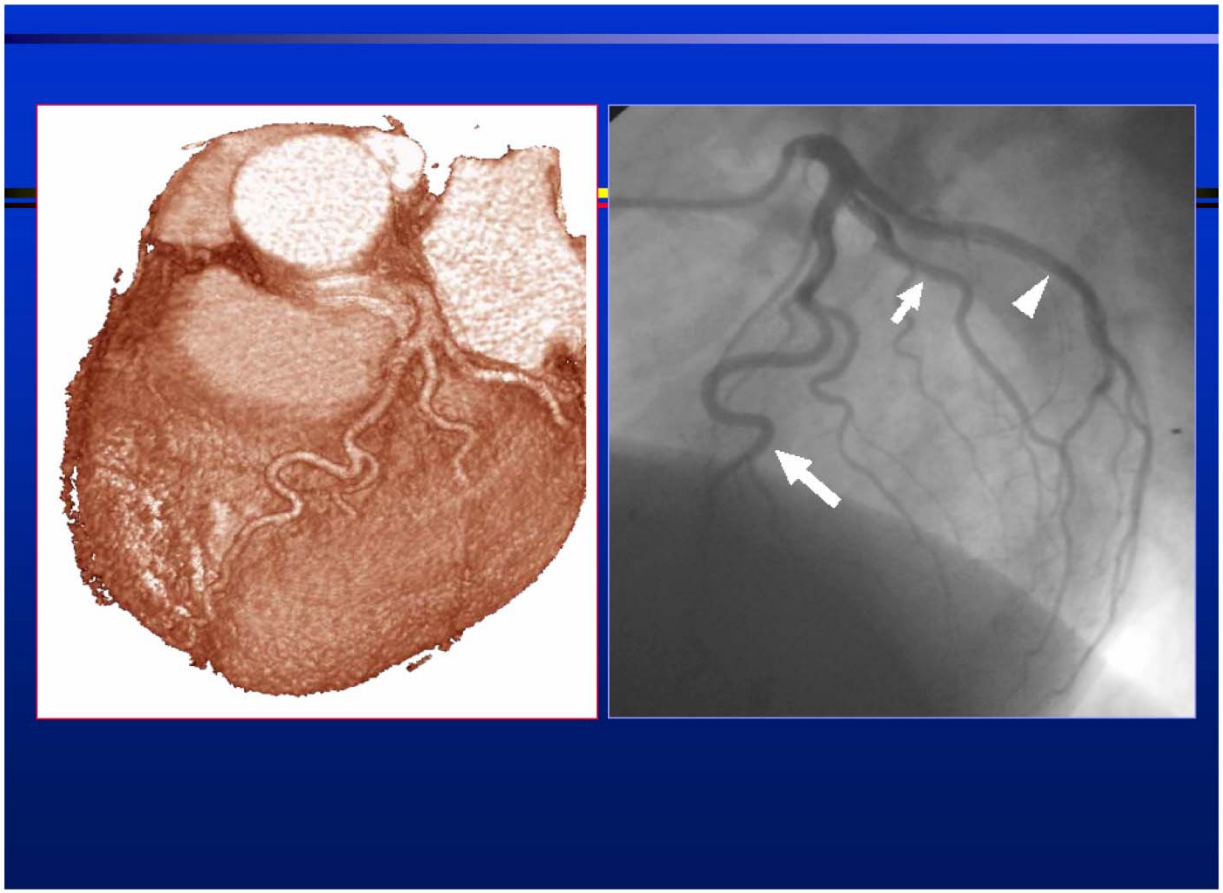
Cumulative Survival in Patients With Moderate (>50%) Plaque by CCTA



Min, J. K. et al. J Am Coll Cardiol 2007;50:1161-1170

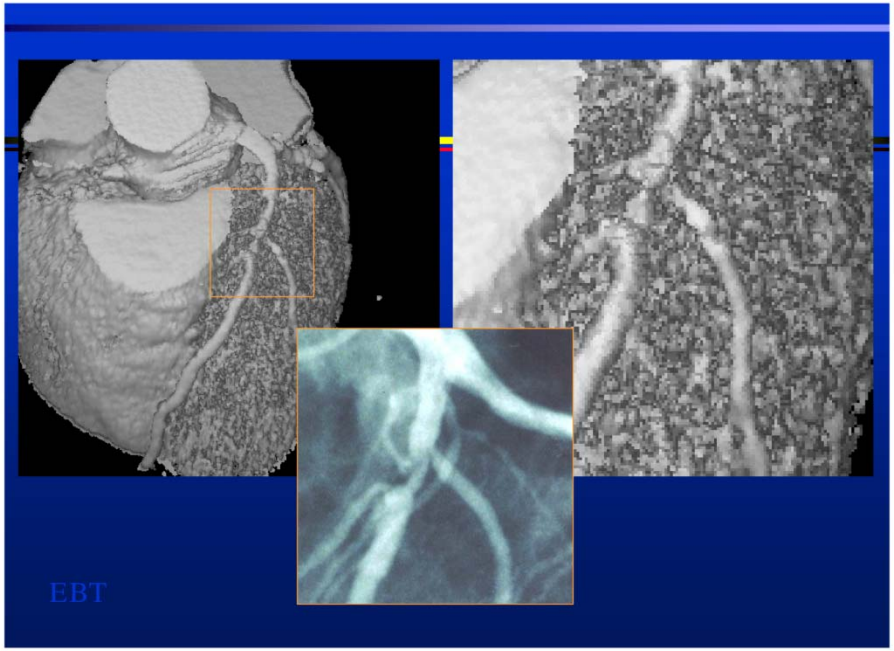
JACC Journal of the American College of Cardiology

No Atherosclerosis: Multiple Risk Factors

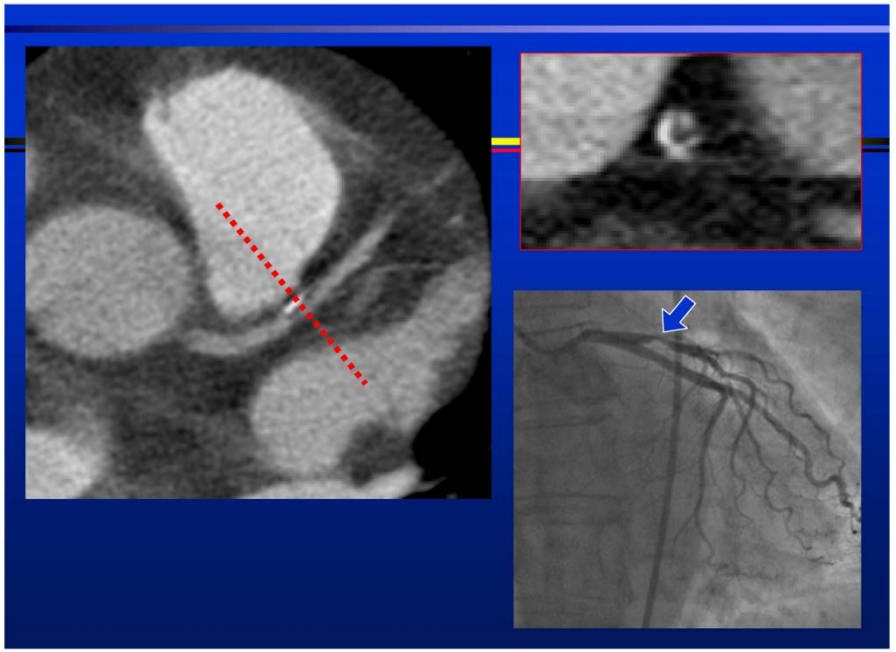


65 year old
HTN
DM
Ex Smoker
LDL 100
CRP elevated
Plays golf

Atherosclerosis : Asymptomatic patient



65 year old male
HTN
DM
Ex Smoker
LDL 100
CRP elevated
Plays golf
Work-up per request of wife



4 Statin Benefit Groups

- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease

†Requires risk discussion between clinician and patient before statin initiation

‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - CAC score ≥300 Agaston units
  - ABI <0.9
- Statin use still requires discussion between clinician and patient

Primary Prevention of a CV Event: What we need to do

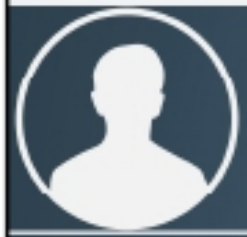
Global Risk Assessment needed :

Risk Calculator

Vulnerable Patient

Vulnerable Plaque

Estimated Risk in an individual :



CLINICAL QUESTION

In a patient with MI, what is the ongoing risk for recurrent thrombotic CV events

- Within 1 year?
- Beyond 1 year?

MI=myocardial infarction.

Prevalence and Incidence of MI in the United States

7.6 million
Americans have a history of MI*

An estimated
750,000
total MIs
occur each year

Over **1/4**
(200,000) of these
will be **recurrent MIs**

~1 recurrent MI
every 2.6 minutes

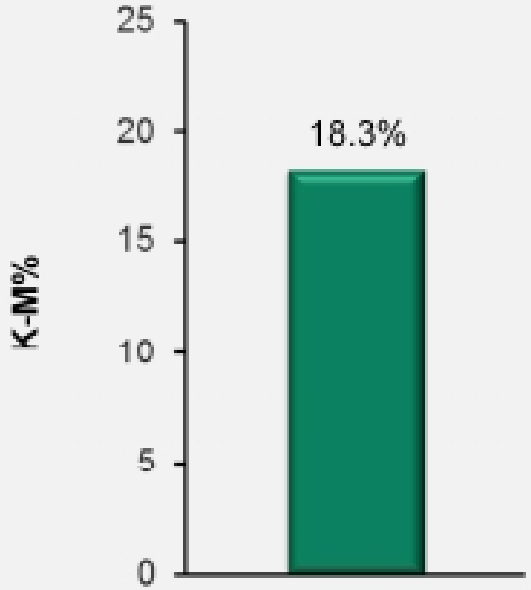
*Represents prevalence in 2012 in patients ≥20 years of age.

Mozaffarian D et al. *Circulation*. 2016. Accessed January 21, 2016.

Risk for Recurrent Thrombotic CV Events Remains High in Prior MI Patients

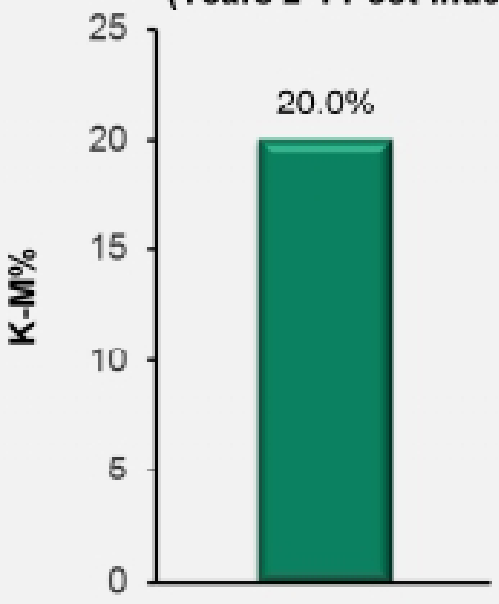
APOLLO HELICON Sweden Analysis

Cumulative 1-Year Incidence of CV Death, MI, or Stroke



Survivors of Index MI (n=97,254)

Cumulative 3-Year Incidence of CV Death, MI, or Stroke (Years 2-4 Post-Index Event)



Survivors Event-free at Year 1 (n=76,687)

Retrospective cohort study that included 108,315 patients from Swedish national registries with a primary diagnosis of acute MI between July 2006 and June 2011. The primary composite end point was risk for non-fatal MI, non-fatal stroke, or cardiovascular death

K-M=Kaplan-Meier.

Jernberg T et al. *Eur Heart J*. 2015;36(19):1163-1170.

Select Risk Factors for Recurrent Thrombotic CV Events in Patients With Prior MI

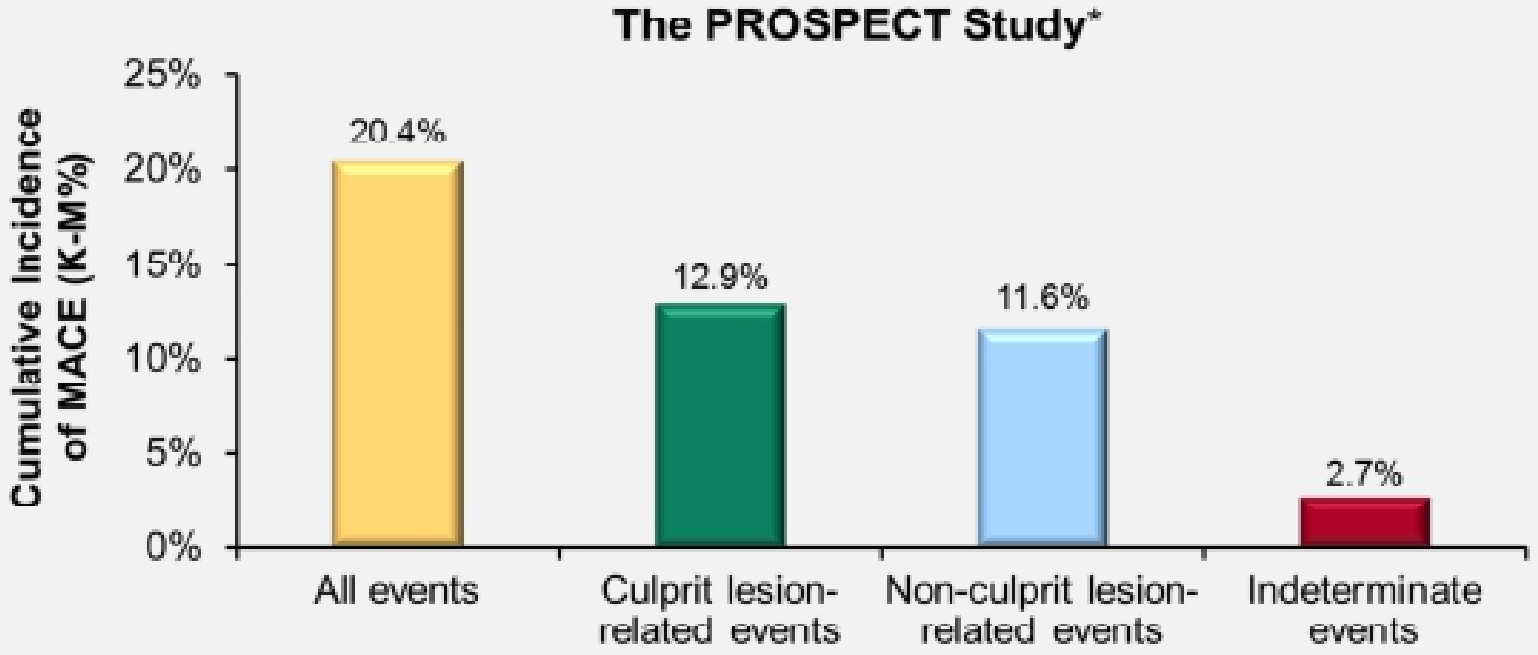
Severity of Disease[1]	CV History[1,2]	Comorbidities[1-3]	Patient Characteristics[2-5]
• Multivessel disease	• Previous MI • Previous CABG	• Dyslipidemia • Hypertension • Diabetes mellitus • Chronic kidney disease	• Obesity • Older age • Smoking

The cumulative incidence of recurrent MI increases as the number of risk factors increases[2]

CABG=coronary artery bypass graft.

1. Kikkert WJ et al. *Am J Cardiol.* 2014;113:229-235. **2.** Nakatani D et al. *Circ J.* 2013;77:439-446. **3.** Thune JJ et al. *Eur J Heart Fail.* 2011;13:148-153. **4.** Leander K et al. *Eur J Cardiovasc Prev Rehabil.* 2007;14:532-537. **5.** Rea TD et al. *Ann Intern Med.* 2002;137:494-500.

Recurrent Thrombotic CV Events Often Originate From a Non-Culprit Lesion in Patients With Prior MI



Prospective evaluation of 697 US and European patients with ACS (~96% MI) who underwent coronary artery imaging using greyscale and radiofrequency IVUS in addition to angiography after successful and uncomplicated PCI. The median follow-up was 3.4 years

*Some patients had both CL-related and NCL-related events, and some patients had multiple CL-related events, multiple NCL-related events, or both at different times (in which case the first event is represented in the time-to-event curve).
PROSPECT=Providing Regional Observations to Study Predictors of Events in the Coronary Tree; MACE=major adverse cardiovascular events (CV death, cardiac arrest, MI or rehospitalization due to unstable or progressive angina); ACS=acute coronary syndrome; IVUS=intravascular ultrasound; PCI=percutaneous coronary intervention;CL=culprit lesion; NCL=non-culprit lesion.

Stone GW et al. *N Engl J Med*. 2011;364(3):226-235.

65-Year-Old Male With Multiple CV Risk Factors and Chest Pain*

Presentation

- Chest pain is moderate-severe in intensity, no radiation, and is accompanied by nausea and diaphoresis

Medical History

- Hyperlipidemia
- Diabetes
- Hypertension

Medications

- Simvastatin 40 mg QHS
- Metformin 500 mg BID
- Lisinopril 10 mg QD
- HCTZ 12.5 mg QD
- ASA 81 mg QD

Family History

- Father died of MI in his 60s

Evaluation

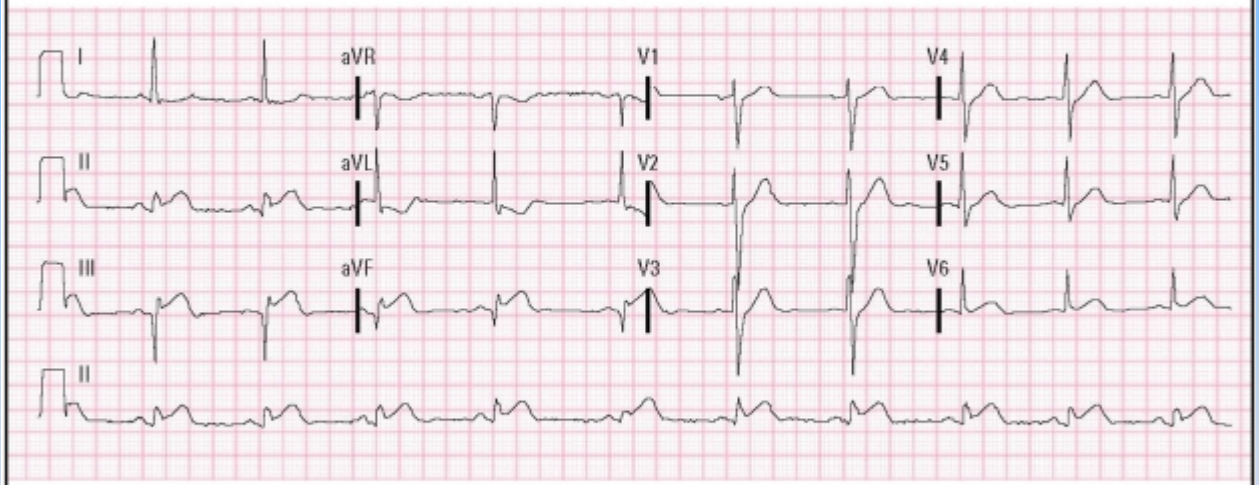
- HR 74 RR 18 BP 148/90
- Wt 113 kg, 5' 8", BMI 38
- Unremarkable physical exam
- EKG – 2 mm ST elevations in inferior leads

EKG

*Hypothetical patient.

QHS=at bedtime; BID=twice daily; QD=once daily; HCTZ=hydrochlorothiazide; ASA=acetylsalicylic acid (aspirin); HR=heart rate; RR=respiratory rate; BP=blood pressure; BMI=body mass index; EKG=electrocardiogram.

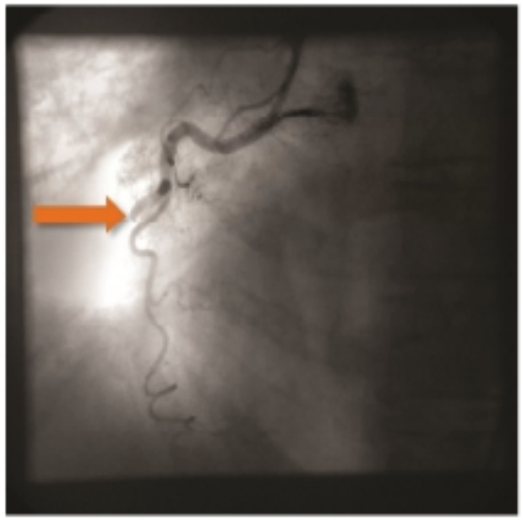
EKG at Initial ACS Event*



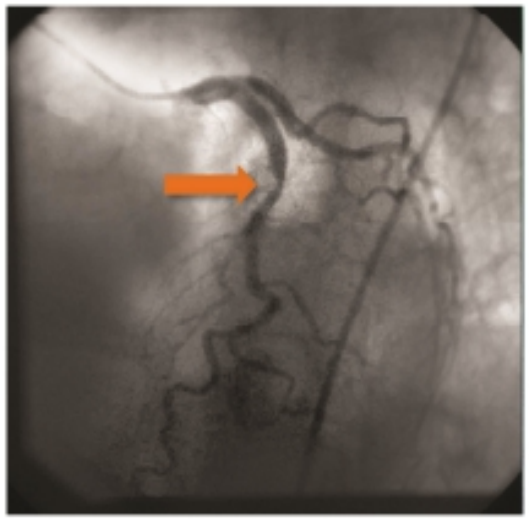
*Hypothetical patient.

Angiography at Initial ACS Event*

Hospital Course	• Angiography at initial ACS event showed multivessel disease – Occlusion of the RCA – Documented intermediate stenosis in LAD



Occlusion of the RCA



Documented intermediate stenosis in LAD

*Hypothetical patient.
RCA=right coronary artery; FFR=fractional flow reserve.

Background

- Patients with myocardial infarction (MI) have higher risk for recurrent ischemic events
- Activated platelets responsible for cardiovascular (CV) ischemic risk
- Use of dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor can help reduce the risk of ischemic events in the first year after acute coronary syndrome (ACS)

Bonaca MP., et al. NEJM. 2015;372(19):1791-1800.

Background: PLATO Trial

- Multi-center randomized double-blind trial
- Compared clopidogrel (loading dose 300-600 mg, maintenance dose 75 mg daily) to ticagrelor (loading dose 180 mg, maintenance dose 90 mg twice daily)
  - In addition to aspirin 75-325 mg
- Patient Population: All ACS patients, with or without ST-segment elevation with an onset of symptoms in the previous 24 hours
- Primary endpoint: composite of death from vascular causes, MI, or stroke

Wallent L, et al. NEJM. 2009; 361 (11):1045-1057.

Patients with ACS
PLATO:Trial Design[1]

UA/NSTEMI and **STEMI** (if intended for primary PCI)
clopidogrel treated or naive, planned for medical or invasive management, randomized within 24 hours of index event prior to or after assessment of coronary anatomy[2] (N=18,624)

BRILINTA (n=9.333)	**Clopidogrel** (n=9.291)
180-mg loading dose*; 90-mg BID maintenance dose	300-mg loading dose†; 75-mg QD maintenance dose
An additional 90-mg dose given pre-PCI if >24 hrs postrandomization	†If pretreated with clopidogrel, no loading dose given. An additional 300-mg dose allowed pre-PCI

6- to 12-month exposure

Primary efficacy endpoint:	CV death/MI‡/stroke
Key secondary efficacy endpoints:	MI‡ alone, CV death alone, stroke alone, total mortality
Primary safety endpoint:	Total Major bleeding

- **BRILINTA 90 mg and clopidogrel were both given in combination with aspirin and other standard therapy**[1]
- 46% of patients in both groups received clopidogrel in hospital prior to randomization[1]
- Patients could have been randomized at any point prior to PCI, including postangiography[1,2]
- Patients were excluded if they had a previous intracranial hemorrhage, gastrointestinal bleeding within 6 months, had a known bleeding diathesis or coagulation disorder, or required treatment with anticoagulants[3]

*Included patients pretreated with clopidogrel.

‡Excluding silent MI.[3]

CV death=vascular death and is defined as death from cardiovascular or cerebrovascular causes and any death without another known cause.

1. Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057. **2.** Data on file, 2379807, AstraZeneca, LP. **3.** BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

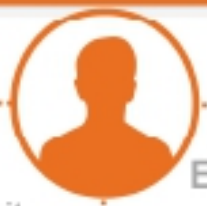
Background: PLATO Trial

Outcome	Ticagrelor vs. Clopidogrel, Hazard Ratio (95% CI)	P-Value
Primary outcome:	9.8 % vs 11.7, 0.84 (0.77-0.92)	<0.001
Secondary Endpoints:		
Death from any cause, MI, or stroke	10.2% vs. 12.3%, 085 (0.77-0.92)	<0.001
Death from vascular causes, MI, stroke, severe recurrent ischemia, TIA or other arterial thrombotic event	14.6% vs. 16.7%, 0.88 (0.81-0.95)	<0.001
MI	5.8% vs. 6.9%, 0.84 (0.75-0.95)	0.005
Death from any cause	4.5% vs. 5.9%, 0.78 (0.69-0.89)	<0.001
Stent thrombosis-definite	1.3% vs. 1.9%, 0.67 (0.50-0.91)	0.009
Adverse Events		
TIMI Major Non-CABG Bleeding	2.8% vs. 2.2%, 1.25 (1.03-1.43)	0.03
PLATO Major Non-CABG Bleeding	4.5% vs. 3.8%, 1.19 (1.02-1.38)	0.03
Dyspnea-Any	13.8% v.s 7.8%, 1.84 (1.68-2.02)	<0.001

Wallent L, et al. NEJM. 2009; 361 (11):1045-1057.

BRILINTA® (ticagrelor) tablets

Diagnosis and Management of Initial ACS Event*



Presentation

- Chest pain is moderate-severe in intensity, no radiation, and is accompanied by nausea and diaphoresis

Medical History

- Hyperlipidemia
- Diabetes
- Hypertension

Medications

- Simvastatin 40 mg QHS
- Metformin 500 mg BID
- Lisinopril 10 mg QD
- HCTZ 12.5 mg QD
- ASA 81 mg QD

Family History

- Father died of MI in his 60s

Evaluation

- HR 74 RR 18 BP 148/90
- Wt 113 kg, 5' 8", BMI 38
- Unremarkable physical exam
- EKG – 2 mm ST elevations in inferior leads

Diagnosis

- STEMI managed with DES placement in the RCA

Management

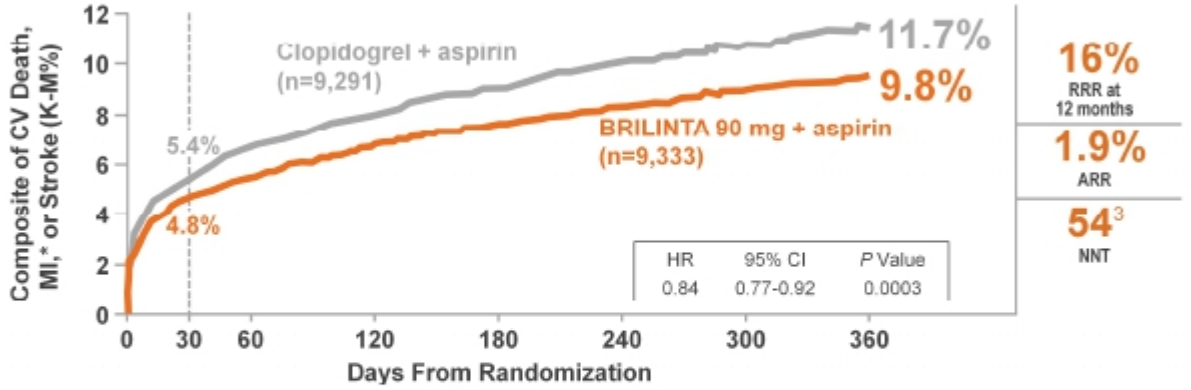
- BRILINTA 180-mg loading dose, followed by 90 mg BID
- ASA 325-mg loading dose, followed by 81 mg QD
- Switched statin to rosuvastatin 20 mg QHS
- Metoprolol tartrate 25 mg BID started
- HCTZ 12.5 mg QD discontinued
- Continued other current medications

*Hypothetical patient.
STEMI=ST-elevation myocardial infarction; DES=drug-eluting stent.

BRILINTA® (ticagrelor) tablets

Patients with ACS
PLATO: BRILINTA 90 mg Provided a Superior Reduction in Thrombotic CV Events vs Clopidogrel at 12 Months[1]

PLATO Primary Efficacy End Point: Composite of CV Death, MI,* or Stroke at 12 Months[1,2]



- **Difference between treatments was driven by CV death and MI* with no difference in stroke[1]**
- BRILINTA 90 mg and clopidogrel were studied with aspirin and other standard therapies[1]
- At 30 days, BRILINTA 90 mg plus aspirin reduced the primary composite end point of CV death, MI,* or stroke by 12% RRR (ARR: 0.6%) vs clopidogrel plus aspirin (4.8% vs 5.4%; HR 0.88, 95% CI: 0.77-1.0)[1,2]
- More than half of the absolute risk reduction with BRILINTA 90 mg plus aspirin was seen after the first 30 days[1,2]

*Excluding silent MI.

RRR=relative risk reduction; ARR=absolute risk reduction; NNT=number needed to treat=1/ARR; ARR=11.67%-9.8%=1.87%; NNT=1/0.0187=53.5; HR=hazard ratio; CI=confidence interval.

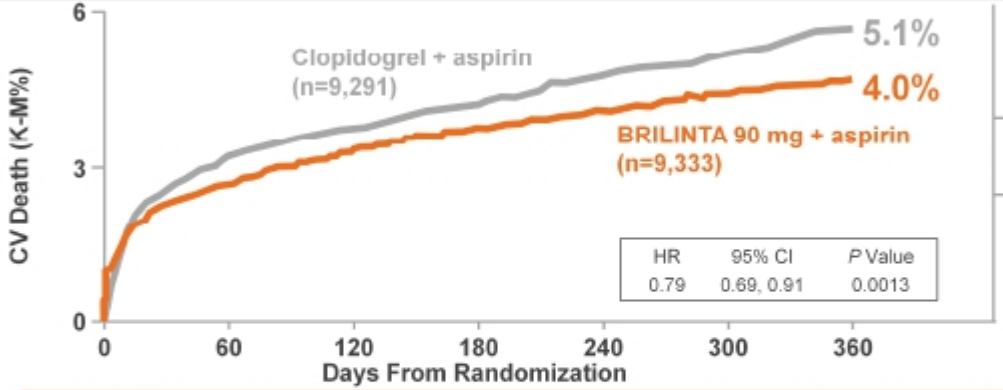
1. BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE. **2.** Wallentin L et al. *N Engl J Med*. 2009;361(11): 1045-1057. **3.** AstraZeneca briefing document. Accessed December 4, 2015.

BRILINTA® (ticagrelor) tablets

Patients with ACS

PLATO: BRILINTA 90 mg Is the First and Only FDA-Approved OAP to Demonstrate Superior Reductions in CV Death vs Clopidogrel[1]

PLATO Secondary Efficacy End Point: CV Death at 12 Months[2-4]



21% RRR at 12 months

1.1% ARR

91 NNT

BRILINTA 90 mg saved more lives than clopidogrel by reducing CV death[2,3]

Additional Secondary Efficacy End Points at 12 Months[2]

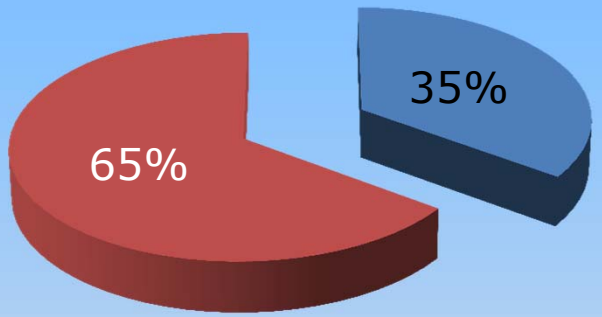
- BRILINTA 90 mg + aspirin reduced the rate of MI*‡ vs clopidogrel + aspirin at 12 months: 5.8% vs 6.9%,‡*P*=0.0045; HR 0.84 (95% CI 0.75, 0.95)
- BRILINTA 90 mg + aspirin was not significantly different from clopidogrel + aspirin in the rate of stroke† at 12 months: 1.5% vs 1.3%,‡*P*=0.22; HR 1.17 (95% CI 0.91, 1.52)

*Excluding silent MI. †Includes patients who could have had other nonfatal events or died. ‡Kaplan-Meier %.
FDA=Food and Drug Administration; NNT=1/ARR; ARR=5.1%-4.0%=1.1%; NNT=1/0.011=91.

1. Data on file, 1795500, AstraZeneca, LP. **2.** Wallentin L et al. *N Engl J Med*. 2009;361(11):1045-1057.
3. Wallentin et al. *N Engl J Med*. 2009;361(11):1045-1057. Supplementary Appendix. **4.** BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

CLOPIDOGREL RESPONSIVENESS: South Asian Study

PRU values after LD of Clopidogrel



PRU <200

PRU ≥200

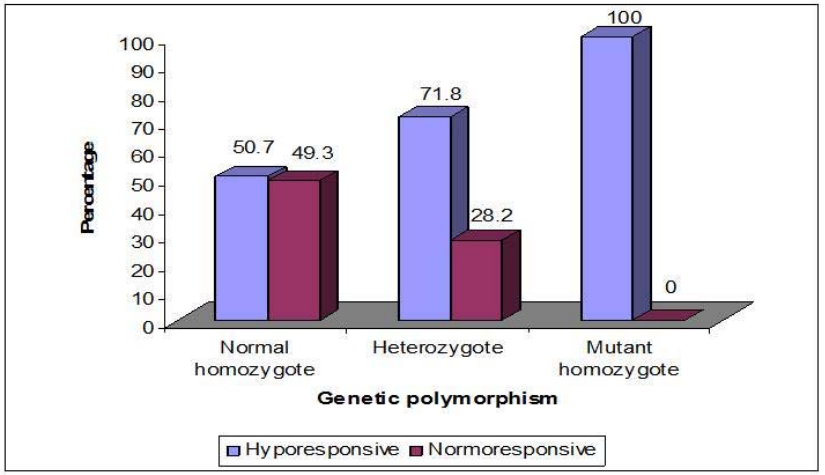


Fig. 1:Frequency Distribution of genetic polymorphism and hypo-responsiveness of clopidogrel in ACS patients

Clopidogrel hypo-responsiveness and the influence of genetic polymorphism in a South Asian population presenting with Acute Coronary Syndrome

Chowdhury H Ahsan [1], M Maksumul Haq[2]; Nurul Amin[2]; Sahela Nasrin[2];
M A Rashid[2]; C M Shaheen Kabir[2]; Muhammad Shahdaat Bin Sayeed[3]; Abul Hasnat[3].
[1] University Medical Center, University of Nevada School of Medicine, Las Vegas, Nevada and [2] Imdad Khan
Vascular Research Center, Ibrahim Cardiac Hospital & Research Institute, Dhaka [3] University of Dhaka, Bangladesh.

Background:

Clopidogrel is a prodrug and acts on P2Y12 platelet receptors after being converted to its active metabolite in the liver by cytochrome P450 enzyme system. There is growing concern regarding the hypo-responsiveness in platelet inhibition after clopidogrel administration. Clopidogrel hypo-responsiveness has been reported to be much higher in South Asians compared to Caucasians. Non-genetic factors like absorption from the gut, proton pump inhibition, drug-drug interaction may result in reduced expression of CYP2C19 enzyme activity. However, genetic polymorphism of the enzyme, CYP2C19 is considered to play a major determinant role in clopidogrel responsiveness: normal homozygote metabolizing clopidogrel normally whereas, heterozygote and mutant homozygote genotypes being slower and slowest metabolizers respectively. This study was designed to find the clopidogrel hypo-responsiveness and CYP2C19 polymorphism by genetic studies and investigate their relationship with its clinical implication in a Bangladeshi, South Asian population presenting with Acute Coronary Syndrome (ACS).

Methods:

120 patients of Bangladeshi origin presenting with ACS who underwent coronary angiography and intervention were studied for clopidogrel responsiveness following the administration of a loading dose (LD) of 600mg. Clopidogrel responsiveness or P2Y12 activity (Platelet Reactivity Unit or PRU value) was measured by VerifyNow system. PRU 208, measured after the LD was defined as clopidogrel hypo-responsiveness. Genotyping of the 120 patients were done by Polymerase Chain Reaction restriction length polymorphism and cross-tabbed with P2Y12 results.

Results:

75 patients out of 120 (62.5%) were found to be hyporesponsive to clopidogrel. Nearly half (46.7%) of them were normal homozygote, 37.3% were heterozygote and 16% were mutant homozygote types.
The frequency of clopidogrel hyporespnsiveness was higher (71.8%) in heterozygote type and all (100%) in mutant homozygote type were hypo-responders to clopidogrel (fig.1). The risk of clopidogrel hyporesponsiveness among heterozygote and mutant homozygote genotpyes was 3.5 fold higher than that with normal homozygote genetic constitution.

Table -1

Genetic polymorphism*	Response to clopidogrel: Hyporesponsive (PRU ≥ 208) (n = 75)	Normoresponsive (PRU < 208) (n = 85)	p-value	Odds Ratio (95% CI)
Heterozygote & mutant homozygote	40(53.3)	11(34.4)	0.002	3.5(1.5-7.9)
Normal homozygote	35(46.7)	34(75.6)		

Table I. Association between genetic polymorphism and clopidogrel hyporesponsiveness
Figures in the parentheses denote corresponding percentage
Data were analyzed using Chi-square (χ^2)

Figure-1

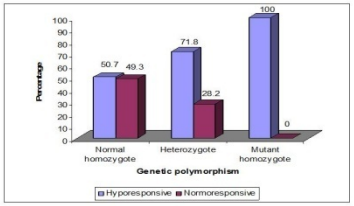


Fig. 1:Frequency Distribution of genetic polymorphism and hypo-responsiveness of clopidogrel in ACS patients

Conclusion:

A substantial proportion of patients with South Asian background presenting with ACS had clopidogrel hypo-responsiveness. One in every three patients was CYP2C19 heterozygote and one in every six was of mutant homozygote. This study showed that non-genetic factors contribute to the hypo-responsiveness to clopidogrel in a significant proportion even in the normal homozygote patients of South Asian origin.

However, individuals with genetic polymorphism with heterozygote or mutant homozygote genotypes had significantly higher chance of being clopidogrel hypo-responders. The findings may have important clinical implications in the management of ACS patients of South Asian origin

Incidence of Clopidogrel Resistance in South Asians and the Impact of Balloon Inflation on Platelet Inhibition in Blood Samples obtained from Guide Catheters: Comparison of Clopidogrel with Prasugrel in a South Asian Population presenting with Acute Coronary Syndrome

Chowdhury H. Ahsan[1], M A Rashid[2], Saidur R. Khan[2], Rezaul M. Karim[2], M. Maksumul Haq[2]
1. University Medical Centre, Las Vegas, United States, 2. Cardiology Department, Ibrahim Cardiac Hospital and Research Institute, Dhaka, Bangladesh
Correspondence: Chowdhury H. Ahsan, M.D., Ph.D.
Clinical Professor of Medicine - University Medical Center of Southern Nevada
E-mail address: chahsan92@yahoo.com

- **Prevalence of CYP2C19 alleles, pharmacokinetic and pharmacodynamic variation of clopidogrel and prasugrel in Bangladeshi population**
- **Muhammad Shahdaat Bin Sayeed[1,†],**
- **Mohd Nazmul Hasan Apu[1,†],**
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- **Maizbha Uddin Ahmed[1],**
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- **M A Rashid[3],**
- **Jae Gook Shin[5] and**
- **Abul Hasnat[1,*]**

- **Article first published online: 23 APR 2015**

CLINICAL QUESTION

Moving forward, how would you manage OAP therapy in this patient* with a history of MI 1 year prior and multiple CV risk factors?

*Hypothetical patient.

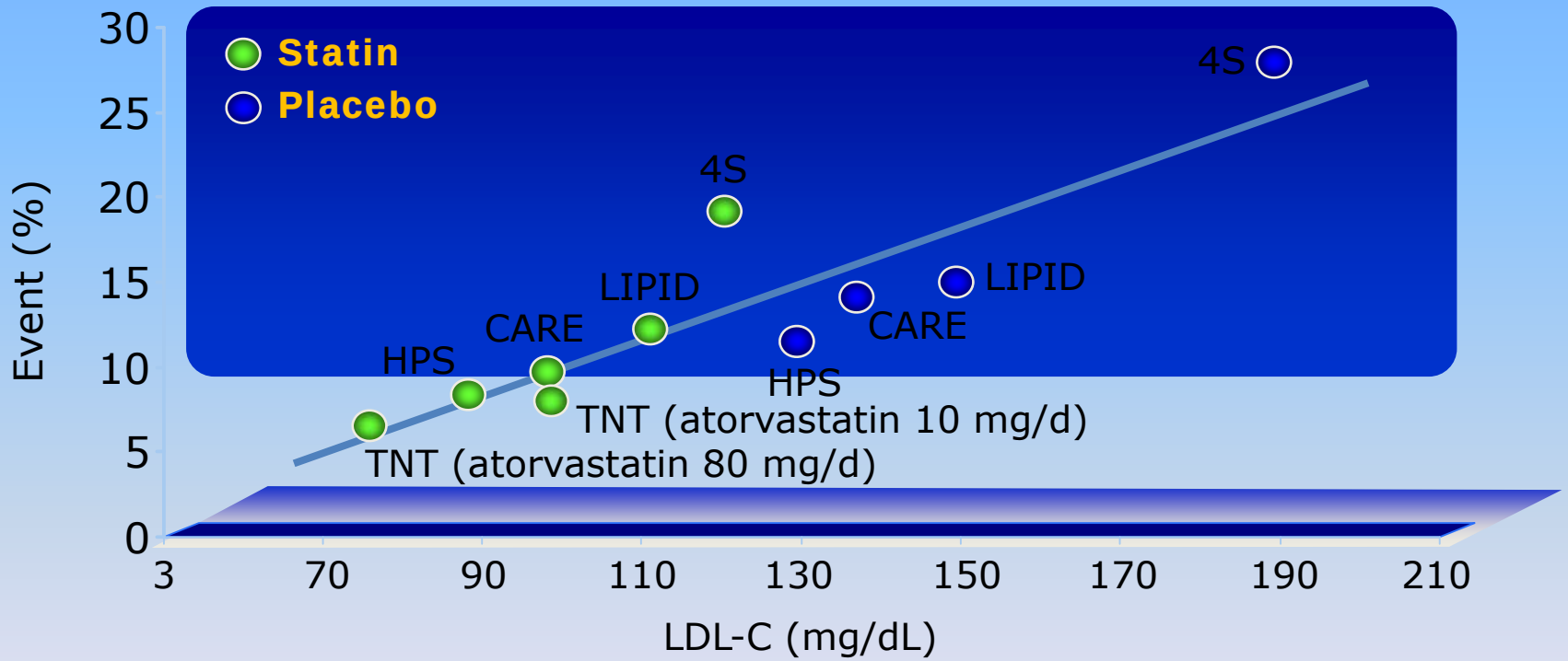
Components of Secondary Prevention

- Cigarette smoking cessation
- Blood pressure control
- Lipid management to goal
- Physical activity
- Weight management to goal
- Diabetes management to goal
- Antiplatelet agents / anticoagulants
- Renin angiotensin aldosterone system blockers
- Beta blockers
- Influenza vaccination

Smith SC Jr et al. *Circulation* 2006;113:2363–2372.

HMG-CoA Reductase Inhibitor: Secondary Prevention

Relationship between LDL-C Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD

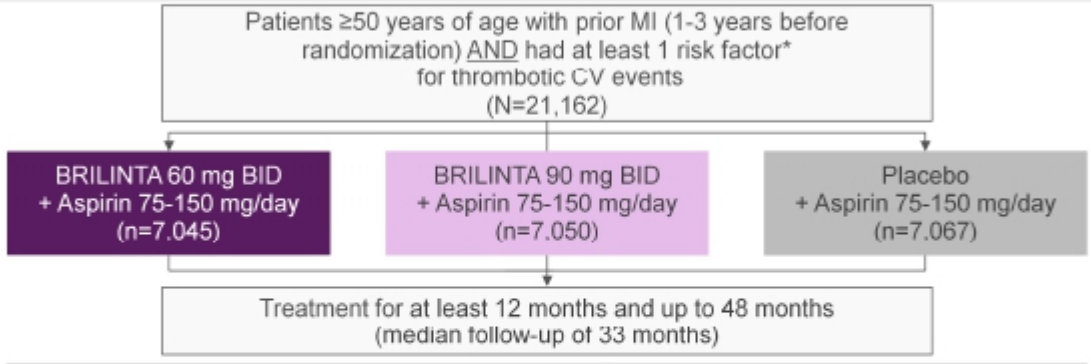


LDL-C=low-density lipoprotein cholesterol; CHD=coronary heart disease; TNT=Treating to New Targets; HPS=Heart Protection Study; CARE=Cholesterol and Recurrent Events Trial; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; 4S=Scandinavian Simvastatin Survival Study.

LaRosa et al. *N Engl J Med* 2005;352:1425–1435.

BRILINTA® (ticagrelor) tablets

Patients with a History of MI
PEGASUS-TIMI 54: Trial Design[1-3]



- **Only the 60-mg dosage strength is approved for use in patients with a history of MI 1 year after an ACS event**[3]
- **In PEGASUS, patients could be randomized regardless of their prior ADP receptor blocker therapy or a lapse in therapy**[3]

*Age ≥65 years, DM requiring medication, ≥1 other prior MI, multivessel CAD, or CrCl <60 mL/min.
ADP=adenosine diphosphate; DM=diabetes mellitus; CAD=coronary artery disease; CrCl=creatinine clearance.

1. Adapted from Bonaca MP et al. *Am Heart J*. 2014;167:437-444. **2.** Bonaca MP et al. *N Engl J Med*. 2015;372(19):1791-1800.
3. BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

Study-Design

Inclusion Criteria	Exclusion Criteria

• Spontaneous MI 1-3 years before enrollment
• Age ≥ 50 years
• One of the following additional high-risk features:
  • Age of 65 years or older
  • Diabetes mellitus requiring medications
  • A second prior spontaneous MI
  • Multivessel CAD
  • Chronic renal dysfunction (CrCl<60 ml/min)
	• Planned use of a $P2Y_{12}$ receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period
	• Bleeding disorder history
	• History of ischemic stroke
	• History of intracranial bleed
	• Central nervous system tumor
	• Intravascular abnormality
	• Gastrointestinal (GI) bleed within the previous 6 months
	• Major surgery within the previous 30 days
	• Renal failure requiring dialysis
	• Concomitant use of potent inducer/inhibitor/substrate of CYP3A4

Bonaca MP., et al. NEJM. 2015;372(19):1791-1800.

Statistical Analysis

- Power:
  - 90-mg dose vs. placebo for the primary endpoint: 1360 events for 90% power to detect a 20% reduction
  - 60-mg dose vs. placebo for the primary endpoint:1360 events to provide 83% power to detect a 19% reduction
- Event probabilities:
  - Kaplan-Meier estimates of cumulative incidence at 36 months
- Hazard ratios:
  - Generated using Cox proportional hazard model

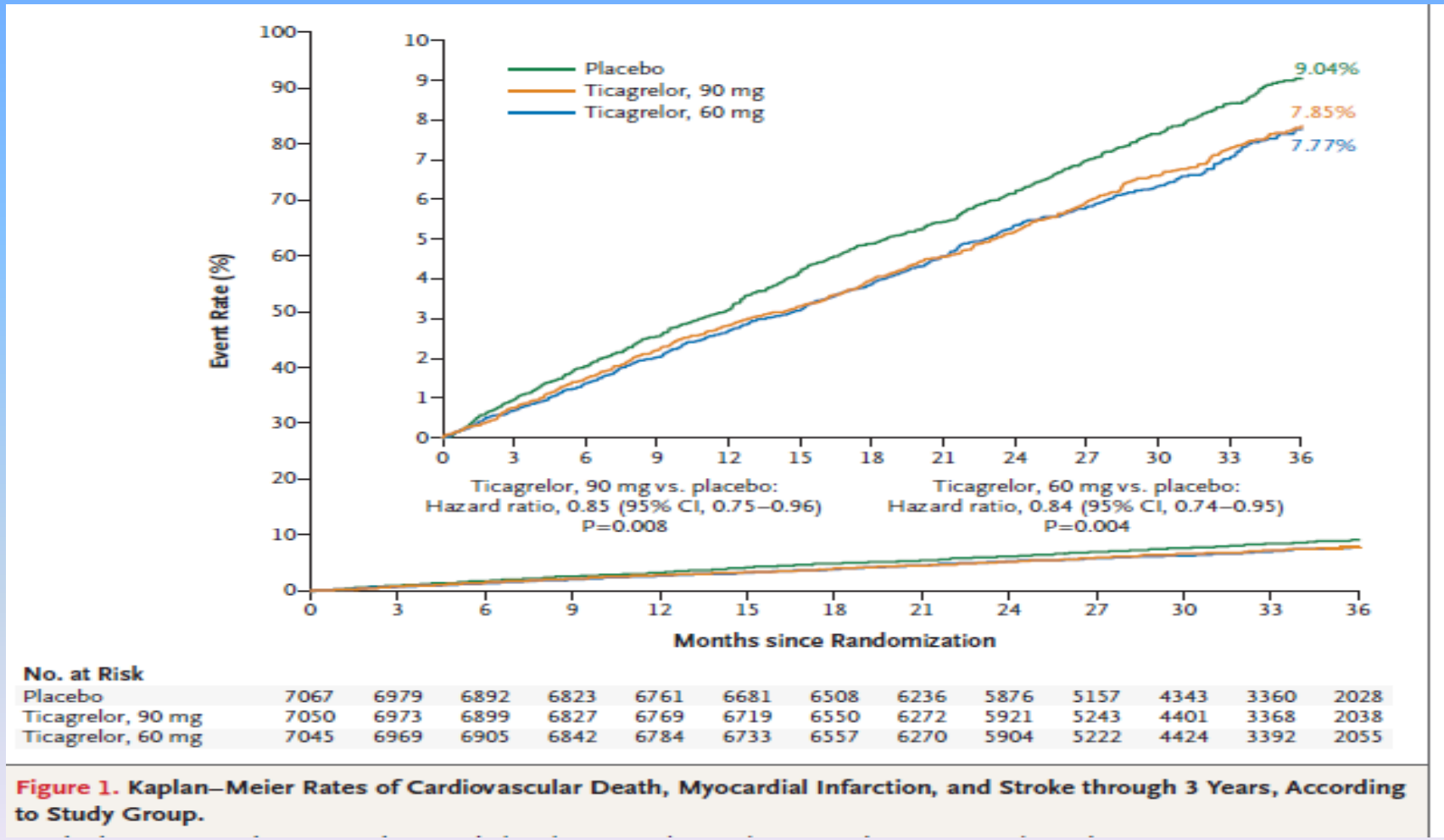
Bonaca MP., et al. NEJM. 2015;372(19):1791-1800.

Study-Design

Primary Endpoint	• Composite of CV death, MI, or stroke
Secondary Endpoint	• CV death and death from any cause • Composite endpoint of death from coronary heart disease, MI, or stroke • Individual components of the composite endpoints • Urgent coronary revascularization • Hospitalization for unstable angina • Transient ischemic attack (TIA)
Safety Endpoint	• Major Bleeding based on the thrombolysis of myocardial infarction (TIMI) definition • Intracranial hemorrhage • Fatal bleeding

Bonaca MP., et al. NEJM. 2015;372(19):1791-1800.

Results



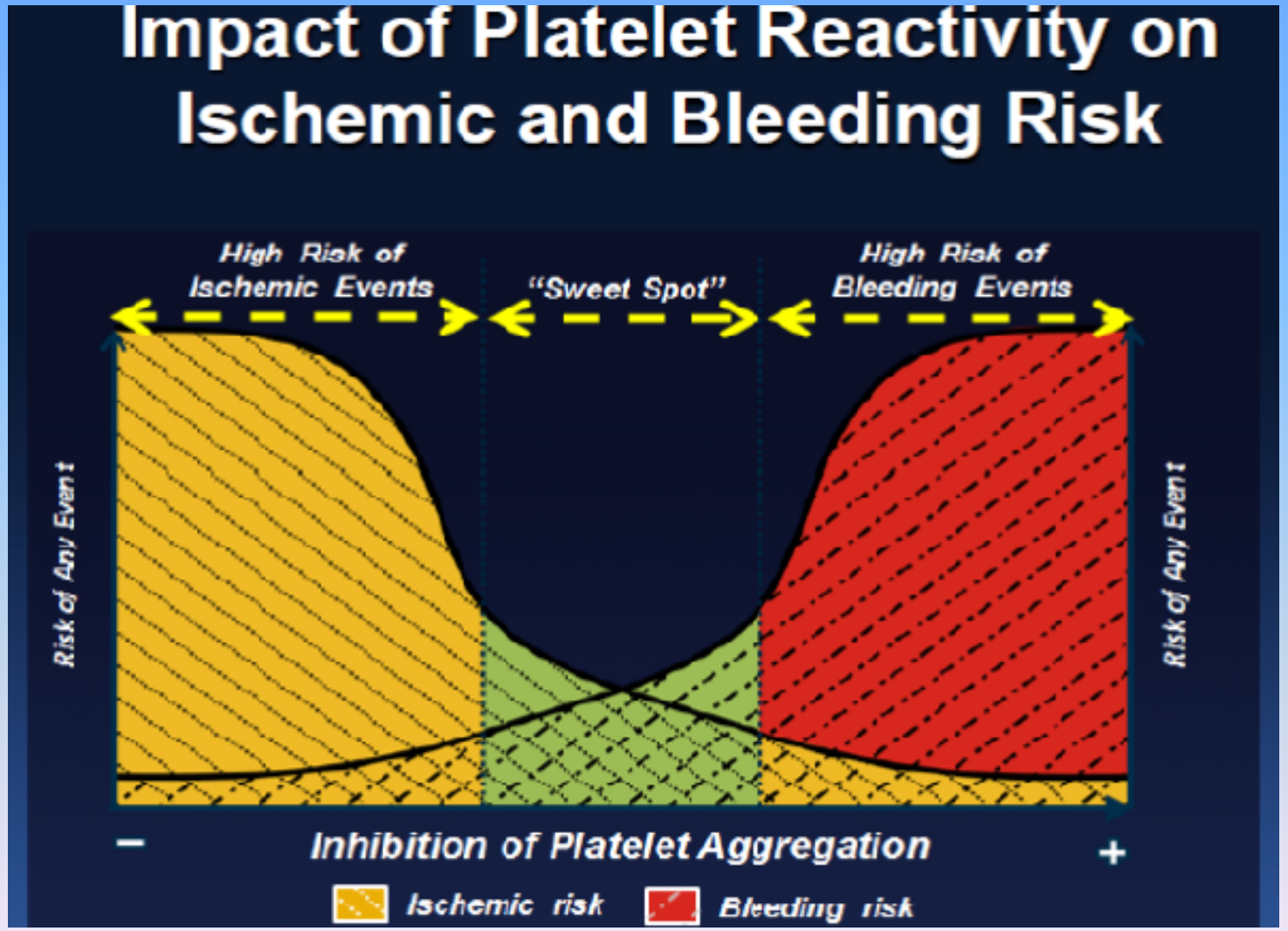
No. at Risk

Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Figure 1. Kaplan–Meier Rates of Cardiovascular Death, Myocardial Infarction, and Stroke through 3 Years, According to Study Group.

Bonaca MP., et al. NEJM. 2015;372(19):1791-1800.

Discussion



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- Diabetes management to goal
- Antiplatelet agents / anticoagulants
- Renin angiotensin aldosterone system blockers
- Beta blockers
- Influenza vaccination

Smith SC Jr et al. *Circulation* 2006;113:2363–2372.

SECONDARY PREVENTION

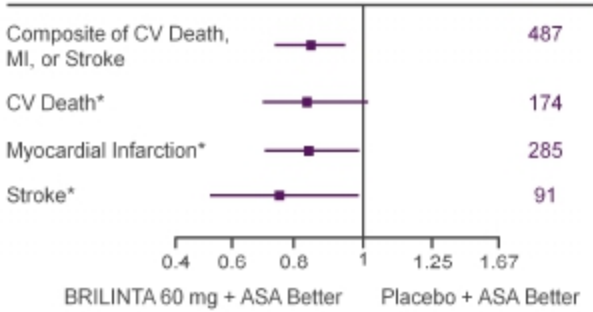
- ADDRESS UNDERLYING RISK AGGREGATE
- MORE AGGRESSIVE RISK REDUCTION:
- EACH RISK FACTOR AND
  - Globally

- ASSESS MI CONSEQUENCES-
  - LV EF CHF arrhythmias Mechanical complications
- INTENSIFY MEDICAL MANAGEMENT
- RE -ASSESSMENT :

- THANK YOU !

BRILINTA® (ticagrelor) tablets

Patients with a History of MI
PEGASUS-TIMI 54: Primary Efficacy End Point and Individual Components[1,2]



End Point	BRILINTA 60 mg + aspirin N=7,045 n (patients with event)	BRILINTA 60 mg + aspirin N=7,045 K-M % at 3 Years	Placebo + aspirin N=7,067 n (patients with event)	Placebo + aspirin N=7,067 K-M % at 3 Years	HR (95% CI)
Composite of CV Death, MI, or Stroke	487	7.8	578	9.0	0.84 (0.74, 0.95)
CV Death*	174	2.9	210	3.4	0.83 (0.68, 1.01)
Myocardial Infarction*	285	4.5	338	5.2	0.84 (0.72, 0.98)
Stroke*	91	1.5	122	1.9	0.75 (0.57, 0.98)

- **The secondary end point of CV death was not statistically significant. The end points of MI and stroke were prespecified exploratory analyses[1]**

*The number of first events for the components of CV death, MI, or stroke are the actual number of first events for each component and do not add up to the number of events in the composite end point.

1. Bonaca MP et al. *N Engl J Med*. 2015;372(19):1791-1800. **2.** BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

Additional Information

BRILINTA® (ticagrelor) tablets

Patients with a History of MI
PEGASUS-TIMI 54: Bleeding Events

	BRILINTA 60 mg + aspirin (n=6,958)		Placebo + aspirin (n=6,996)	
	n (%) Patients With Event	Events/100 Patient Years	n (%) Patients With Event	Events/100 Patient Years
TIMI Major	115 (1.7)	0.78	54 (0.8)	0.34
Fatal	11 (0.2)	0.08	12 (0.2)	0.08
ICH	28 (0.4)	0.19	23 (0.3)	0.14
TIMI Major or Minor	168 (2.4)	1.15	72 (1.0)	0.45

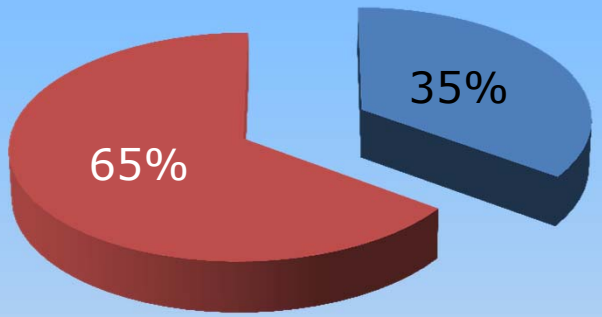
- **The bleeding profile of BRILINTA 60 mg + aspirin compared to placebo + aspirin was consistent across multiple pre-defined subgroups (e.g., by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, stent, and medical history) for TIMI Major and TIMI Major or Minor bleeding events**
- Discontinuation of BRILINTA will increase the risk of MI, stroke, and death. When possible, interrupt therapy with BRILINTA for 5 days prior to surgery that has a major risk of bleeding. If BRILINTA must be temporarily discontinued, restart as soon as possible

Bleeding category definitions: TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hb) of ≥5 g/dL, or a fall in hematocrit (Hct) of 15%. **Fatal:** A bleeding event that directly led to death within 7 days. **TIMI Minor:** Clinically apparent with 3-5 g/dL decrease in Hb.
ICH=intracranial hemorrhage.

BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

CLOPIDOGREL RESPONSIVENESS: South Asian Study

PRU values after LD of Clopidogrel



PRU <200

PRU ≥200

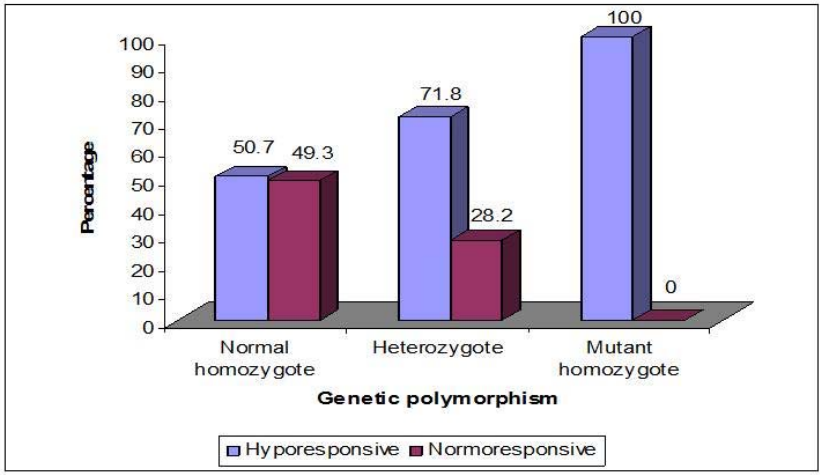


Fig. 1:Frequency Distribution of genetic polymorphism and hypo-responsiveness of clopidogrel in ACS patients

Clopidogrel hypo-responsiveness and the influence of genetic polymorphism in a South Asian population presenting with Acute Coronary Syndrome

Chowdhury H Ahsan [1], M Maksumul Haq[2]; Nurul Amin[2]; Sahela Nasrin[2];
M A Rashid[2]; C M Shaheen Kabir[2]; Muhammad Shahdaat Bin Sayeed[3]; Abul Hasnat[3].
[1] University Medical Center, University of Nevada School of Medicine, Las Vegas, Nevada and [2] Imdad Khan
Vascular Research Center, Ibrahim Cardiac Hospital & Research Institute, Dhaka [3] University of Dhaka, Bangladesh.

Background:

Clopidogrel is a prodrug and acts on P2Y12 platelet receptors after being converted to its active metabolite in the liver by cytochrome P450 enzyme system. There is growing concern regarding the hypo-responsiveness in platelet inhibition after clopidogrel administration. Clopidogrel hypo-responsiveness has been reported to be much higher in South Asians compared to Caucasians. Non-genetic factors like absorption from the gut, proton pump inhibition, drug-drug interaction may result in reduced expression of CYP2C19 enzyme activity. However, genetic polymorphism of the enzyme, CYP2C19 is considered to play a major determinant role in clopidogrel responsiveness: normal homozygote metabolizing clopidogrel normally whereas, heterozygote and mutant homozygote genotypes being slower and slowest metabolizers respectively. This study was designed to find the clopidogrel hypo-responsiveness and CYP2C19 polymorphism by genetic studies and investigate their relationship with its clinical implication in a Bangladeshi, South Asian population presenting with Acute Coronary Syndrome (ACS).

Methods:

120 patients of Bangladeshi origin presenting with ACS who underwent coronary angiography and intervention were studied for clopidogrel responsiveness following the administration of a loading dose (LD) of 600mg. Clopidogrel responsiveness or P2Y12 activity (Platelet Reactivity Unit or PRU value) was measured by VerifyNow system. PRU 208, measured after the LD was defined as clopidogrel hypo-responsiveness. Genotyping of the 120 patients were done by Polymerase Chain Reaction restriction length polymorphism and cross-tabbed with P2Y12 results.

Results:

75 patients out of 120 (62.5%) were found to be hyporesponsive to clopidogrel. Nearly half (46.7%) of them were normal homozygote, 37.3% were heterozygote and 16% were mutant homozygote types.
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Figures in the parentheses denote corresponding percentage
Data were analyzed using Chi-square (χ^2)

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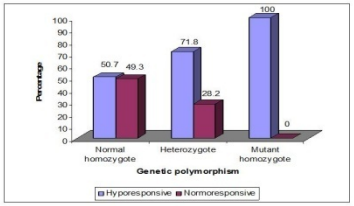

Fig. 1:Frequency Distribution of genetic polymorphism and hypo-responsiveness of clopidogrel in ACS patients

Conclusion:

A substantial proportion of patients with South Asian background presenting with ACS had clopidogrel hypo-responsiveness. One in every three patients was CYP2C19 heterozygote and one in every six was of mutant homozygote. This study showed that non-genetic factors contribute to the hypo-responsiveness to clopidogrel in a significant proportion even in the normal homozygote patients of South Asian origin.

However, individuals with genetic polymorphism with heterozygote or mutant homozygote genotypes had significantly higher chance of being clopidogrel hypo-responders. The findings may have important clinical implications in the management of ACS patients of South Asian origin

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Correspondence: Chowdhury H. Ahsan, M.D., Ph.D.
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- **Article first published online: 23 APR 2015**

SVT AND AF:

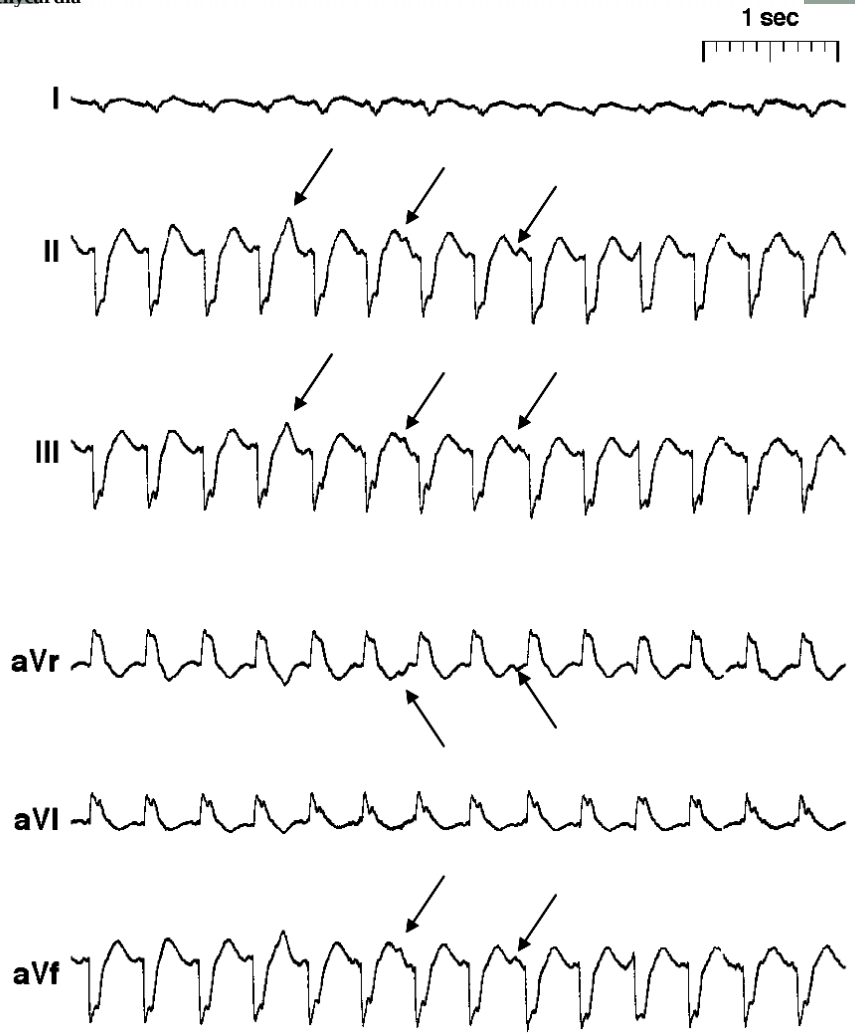
REVIEW OF CURRENT GUIDELINE ON EP INTERVENTIONS

Muhammad R. Marwali
Valley Cardiology
Fayetteville, NC

Supraventricular Tachycardia

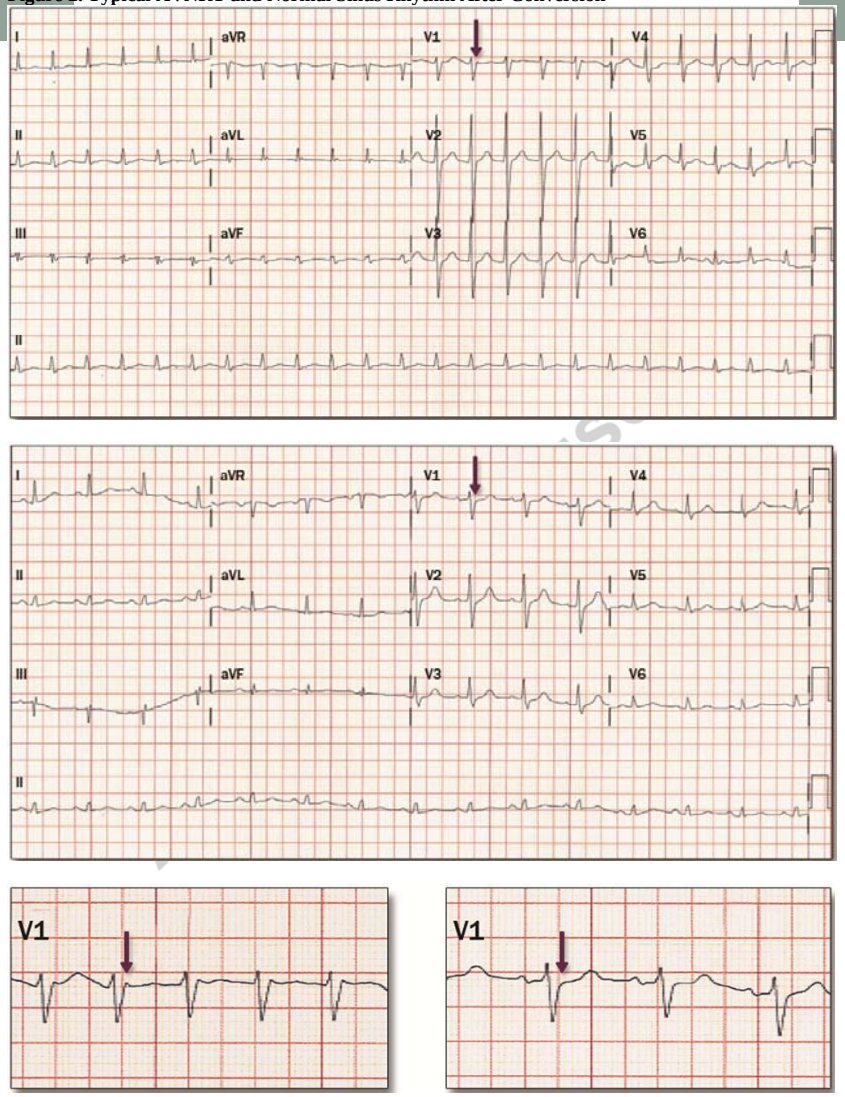
- Prevalence: 2.25 per 1,000 persons
- Incidence: 36 per 100,000 persons per year
- There are approximately 89,000 new cases per year and 570,000 persons with PSVT
- Women have twice the risk of men of developing PSVT
- Middle-aged or older, AVNRT is more common
- Adolescents, the prevalence may be more balanced between AVRT and AVNRT, or AVRT may be more prevalent

Figure 1. ECG Showing AV Dissociation During VT in a Patient With a Wide–QRS Complex Tachycardia



*P waves are marked with arrows.
AV indicates atrioventricular; ECG, electrocardiogram; and VT, ventricular tachycardia.
Reproduced with permission from Blomström-Lundqvist et al. (11).

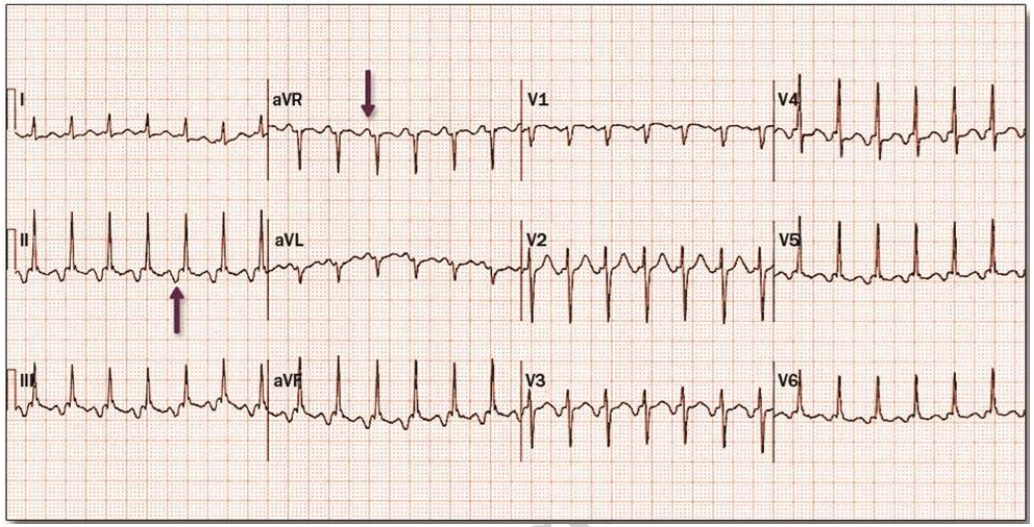
Figure 2. Typical AVNRT and Normal Sinus Rhythm After Conversion



Upper panel: The arrow points to the P waves, which are inscribed at the end of the QRS complex, seen best in the inferior leads and as a slightly positive R′ (pseudo r prime) in lead V1. The reentrant circuit involves anterograde conduction over a

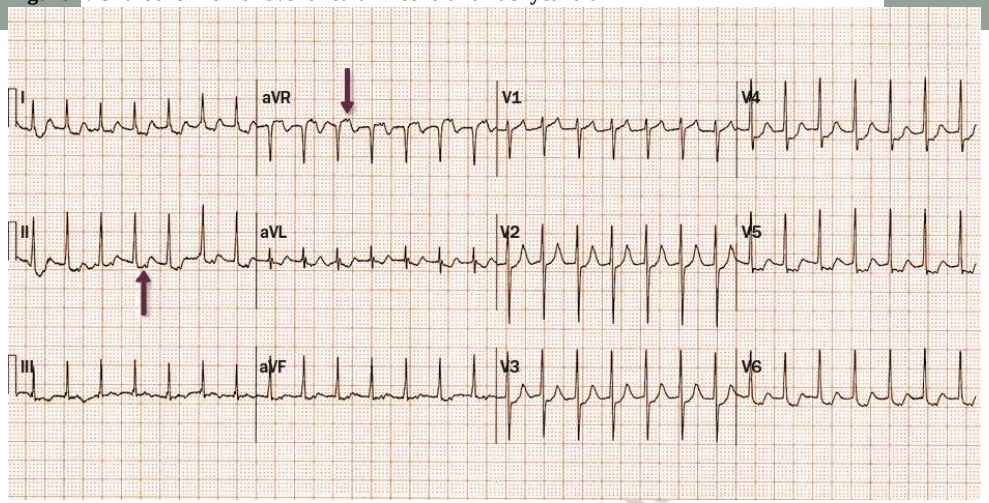
slow atrioventricular node pathway, followed by retrograde conduction in a fast atrioventricular node pathway. Typical AVNRT is a type of short RP tachycardia.
Middle panel: When the patient is in sinus rhythm, the arrow indicates where the R′ is absent in V1.
Bottom panels: Magnified portions of lead V1 in AVNRT (left) and sinus rhythm (right) are shown.
AVNRT indicates atrioventricular nodal reentrant tachycardia.

Figure 3. Atypical AVNRT



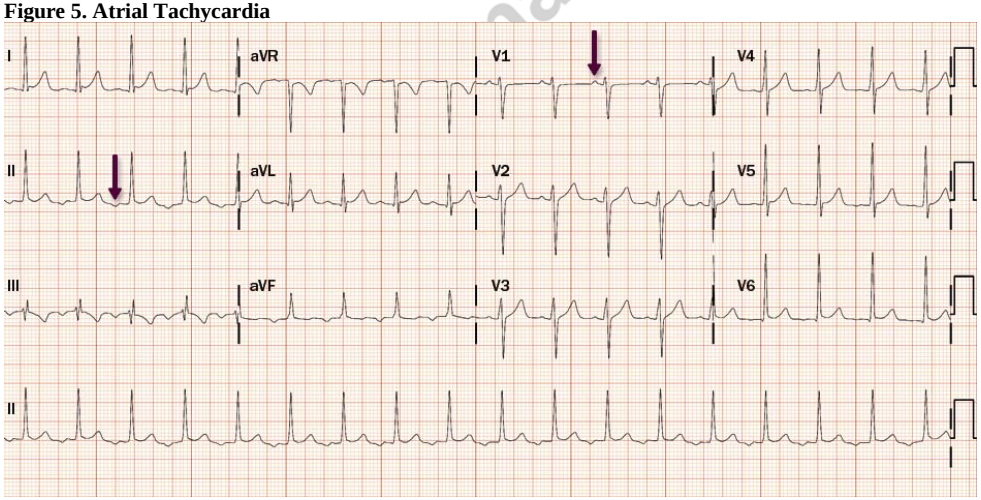
Arrows point to the P wave. The reentrant circuit involves anterograde conduction over a fast atrioventricular node pathway, followed by retrograde conduction in a slow atrioventricular node pathway, resulting in a retrograde P wave (negative polarity in inferior leads) with long RP interval. This ECG does not exclude PJRT or a low septal atrial tachycardia, which can appear very similar to this ECG.
AVNRT indicates atrioventricular nodal reentrant tachycardia; ECG, electrocardiogram; and PJRT, permanent form of junctional reciprocating tachycardia.

Figure 4. Orthodromic Atrioventricular Reentrant Tachycardia



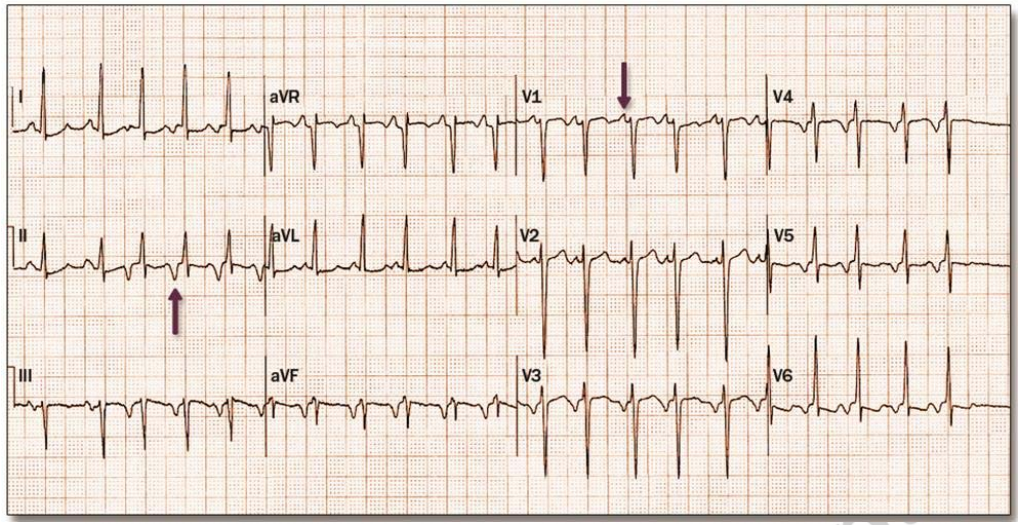
Arrows point to the P waves, which are inscribed in the ST segment after the QRS complex. The reentrant circuit involves anterograde conduction over the atrioventricular node, followed by retrograde conduction over an accessory pathway, which results in a retrograde P wave with short RP interval.

Figure 5. Atrial Tachycardia



Arrows point to the P wave, which is inscribed before the QRS complex. The focus of this atrial tachycardia was mapped during electrophysiological study to an area near the left inferior pulmonary vein.

Figure 6. Permanent Form of Junctional Reciprocating Tachycardia (PJRT)



Tachycardia starts after 2 beats of sinus rhythm. Arrows point to the P wave, which is inscribed before the QRS complex. The reentrant circuit involves anterograde conduction over the atrioventricular node, followed by retrograde conduction over a slowly conducting (or decremental) accessory pathway, usually located in the posteroseptal region, to provide a retrograde P wave with long RP interval. This ECG does not exclude atypical AVNRT or a low septal atrial tachycardia, which can appear very similar to this ECG.

AVNRT indicates atrioventricular nodal reentrant tachycardia; ECG, electrocardiogram; and PJRT, permanent form of junctional reciprocating tachycardia.

Differential Diagnosis of Wide QRS complex tachycardia

- VT
- SVT with pre-existing BBB or IVCD
- SVT with aberrant conduction
- SVT with wide QRS related to electrolyte or metabolic disorder
- SVT with conduction over an accessory pathway (pre-excitation)
- Paced rhythm
- artifact

Table 5. ECG Criteria to Differentiate VT From SVT in Wide-Complex Tachycardia

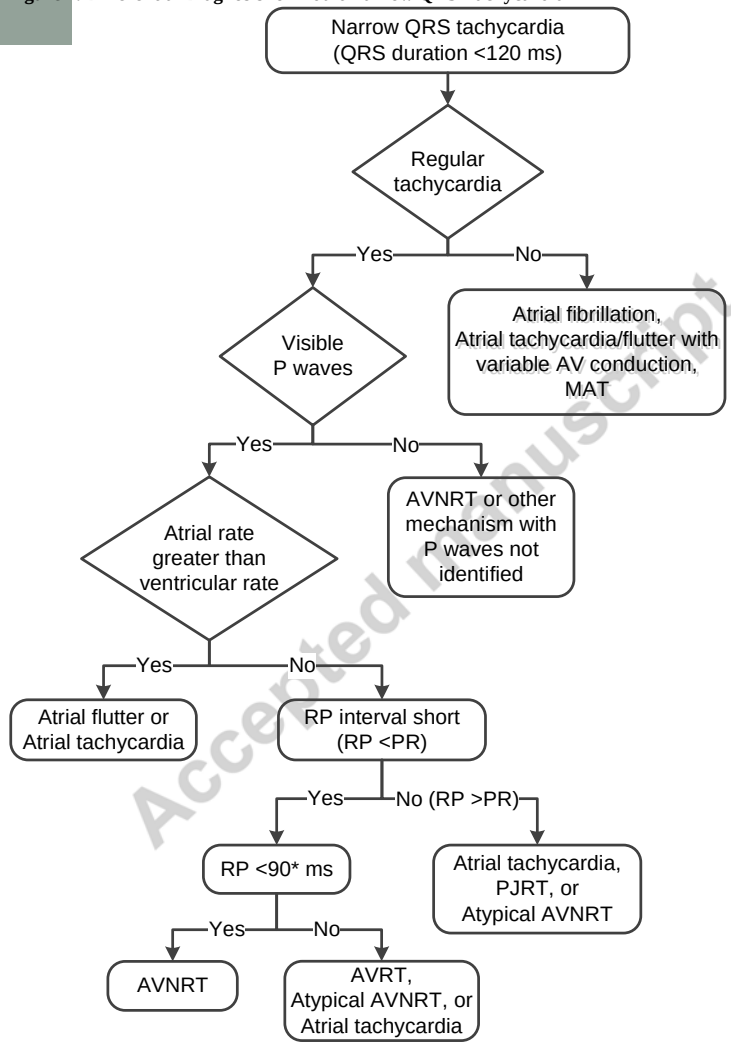
Findings or Leads on ECG Assessed	Interpretation
QRS complex in leads V1-V6 (Brugada criteria) (73)	Lack of any R-S complexes implies VT R-S interval (onset of R wave to nadir of S wave) >100 ms in any precordial lead implies VT
QRS complex in aVR (Vereckei algorithm) (74)	Presence of initial R wave implies VT Initial R or Q wave >40 ms implies VT Presence of a notch on the descending limb at the onset of a predominantly negative QRS implies VT
AV dissociation*	Presence of AV dissociation (with ventricular rate faster than atrial rate) or fusion complexes implies VT
QRS complexes in precordial leads all positive or all negative (concordant)	Suggests VT
QRS in tachycardia that is identical to sinus rhythm (78)	Suggests SVT
R-wave peak time in lead II SVT (78)	R-

*AV dissociation is also a component of the Brugada criteria (73).
AV indicates atrioventricular; ECG, electrocardiogram; SVT, supraventricular tachycardia; and VT, ventricular tachycardia.

Wide QRS complex tachycardia

- LVEF
- h/o CAD

Figure 7. Differential Diagnosis for Adult Narrow QRS Tachycardia

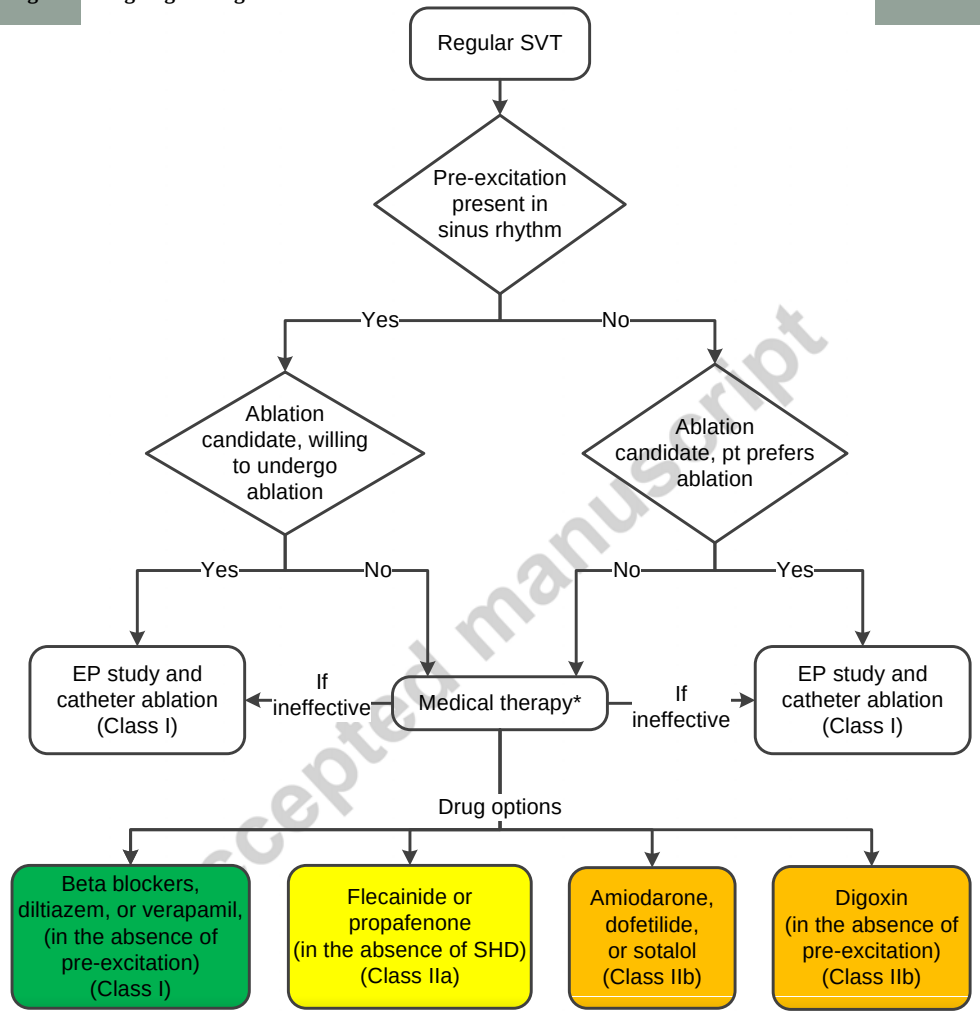


Patients with junctional tachycardia may mimic the pattern of slow-fast AVNRT and may show AV dissociation and/or marked irregularity in the junctional rate.
*RP refers to the interval from the onset of surface QRS to the onset of visible P wave (note that the 90-ms interval is defined from the surface ECG (79), as opposed to the 70-ms ventriculoatrial interval that is used for intracardiac diagnosis (80)).

COR	LOE	Recommendations
I	B-R	**1. Oral beta blockers, diltiazem, or verapamil is useful for ongoing management in patients with symptomatic SVT who do not have ventricular pre-excitation during sinus rhythm (46, 98, 99).**
See Online Data Supplement 2.		Although many patients prefer to undergo potentially curative therapy with ablation, given its high success rate, and although ablation may be mandatory therapy for patients in certain occupations (e.g., pilots, bus drivers), patients may prefer not to undergo ablation or may not have access to a cardiac electrophysiologist. In these latter cases, pharmacological therapy with AV nodal blockers is an appropriate option for long-term prophylactic therapy. Pharmacological therapy with verapamil (dosage up to 480 mg/d) has been studied in RCTs, with reductions documented in SVT episode frequency and duration as recorded by Holter monitoring or subjective episode frequency recording in diaries (98). Evidence for beta blockers is limited. One small study randomized patients with SVT to digoxin (0.375 mg/d), propranolol (240 mg/d), or verapamil (480 mg/d), with 1 week of placebo washout between drug regimens (99). Reduction in the number of episodes and duration of SVT (ascertained by diary and weekly 24-h Holter) was similar among the treatment groups, and all 3 medications were well tolerated (99).
I	B-NR	**2. EP study with the option of ablation is useful for the diagnosis and potential treatment of SVT (36, 100-106).**
See Online Data Supplement 2.		EP testing with the option of ablation is useful as first-line therapy for treatment of symptomatic SVT, as it provides the potential for definitive cure without the need for chronic pharmacological therapy. Large registry studies report high success rates for ablation of both AVNRT and AVRT, with infrequent but potentially serious complications (Table 8).
I	C-LD	**3. Patients with SVT should be educated on how to perform vagal maneuvers for ongoing management of SVT (82).**
See Online Data Supplement 2.		When properly performed, vagal maneuvers can terminate SVT, so patient education on this maneuver may help to avoid a more prolonged tachycardia episode and reduce the need to seek medical attention. Vagal maneuvers should be performed with the patient in the supine position. Patients can be taught to perform a Valsalva maneuver by forcefully exhaling against a closed airway for 10 to 30 seconds, equivalent to at least 30 mm Hg to 40 mm Hg (82, 84). Another vagal maneuver based on the classic diving reflex consists of applying an ice-cold, wet towel to the face (85).
IIa	B-R	**1. Flecainide or propafenone is reasonable for ongoing management in patients without structural heart disease or ischemic heart disease who have symptomatic SVT and are not candidates for, or prefer not to undergo, catheter ablation (45, 46, 107-112).**
See Online Data Supplement 2.		Several RCTs have demonstrated the efficacy of daily therapy with propafenone (450 mg/d to 900 mg/d) or flecainide (100 mg/d to 300 mg/d) to prevent recurrences of SVT in symptomatic patients (45, 46, 107-112). In 1 RCT, the probability of 12 months of effective (defined as <2 attacks of arrhythmia) and safe treatment was 86% for propafenone and 93% for flecainide (109). However, flecainide and propafenone have a risk of proarrhythmia in patients with structural heart disease or ischemic heart disease, so these drugs are contraindicated in these patient groups (113). These drugs, though often effective, have potential side effects and as such should be reserved for patients for whom beta blockers, diltiazem, or verapamil are ineffective or cannot be prescribed.
IIb	B-R	**1. Sotalol may be reasonable for ongoing management in patients with symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation (114).**

See Online Data Supplement 2.		Sotalol is a class III antiarrhythmic agent with beta-blocker properties. Unlike flecainide and propafenone, it can be used in patients with structural heart disease or ischemic heart disease. One study randomized patients with reentrant SVT (AVNRT or AVRT) or other atrial tachyarrhythmias (e.g., AF, atrial flutter, AT) to sotalol at a dose of 80 mg or 160 mg twice daily or placebo and found significant reductions in recurrence risk, including for patients with reentrant SVT, with no proarrhythmic adverse effects (114). Because of the potential for proarrhythmia, sotalol should be reserved for patients who are not candidates for catheter ablation and for whom beta blockers, diltiazem, or verapamil are ineffective or cannot be prescribed.
IIb	**B-R**	**2. Dofetilide may be reasonable for ongoing management in patients with symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation and in whom beta blockers, diltiazem, flecainide, propafenone, or verapamil are ineffective or contraindicated (107).**
See Online Data Supplement 2.		Dofetilide is a class III antiarrhythmic agent that, unlike sotalol, does not have beta-blocker properties. It may be reasonable in patients with structural heart disease or ischemic heart disease. In a trial of 122 patients randomized to dofetilide, propafenone, or placebo, the probability of remaining free of SVT after 6 months of treatment was 50% for dofetilide, 54% for propafenone, and 6% for placebo, with $p<0.001$ for either dofetilide or propafenone compared with placebo (107). Because of the potential for proarrhythmia, dofetilide should be reserved for patients who are not candidates for catheter ablation and for whom beta blockers, diltiazem, flecainide, verapamil, or propafenone are ineffective or cannot be prescribed.
IIb	**C-LD**	**3. Oral amiodarone may be considered for ongoing management in patients with symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation and in whom beta blockers, diltiazem, dofetilide, flecainide, propafenone, sotalol, or verapamil are ineffective or contraindicated (115).**
See Online Data Supplement 2.		Evidence for amiodarone for the ongoing management of SVT is limited. The drug was evaluated in a small retrospective study and was found to be effective in suppressing AVNRT during outpatient follow-up (115). Amiodarone is a second-line agent for patients who are not able to take beta blockers, diltiazem, dofetilide, flecainide, propafenone, sotalol, or verapamil given the toxicity and side effects that may develop with long-term amiodarone therapy.
IIb	**C-LD**	**4. Oral digoxin may be reasonable for ongoing management in patients with symptomatic SVT without pre-excitation who are not candidates for, or prefer not to undergo, catheter ablation (99).**
See Online Data Supplement 2.		Evidence for the use of digoxin is limited. One small study randomized patients with SVT to digoxin (0.375 mg/d), propranolol (240 mg/d), and verapamil (480 mg/d), with 1 week of placebo washout between drug regimens (99). Overall, episodes and duration of SVT (ascertained by diary and weekly 24-h Holter) were similar, and all 3 medications were well tolerated (99). However, the dose of digoxin used was higher than that commonly used in clinical practice today, and in view of the risk of toxicity, digoxin should be reserved for patients who cannot take beta blockers, diltiazem, or verapamil or a class Ic agent (flecainide or propafenone) and must be used with caution in the presence of renal dysfunction. In some clinical studies, digoxin levels >1.2 ng/mL were associated with worse clinical outcomes, while levels <0.8 ng/mL were considered optimal; therefore, caution is advised (116).

Figure 9. Ongoing Management of SVT of Unknown Mechanism



Colors correspond to Class of Recommendation in Table 1; drugs listed alphabetically.
*Clinical follow-up without treatment is also an option.
EP indicated electrophysiological; pt, patient; SHD, structural heart disease (including ischemic heart disease); SVT, supraventricular tachycardia; and VT, ventricular tachycardia.

Atrial Fibrillation

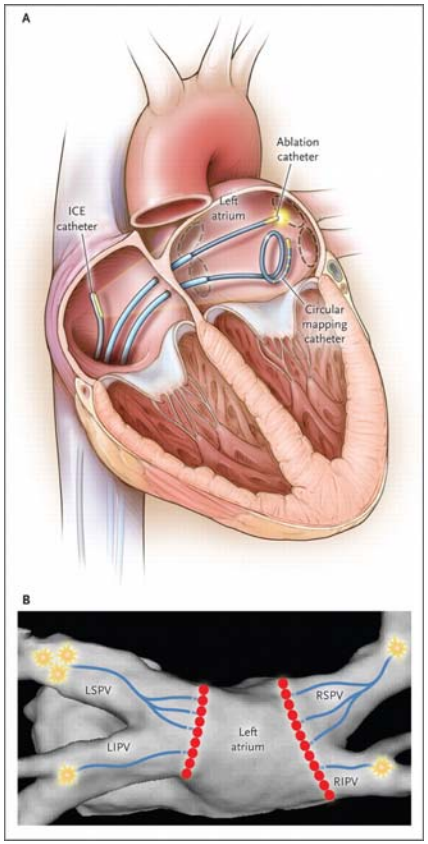
- Atrial fibrillation affects up to 5 million people in the United States, and data suggest that as the population ages, the incidence will continue to increase
- The rate of ischemic stroke among patients with nonvalvular atrial fibrillation averages 5% per year.
- The rate of death among patients with atrial fibrillation is about double that among patients with normal sinus rhythm
- The overall cost of treating recurrent atrial fibrillation has been estimated to be more than $6.5 billion per year.

TABLE 4 Definitions of AF: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Long-standing persistent AF	• Continuous AF >12 mo in duration.
Permanent AF	• The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

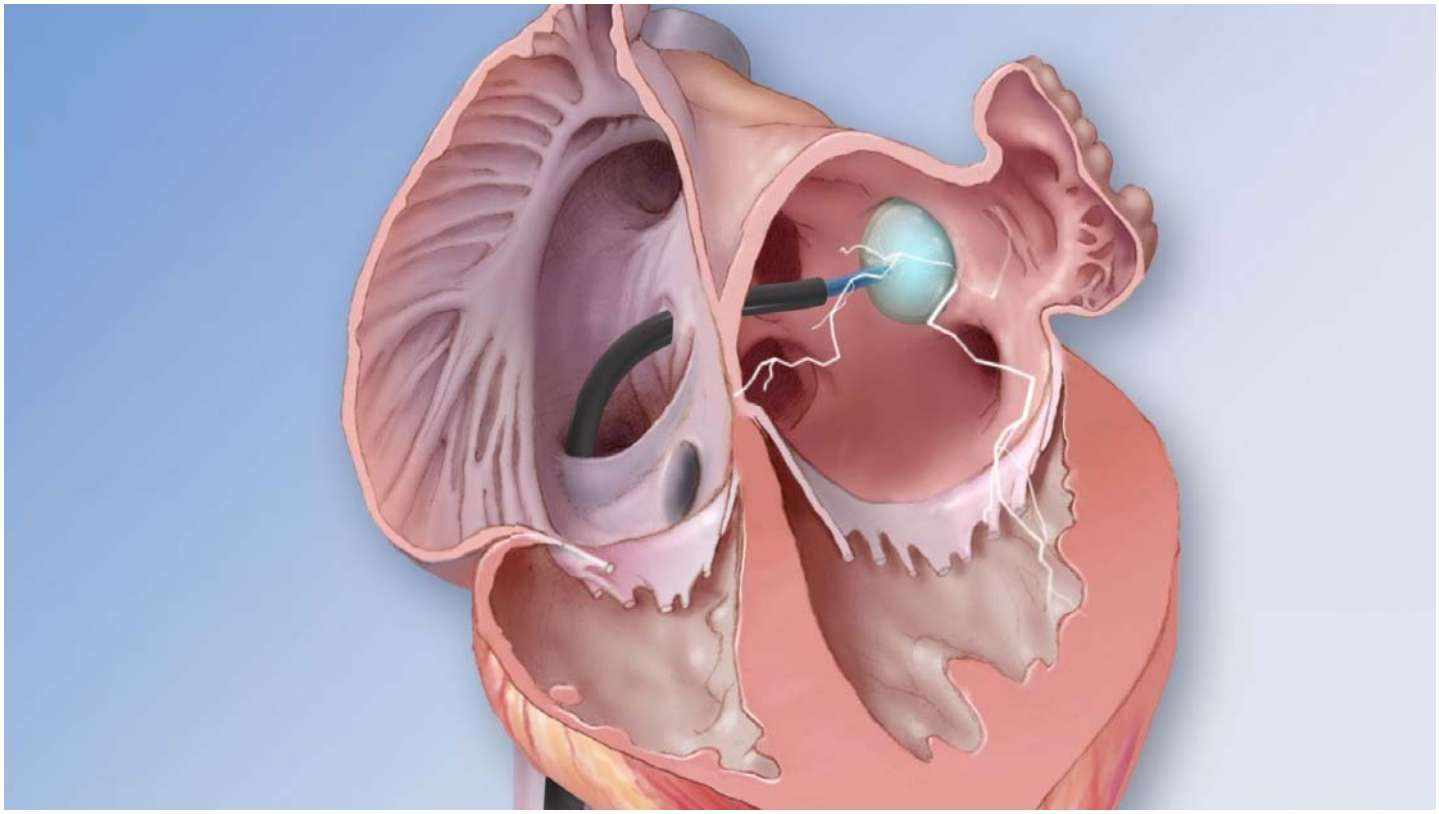
AF indicates atrial fibrillation.

Catheter Placement during Atrial Fibrillation Ablation and RF Catheter Ablation



Wazni O et al. N Engl J Med 2011;365:2296-2304.

Cryo-balloon Catheter Ablation



From: **Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation: A Randomized Controlled Trial**

JAMA. 2010;303(4):333-340. doi:10.1001/jama.2009.2029

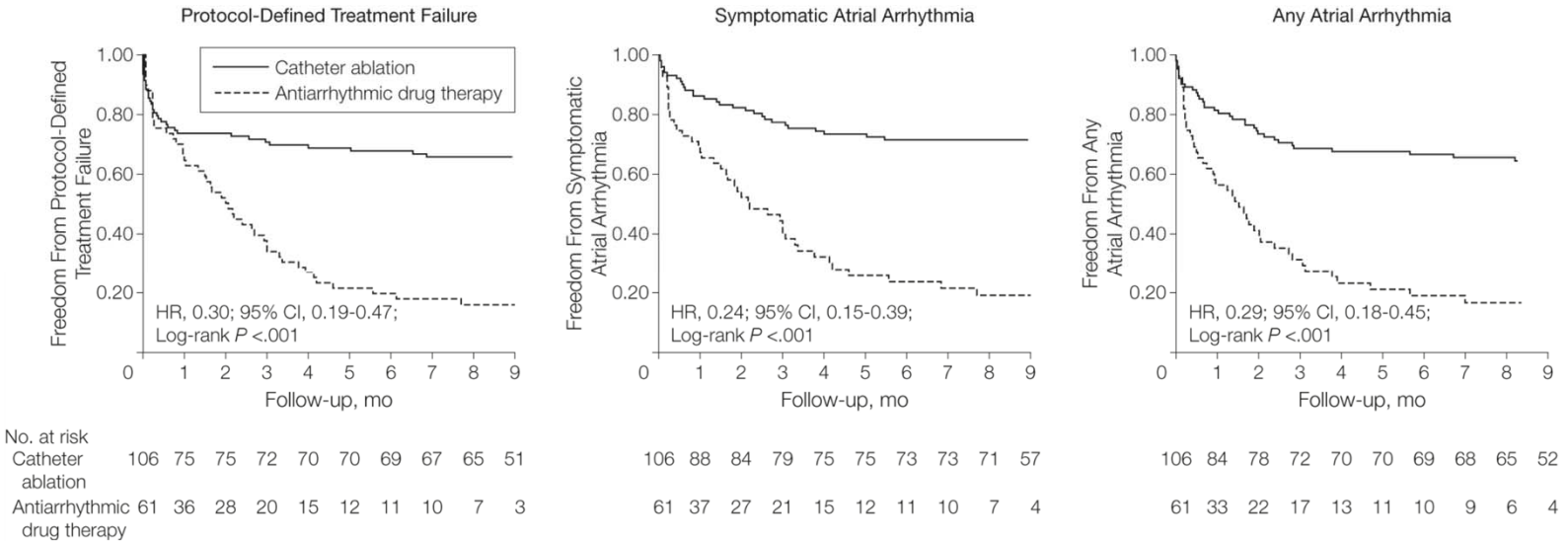
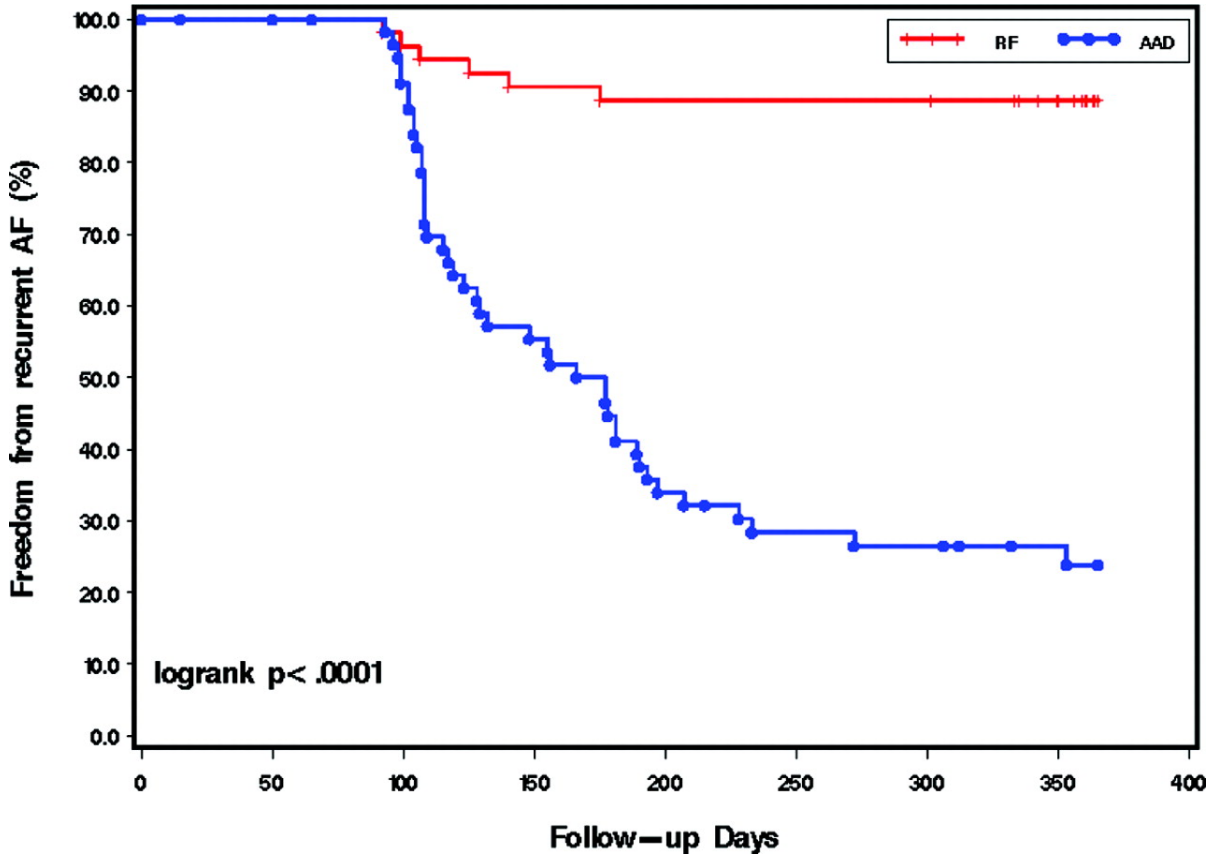


Figure Legend:

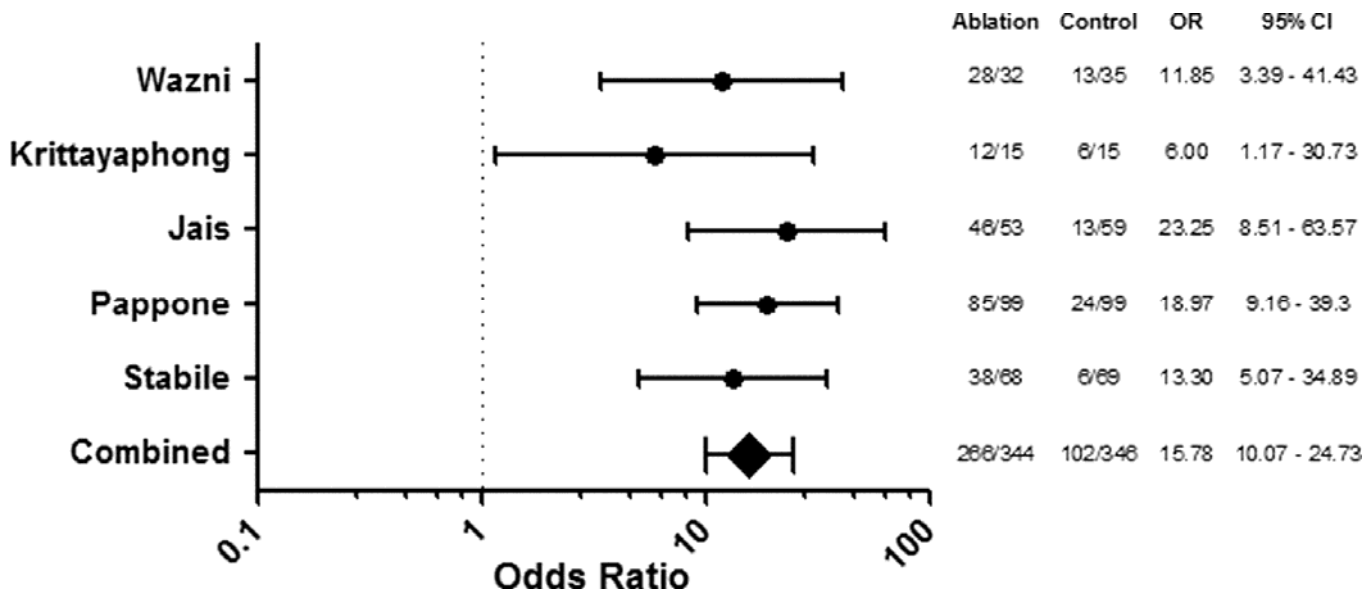
HR indicates hazard ratio; CI, confidence interval.

Figure 1. Kaplan–Meier analysis for time to recurrent AF after the 90-day treatment adjustment period for both groups.



Pierre Jaïs et al. Circulation. 2008;118:2498-2505

Figure 2. ORs (ablation versus control) for freedom from atrial fibrillation at 12 months.



Jonathan P. Piccini et al. Circ Arrhythm Electrophysiol. 2009;2:626-633

6.3. AF Catheter Ablation to Maintain Sinus Rhythm: Recommendations

CLASS I

1. AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired (363,392–397). *(Level of Evidence: A)*
2. Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. *(Level of Evidence: C)*

CLASS IIa

1. AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (394,398–400). *(Level of Evidence: A)*
2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy (401–403). *(Level of Evidence: B)*

CLASS IIb

1. AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired (363,404). *(Level of Evidence: B)*
2. AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired. *(Level of Evidence: C)*

CLASS III: HARM

1. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure. *(Level of Evidence: C)*

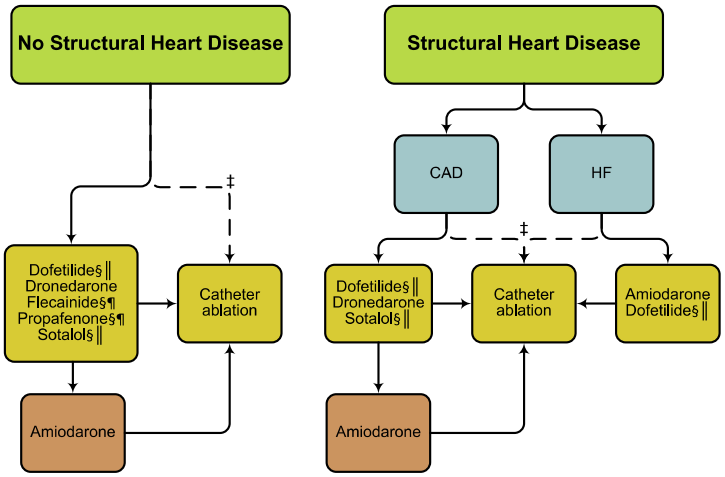


FIGURE 7 **Strategies for Rhythm Control in Patients With Paroxysmal* and Persistent AF†**

*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation).
†Drugs are listed alphabetically.
‡Depending on patient preference when performed in experienced centers.
§Not recommended with severe LVH (wall thickness >1.5 cm).
‖Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia.
¶Should be combined with AV nodal blocking agents.
AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.

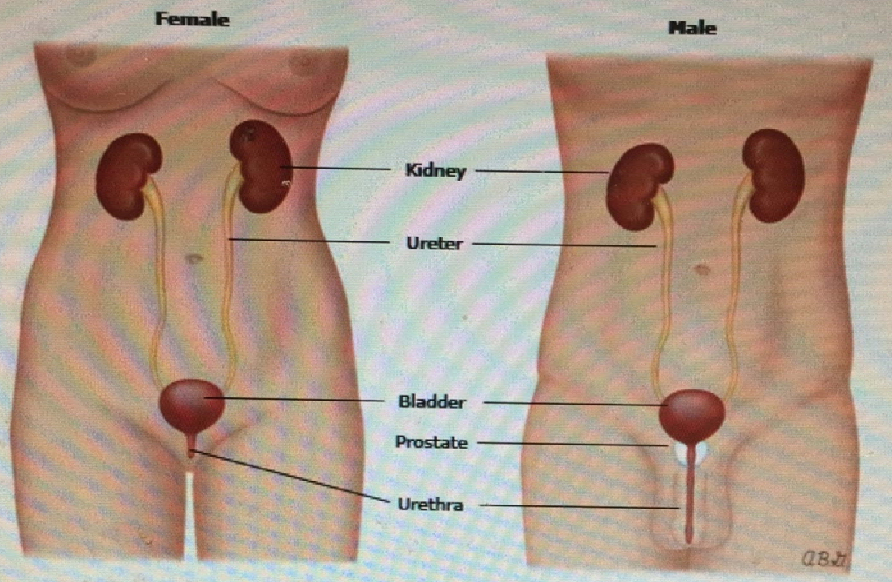
Summary

- SVT ablation is class I indication before medical therapy
- Symptomatic paroxysmal AF is class IIa indication before failing AAD
- If LVEF severely reduced and/or h/o CAD, WCT is more likely VT

EVALUATION OF HEMATURIA AND PROTEINURIA

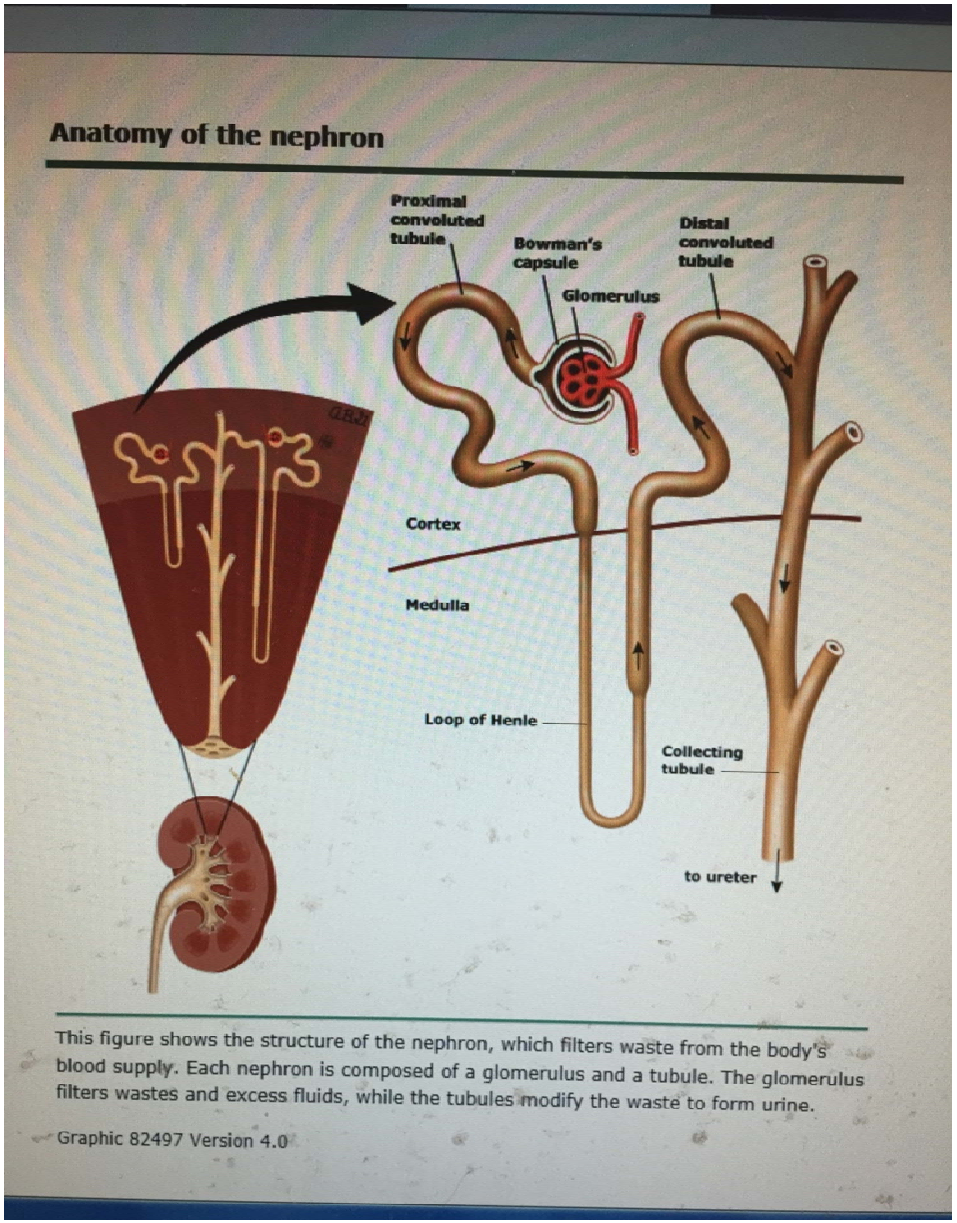
Tapasi Saha MD, FASN
Director of Peritoneal Dialysis, Regional Kidney Care
Clinical Assistant Professor
East Tennessee State University, School of Medicine

Anatomy of the urinary tract



Urine is made by the kidneys. It passes from the kidneys into the bladder through two tubes called the ureters. Then it leaves the bladder through another tube, called the urethra.

Graphic 79864 Version 6.0


Anatomy of the nephron
Proximal convoluted tubule
Bowman's capsule
Glomerulus
Distal convoluted tubule
Cortex
Medulla
Loop of Henle
Collecting tubule
to ureter
This figure shows the structure of the nephron, which filters waste from the body's blood supply. Each nephron is composed of a glomerulus and a tubule. The glomerulus filters wastes and excess fluids, while the tubules modify the waste to form urine.
Graphic 82497 Version 4.0

Evaluation of Hematuria

- The kidneys are bean-shaped, approximately fist-size organs that are located in the mid-back, just below the rib cage on each side of the body
- The kidneys filter the body's blood supply with tiny structures known as nephron. Each nephron is composed of a glomerulus (filters wastes and excess fluids) and a tubules (modify the waste to form urine)

Evaluation Of Hematuria

Normally kidney filter toxins out of the blood stream and excrete them in the urine

In people with glomerular disease red blood cells and protein may be excreted in the urine while the toxins may be retained

Evaluation Of Hematuria

- 24 years old white female was referred to me by primary care doctor for evaluation of hematuria
- How do you evaluate this patient ?
- 60 years old female referred for hematuria
- How will you evaluate ?

Evaluation of Hematuria

- Evaluation should address three questions
  a) Are there any clue from history or physical exam that suggest particular diagnosis b) does hematuria glomerular or non glomerular bleeding
  c) Is the hematuria transient or permanent

Assessment of patients with hematuria

- History:
  Timing of hematuria - Hematuria macroscopic and sustained - throughout the stream kidney origin , early in the stream urethral , late in the stream bladder or prostate
  color of urine –Glomerular bleeding smoky brown (Coca-Cola urine) whereas bladder or prostate bleeding typically result in bright red blood
- Family history – Polycystic disease, hereditary nephritis , sickle cell disease
- Duration of hematuria- transient or persistent , associated dysuria/frequency- infection most likely but also can be due to hemorrhagic cystitis, bladder malignancy
- Unilateral flank pain- may indicate obstruction (by calculus or clot) but can be due to malignancy
- Recent upper respiratory tract infection- IgA nephropathy or post infectious GN
- Travel history- Schistosomiasis or TB
- History of trauma, exercise , menstruation, history of diabetes
- Medication history- Cyclophosphamide
- Family history of PCKD, thin basement membrane disease, sickle cell Anemia, Alport syndrome

Evaluation Of Hematuria

- When you have blood in the urine first thing to decide glomerular or non-glomerular origin
- Extra-glomerular hematuria- Red or pink color urine
- Glomerular hematuria- smoky brown or cola color, no clots, proteinuria usually >500 ng/day , dysmorphic RBC, RBC cast may be present
- Isomorphic RBCs (small, anucleated cells shaped as biconcave disks) which has similar appearance to erythrocytes in the circulation can be seen with any cause of hematuria
- Dysmorphic RBCs (which have an altered morphology) are suggestive of glomerular disease)
- RBCs that have an membrane protrusions (acanthocytes)- a Subset of dysmorphic RBC
- The concomitant presence of RBC cast and or albuminuria – increase the likelihood that hematuria is of glomerular origin

Hematuria

- Hematuria is the presence of erythrocytes in the urine
- Microscopic hematuria – Presence of two or more red blood cells per high power field
- Transient hematuria- UTI, trauma, ureteral stones, prostatitis, Endometriosis
- Transient hematuria may occur after exercise or sexual intercourse
- Avoid urine testing after strenuous exertion (Joggers's nephritis) or menstruation
- Persistent hematuria- Sickle cell disease, polycystic kidney disease, cancer of bladder kidney ,prostate and BPH
- Urethral catheterization and bladder trauma can also increase number of erythrocytes in the urine
- Hematuria present in up to 3 to 6% of healthy young adults, which is transient and of no consequences and interestingly it is present in 5% to 10% of relatives of patients with chronic kidney disease

Evaluation Of Hematuria

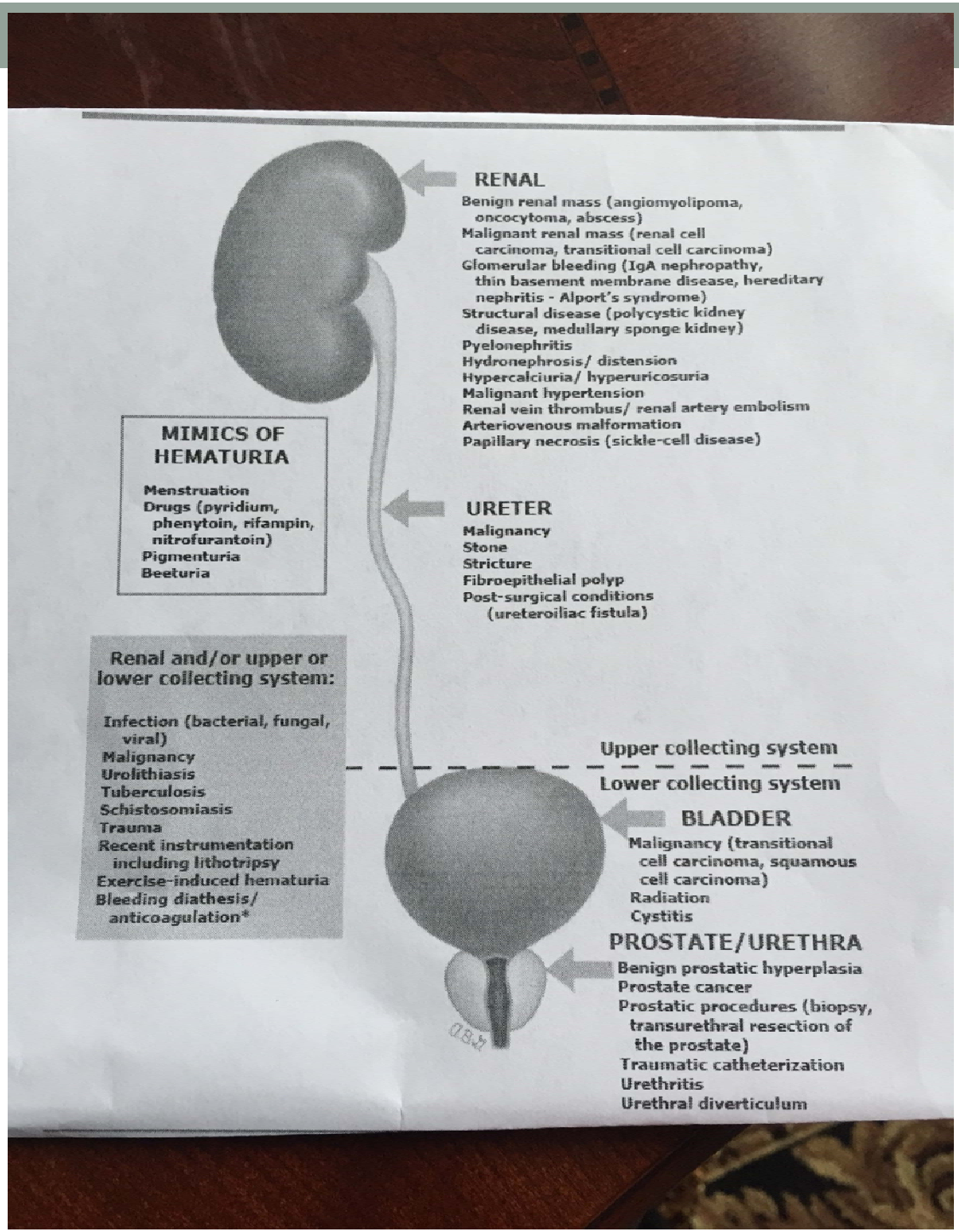
- Urinalysis – Dipstick – Reagent strips for blood rely on peroxidase activity of hemoglobin to catalyze the organic peroxidase with subsequent oxidation of an indicator dye. Free hemoglobin produces a homogenous color, intact RBC cause punctate staining. False positive in the presence of hemoglobin/myoglobin (both has peroxidase activity) or urine is contaminated with other oxidants such as povidone –iodine, hypochlorite or bacterial peroxidase. False negative if the dipsticks incorrectly stored or expired or in patients who consume large amount of Vitamin C
- Urinalysis: urine should be collected in a clean container, patient should be asked to clean external genitalia and provide a midstream specimen for analysis . In patient with indwelling catheters recently produced urine sample should be obtained (from the catheter tubing not from drainage bag)

Urine Dipstick

- Urine dipstick - Urine sample (10 to 15 ml) should be fresh, storage cause erythrocyte damage , prolong centrifugation can disrupt the RBC cast
- False positive dipstick a) Semen is present in the urine after ejaculation
  b) Alkaline urine with a PH >9 or urine contamination with oxidizing agents (povidone iodine , hypochlorite) used to clean the perineum
  c) Presence of Myoglobinuria
  d) Rarely very dilute urine result in osmotic lysis of almost all of the RBC (forming Ghost cells) cause false positive result as the dipstick detects hemoglobin without visible RBC
- False negative dipstick tests- Patient taking large quantities of vitamin C

Approach to Hematuria

- Centrifugation is the first step in analyzing red-brown urine because hematuria only present in the sediment
- If the supernatant is red-brown the presence of hemoglobin or myoglobin should be tested with dipsticks.
- Hemoglobin or myoglobin can be more accurately assessed by urinary electrophoresis
- If the dipstick is negative for heme rare causes of urine discoloration including prophyria, beet root ingestion or the use of drugs
  rifampin, pyridium, phenytoin, nitrofurantoin should be considered


RENAL
Benign renal mass (angiomyolipoma, oncocytoma, abscess)
Malignant renal mass (renal cell carcinoma, transitional cell carcinoma)
Glomerular bleeding (IgA nephropathy, thin basement membrane disease, hereditary nephritis - Alport's syndrome)
Structural disease (polycystic kidney disease, medullary sponge kidney)
Pyelonephritis
Hydronephrosis/ distension
Hypercalciuria/ hyperuricosuria
Malignant hypertension
Renal vein thrombus/ renal artery embolism
Arteriovenous malformation
Papillary necrosis (sickle-cell disease)
MIMICS OF HEMATURIA
Menstruation
Drugs (pyridium, phenytoin, rifampin, nitrofurantoin)
Pigmenturia
Beeturia
URETER
Malignancy
Stone
Stricture
Fibroepithelial polyp
Post-surgical conditions (ureteroiliac fistula)
Renal and/or upper or lower collecting system:
Infection (bacterial, fungal, viral)
Malignancy
Urolithiasis
Tuberculosis
Schistosomiasis
Trauma
Recent instrumentation including lithotripsy
Exercise-induced hematuria
Bleeding diathesis/ anticoagulation*
Upper collecting system
Lower collecting system
BLADDER
Malignancy (transitional cell carcinoma, squamous cell carcinoma)
Radiation
Cystitis
PROSTATE/URETHRA
Benign prostatic hyperplasia
Prostate cancer
Prostatic procedures (biopsy, transurethral resection of the prostate)
Traumatic catheterization
Urethritis
Urethral diverticulum

Exercise- induced Hematuria

- Exercise induced hematuria - Can be gross or microscopic that occurs after strenuous exercise and resolves with rest (within several days to one week after cessation of exercise) in individuals with no apparent underlying kidney or urinary tract pathology
  Noncontact sports such as rowing , swimming and stationary bike riding (eg , spinning)

Mechanism- a) Renal ischemia due to shunting of blood to the exercising muscles b) lactic acidosis due to anaerobic conditions increase glomerular permeability which allow the passage of erythrocytes into the urine

- Hematuria due to direct trauma to the kidney with contact sports like football and boxing
- Evaluation – warranted if the hematuria persists beyond one week of no exercise and even with transient hematuria in patient over 50 years are at increased risk for bladder or kidney cancer

Macroscopic Hematuria

- Risk factor for Urological Malignancy
  1. Age greater than 40
  2. H/O smoking
  3. Occupational exposure to benzene or amine dyes (printers , or painters)
  4. History of gross hematuria
  5. H/O chronic cystitis
  6. H/O Pelvic irradiation
  8. H/O Analgesic abuse
  9. H/O previous cyclophosphamide use

Macroscopic Hematuria

- Macroscopic hematuria if brisk and associated with clots most commonly associated with extra-glomerular processes that vary with age
- Most common causes- Infection and inflammation of prostate and bladder or kidney stones. In patients over age 40 malignancy should be ruled out

Glomerular Hematuria

- Damage to the glomerular basement membrane can allow passage of RBC from the glomerular capillaries into bowman capsule by infiltrating leukocytes ,immune complexes , activated glomerular cell - inflammatory condition- IgA nephropathy, Crescentic GN **, non inflammatory condition** Alport Syndrome, thin basement membrane disease or Diabetic nephropathy
- Inflammation of tubules – Transit of RBC from peritubular capillaries into the tubular lumen- In Tubulo-interstitial nephritis or Acute tubular necrosis
- Findings suggest glomerular proteinuria- RBC cast, proteinuria exceeding 500 mg/day and dysmorphic RBC
- Presence of granular cast, oval fat bodies together with RBC cast-suggest Kidney lesion
- RBC – usually uniform and round - extra-renal bleeding source
- Dysmorphic RBC in glomerular and tubular sources
- In severe glomerular bleeding (IgA nephropathy or Crescentic GN) mixture of dysmorphic and non –dysmorphic RBC seen
- Acanthocytes- are dysmorphic RBC with multiple bubble like projection

Macroscopic Hematuria

- Macroscopic hematuria of glomerular origin- IgA nephropathy , renal vasculitis
- Persistent isolated glomerular hematuria – Confers increased risk for ESRD-
- a) IgA nephropathy associated with positive family history and macroscopic hematuria
- b) Alport syndrome – X-linked recessive disease – mutation of alfa 5 chain of type 4 collagen associated with high frequency hearing loss , corneal disorder and positive family history
- c) Thin basement membrane disease with positive family history and autosomal dominant pattern of inheritance

Macroscopic Hematuria

- Rare causes – Hereditary Hemorrhagic Telangiectasia , Schistosomiasis and radiation cystitis .
  Arteriovenous malformation can be congenital or acquired can cause macroscopic hematuria- diagnostic test CT or Angiogram
- Nutcracker Syndrome- where the left renal vein is compressed between the aorta and proximal superior mesenteric artery can cause left flank pain , orthostatic proteinuria and hematuria- treatment
  - stenting/transposition of the artery
- Loin pain hematuria syndrome- Dysmorphic RBC in the urine and loin pain but usually with normal kidney function

Evaluation of Hematuria

- Approach to the patient with red or brown urine –
  - a) Centrifuge the urine – if sediment red -hematuria
  - b) if supernatant red dipstick heme -if negative beeturia , phenazopyridine , porphyria if dipstick heme positive –myoglobin, hemoglobin, if plasma clear- myoglobinuria if plasma red- hemoglobinuria
- Hematuria confirmed- if yes – if intermittent hematuria – infection, joggers nephritis, menstruation, catheter associated
- If hematuria confirmed- sustained and macroscopic – if throughout the stream kidney origin, if early in the stream urethral origin, if late in the stream bladder or prostate origin
- If hematuria confirmed, sustained and microscopic – urine microscopy for casts- if cast present and proteinuria present Glomerulonephritis if no proteinuria thin membrane disease or Alport syndrome

Approach to Hematuria

- Hematuria is common , particularly young adult patients , is usually transient and of no consequence. However there is appreciable risk for malignancy in patient over age 35 years even if transient
- Confirmed hematuria , an imaging study of kidney and collecting systems should be obtained for all patient with gross or microscopic hematuria who have no evidence of glomerular bleeding
- CT urography – in most patient with unexplained hematuria (macroscopic or microscopic) ultrasound if pregnant or if has contraindication to iodinated contrast- CT without contrast MRI or ultrasound
- Cystoscopy should be performed in all patient over age 35 with gross hematuria or microscopic hematuria who have no evidence of glomerular hematuria , nephrolithiasis, infection, trauma , vigorous exercise, menstruation , recent urological procedure. Patient who have blood clots should have cystoscopy even if they have evidence of glomerular lesion because blood clot never associated with glomerular bleeding
- Who has negative evaluation should be followed by annual urinalysis and blood pressure monitoring, patient with persistent microscopic hematuria and risk factor for malignancy should be offered cystoscopic and imaging reevaluation in three to five years from initial presentation

Role Of Renal Biopsy

- Indication for renal biopsy in patient with glomerular hematuria - presence of risk factors for progressive disease proteinuria , elevation of serum creatinine, new onset hypertension >140/90 (from previous baseline 1oo/60 to 130/80 mmHg) associated with progressive disease
- Renal biopsy is not performed for isolated glomerular hematuria (no proteinuria , no elevation of creatinine, no elevation of blood pressure from the previous value and no systemic manifestations) since there is no specific therapy for these conditions and the renal prognosis is excellent as long as there is no evidence of progressive disease. In addition management of these patient is not affected by biopsy result . If renal biopsy performed in such patients the most common findings are normal renal biopsy or one of the four disorder IgA nephropathy , thin basement membrane disease (benign familiar hematuria), mild non specific glomerular hematuria and hereditary nephritis (Alport syndrome) .

Proteinuria

- Proteinuria is a marker of kidney disease/glomerular disease and plays a role in screening, diagnosis and monitoring , prevalence 2% in general population
- Renal protein Handling- three are three major components a) Amount of protein presented to the glomerular capillary (filtered load) which is dependent on both the protein concentration in the plasma and GFR. b) The second major determinant relates to permeability (the ability to traverse the glomerular capillary barrier) which is dependent both on the integrity of the glomerular capillary wall and the specific attributes of particular protein molecules. The glomerular capillary wall consists of three layers Fenestrated endothelium , the glomerular basement membrane and the epithelial cells which are attached to the basement membrane by foot processes
- Third component is the proximal tubule- Some protein filtered and then catabolized and reabsorbed in the proximal

Renal Protein Handling

- Thus the amount of protein in the urine depends on how much gets there, how well it passes through the glomerular barrier and whether or not proximal tubules degrades it if the protein does get into the glomerular filtrate

Proteinuria

- The primary barrier to the filtration is GBM
- The factors that determine the ability of protein molecules to pass through the basement membrane are ***molecular size , shape and charge*** .The glomerular capillary wall highly permeable to small solutes and water but limits passage of larger molecules inulin 52000 completely filtered while albumin 69000 is filtered only to a small degree . There is inverse relationship between the molecular size and degree of filtration suggest pores (functional not structural) may exists within GBM . There is not much known about the molecular shape. Molecular charge is another important determinant . Glomerular capillary wall contain sialoprotein and proteoglycans such as heparin sulfate that are negatively charged. Most circulating macromolecules are anionic. So filtration of albumin and other macromolecules limited in part by electrostatic repulsion .

Proteinuria

In health proteinuria result from tubular protein excretion particularly Tamm-Horsfall protein. Albumin is the predominant protein filtered by the glomerulus ,is therefore most consistent marker of glomerular pathology .in health albumin contributes little or no proteinuria (around 12 mg/24 hours) as proteins crossing the GBM are mainly reabsorbed and degraded by receptor mediated endocytosis. This process shows a preference for cationic protein and only a limited capacity for albumin ,so even minor glomerular abnormalities increase albuminuria

Evaluation Of proteinuria

- Normal protein excretion – Less than 100 mg/24 hours
- Proteinuria more than 200 mg/24 hours suggest glomerular disease
- Increase protein excretion- standing, during exertion, fever , pressor agents such as angiotensin , norepinephrine
- Asymptomatic proteinuria- by dipstick – high school athletics, entry to arm forces or at antenatal visit
- Frothy urine – when the protein excretion is high with associated edema/hypoalbuminemia as part of nephrotic syndrome
- Frothy urine not associated with nephrotic syndrome bilirubinuria retrograde ejaculation

Proteinuria

- Microalbuminuria – 30 to 300 mg/24 hours (20 to 200 Ug/min)
- Urinary albumin/creatinine ratio 17 to 250 mg/g for men and 25 to 355 mg/g for women
- Albumin induce inflammatory and fibrogenic mediators such as TGF beta that cause tubular injury

Investigation Of Proteinuria

- Proteinuria suspected- urine dipstick positive for protein on two occasion (false positive proteinuria after the radiocontrast, alkaline urine PH>9 , drugs tolbutamide, cephalosporins, dipstick will underestimate proteinuria in the presence of dilute urine Specific gravity <1.005 and presence of light chains) confirmed the proteinuria by laboratory testing with sulfosalicylic acid can detect lower level of proteinuria (up to 5 mg/dl) as well as other non albumin protein ,Strongly positive SSA test in the presence of negative urine dipstick indicates the presence of globulins such as light chain, testing should be avoided within 24 hours of contrast due to false positive result urine microscopy, quantitate proteinuria, urine culture, blood test (GFR) if transient proteinuria and other test normal reassure and discharge . If proteinuria persistent consider immunological test and ultrasound, if proteinuria less than 0.5g /24 hours and normal sediments or diabetes with progressive proteinuria observe. If proteinuria >0.5 g/24 hours with SLE or >1g/24 hours +/- systemic disease or nephrotic syndrome consider kidney biopsy

Evaluation Of proteinuria

- Proteinuria on dipstick is graded from trace to 4 plus as follow - Trace 15 to 30 mg/dl
- 1+ 30 to 100 mg/dl
- 2+ 100 to 300 mg/dl
- 3+ 300 to 1000 mg/dl
- 4+ More than 1000 mg/dl

Proteinuria

- Transient proteinuria – 4% of men and 7% of women. Vigorous exercise, fever can increase proteinuria.
- Orthostatic proteinuria defined by increased protein excretion in upright position and normal protein excretion in supine or recumbent position , orthostatic proteinuria accounts for 60% of all childhood cases of persistent daytime proteinuria and 75% of proteinuria in adolescent patients. Uncommon in patient older than 30 years. Protein excretion never exceeds more than 1 g/24 hours. Diagnosis by comparison of the protein- to creatinine ratio in urine samples collected in recumbent and upright position , split urine collection (split 24 hours collection) day and night in separate container
- Persistent proteinuria less than 2g/24 hours and not accompanied by worrisome features such as reduced GFR, hematuria, +ve immunological test or sign/symptoms of systemic disease may be observed for several months

Proteinuria

- Glomerular proteinuria – The GBM is a high capacity ultrafiltration membrane with protein passing across by convection or by diffusion down a concentration gradient. Mutation of podocytes cell surface proteins such as (nephrin or podocin) or of podocyte intracellular proteins that contribute to the integrity of the membrane result in proteinuria. The membrane is negatively charged because of the heparin sulfate in the glomerular endothelial wall that prevent similarly charged proteins (such as albumin) from passing across. Any glomerular pathology that impairs the ability of the GBM to maintain it's charge results in proteinuria .
- Causes of primary glomerular proteinuria – Minimal change disease, IgA nephropathy Focal segmental glomerulosclerosis , Membranous glomerulonephritis, Membrano-proliferative glomerulopathy, Fibrillary GN, Crescentic glomerulonephritis
- Causes of secondary glomerular disease – SLE, Vasculitis , amyloidosis , DM, Scleroderma, Malignancy, Myeloma, Infection (bacterial, viral , fungal), Drugs (Gold, penicillamine, lithium, non- steroidal, Familial (Alport syndrome , Fabry disease), Other (Preeclampsia, transplant glomerulopathy, reflux nephropathy)

Proteinuria

- Two third of urinary protein filtered is glomerular proteinuria (glomerular proteinuria only type detected on dipsticks and responsible for most cases of persistent proteinuria) and the remaining third is secreted (Tubular Proteinuria)
  Tubular proteinuria- result from increase excretion of low molecular weight proteins such as alfa-2 and beta -2 microglobulin and retinol binding protein. Due to failure of the proximal tubules to reabsorbs these proteins that normally filtered or secreted by the renal tubules can cause tubular proteinuria. These are detectable by protein electrophoresis. Proteinuria usually 200 to 2000 mg/24 hours although mixed glomerular or tubular proteinuria can co-exist.
- Causes of tubular proteinuria - **drugs and toxins** : light chain nephropathy, Heavy metals poisoning (Lead, cadmium). Aristolochic acid Tetracycline. **Tubulointerstitial nephritis**, SLE, Sjogren Syndrome, **Other- fanconi syndrome**

Evaluation of Proteinuria

- Overflow proteinuria – Occurs when there is increased production of low molecular weight proteins leading to increased glomerular filtration and excretion .This is almost always due to immunoglobulins light chain in multiple myeloma but may be also due to lysozyme (in acute myelo-monocytic leukemia) , myoglobin (in rhabdomyolysis) or free hemoglobin (in intravascular hemolysis) that is not bound to heptoglobin.
- Patient with multiple myeloma also may develop a component of tubular proteinuria since the excreted light chains are toxic to the tubules leading to diminished reabsorption
- In all these cases increased production of specific protein exceed the proximal tubular reabsorptive capacity.

Evaluation Of Proteinuria

Immunologic testing identifies circulating autoantibodies, abnormal complement levels and pathologic immunoglobulins or immune complexes

- SLE – ANA , Anti-dsDNA, low c3, C4, antibodies to extractable nuclear antigen (Ro, Sm, RNP)
- Microscopic polyangitis- positive MPO –ANCA
- Wegner = positive RR3 ANCA
- Cryoglobulinemia- Positive rheumatoid factor
- Membranous /MPGN - cancer of breast, colon, stomach , lungs
- Minimal change disease- Hodgkin and non Hodgkin Lymphoma
- Fibrillary GN and overflow proteinuria – Associated with monoclonal Gammopathies

Evaluation of Proteinuria

- Myoglobinuria- Drug toxicity , inherited muscle enzyme deficiency
- Hemoglobinuria- by intravascular hemolysis paroxysmal nocturnal hemoglobinuria
- Patient with tubular proteinuria – screen for heavy metal poisoning and also for systemic disease – SLE, Sjogren syndrome or malignancy
- Alport disease- Audiometry
- Fabry disease- Plasma alfa -galactocidase deficiency
- Post streptococcal GN- ASO , C3/C4
- Infective Endocarditis – echocardiography, C3/C4, rheumatoid factor

Evaluation of Proteinuria /Hematuria

- Renal Ultrasounds- To rule out mass
- Doppler US – To rule out non glomerular hematuria with nephrotic range proteinuria (renal vein thrombosis)

Evaluation of Proteinuria

- History- DM, HTN , previous history of glomerular injury , systemic disease
- Exam- BP, fluid balance , cardiac status ,evaluation for signs of vasculitis or other systemic diseases
- Transient proteinuria in up to 4% of men and 7% of women , exercise , fever use of pressor agents increase proteinuria
- Orthostatic proteinuria – considered in adolescent patients frequency 2 to 5% uncommon in those older than 30
- Lab- Presence of proteinuria in dipstick (more than one occasion) confirmed by lab analysis and quantification, urine microscopy should be performed to look for other signs of glomerular disease such as hematuria , RBC cast
- Immunological testing - to identify circulating autoantibodies, abnormal complement levels and pathologic immunoglobulins or immune complexes
- Renal US
- Renal biopsy

Indication of kidney biopsy in patient with proteinuria

- Proteinuria of glomerular or tubular origin without a clear cause
- Progressive proteinuria with rise in creatinine
- Nephrotic syndrome
- Persistent proteinuria greater the 0.5g/24 hours with history of lupus
- Or when there is suspicion of vasculitis
- Patient with longstanding diabetes with progressive microalbuminuria kidney biopsy is not justified , however a diabetic or hypertensive patient who suddenly develops nephrotic range proteinuria often has another cause

Available Treatment Options For People With Uncontrolled Seizures

Content provided by Cyberonics

Epilepsy Connections™
SHARE. EDUCATE. EMPOWER.

Topics for today's discussion

- Seizures and epilepsy
- Drug-resistant epilepsy
- Your treatment options
  - Diet treatments
  - Brain surgery
  - RNS®
  - VNS Therapy®

Seizures

- 5% of the population will have **at least 1 seizure** in their lifetime
- Seizures result from an **electrochemical disorder** in the brain
- Each brain cell either **excites or inhibits** other brain cells
- A seizure is the result of **imbalanced discharges**
- **A seizure is like an electrical storm in the brain**

Fisher, R., Overview of Epilepsy. Epilepsy.com.
What is a Seizure? Accessed from http://www.epilepsy.com/learn/epilepsy-101/what-seizure on August 27, 2014.
What Happens During a Seizure? Accessed from http://www.epilepsy.com/learn/epilepsy-101/what-happens-during-seizure on August 27, 2014.

Seizure terms

Ictal phase: the seizure itself, including the aura

Postictal phase: period after the seizure; "regrouping" time for brain to rest

- Usually seizures are **self-limiting** under 2 minutes
- Status epilepticus: **Life-threatening** event greater than 30 minutes

What Happens During a Seizure? Accessed from http://www.epilepsy.com/learn/epilepsy-101/what-happens-during-seizure on August 27, 2014.
Boggs JG. Mortality Associated with Status Epilepticus. Epilepsy Currents, Vol. 4, No. 1 (January/February) 2004 pp. 25-27.
Seizures. Accessed from http://www.nlm.nih.gov/medlineplus/seizures.html on August 29, 2014.

Types of seizures

- Generalized Seizure – affects the **entire brain**
- Focal Seizures
  - Affect a **single or multiple** different areas of the brain
  - 2 types
    - Simple – **without loss** of consciousness
    - Complex – with change or **loss of consciousness**
  - Seizure symptoms relate to the part of the brain affected by the seizure

Types of Seizures. Accessed from http://www.epilepsy.com/learn/types-seizures on August 27, 2014.
Fisher, R., Overview of Epilepsy. Epilepsy.com.
Simple Partial Seizures. Accessed from http://www.epilepsy.com/learn/simple-partial-seizures on August 27, 2014.
Complex Seizures. Accessed from http://www.epilepsy.com/learn/complex-partial-seizures on August 27, 2014.

Epilepsy

- More than **2 unprovoked** seizures
- Affects **1%** of world's population
- **About 3 million** people in the US have epilepsy

About Epilepsy: The Basics. Accessed from http://www.epilepsy.com/learn/about-epilepsy-basics on August 26, 2014.
WHO Fact Sheet No. 999: Epilepsy. Accessed from http://www.who.int/mediacentre/factsheets/fs999/en on April 24, 2014.
Elliott RE, et al. Impact of Failed Intracranial Epilepsy surgery on the Effectiveness of Subsequent Vagus Nerve Stimulation. Neurosurgery 69:1210-1217, 2011.
Passaro EA. Identification of Potential Epilepsy Surgery Candidates. Accessed from http://emedicine.medscape.com/article/1185635-overview on August 27, 2014.

Treatment goals

- **Reduce the number** of **or eliminate** seizures
- **Reduce the intensity** of seizures
- Minimize or **eliminate the side effects** of treatment
- Improve **recovery period**
- Improve **quality of life**

Wheless Chapter, Figure 2. 2008.

Current treatments available

Medications

Diet treatments

Brain surgery

RNS®

VNS Therapy®

Medications

- There are **more than 20 anti-seizure medications** available in the US
- Most **common** treatment
- Selected based on **individual patient needs**
- Can be prescribed **alone or with other** medications or treatments

Seizure Medication List. Accessed from http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/seizure-and-epilepsy-medicines/seizure-medication-list on August 28, 2014.
Seizure and Epilepsy Medicines. Accessed from http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/seizure-and-epilepsy-medicines on August 28, 2014.
Fisher, R., Overview of Epilepsy. Epilepsy.com.

Medications

- Possible side effects
  - Difficulty thinking, learning, remembering
  - Sleepiness/tiredness
  - Weight changes
  - Liver and kidney problems
  - Depression
  - Dental problems (gum dysplasia)

Side Effects. Accessed from http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/seizure-and-epilepsy-medicines/side-effects on August 28, 2014.
Fisher, R., Overview of Epilepsy. Epilepsy.com.

Drug-resistant epilepsy (aka uncontrolled seizures)

Drug-resistant epilepsy

1. Medicines alone haven't provided adequate seizure control
2. The side effects from medicines may be affecting your quality of life

Epilepsy Treatments Beyond Medication. Epilepsy Foundation.
Kwan P, et al. Lancet Neurol. 2010;9:27-29.
Fisher, R., Overview of Epilepsy. Epilepsy.com.

Drug-resistant epilepsy

- After 2 drugs fail to control seizures, **seizure freedom is not likely** with additional **drug treatments alone**

Mohanraj R and Brodie MJ. Eur J Neurol. 2006:13:277-282.
Kwan P, et al. Lancet Neurol. 2010;9:27-29.
WHO Fact Sheet No. 999: Epilepsy. Accessed June 2014 at http://www.who.int/mediacentre/factsheets/fs999/en/.

Ketogenic Diet

- Most effective in **children**
- **Not a long-term** option (~1-2 years)
- Usually starts with **hospitalization** and fasting
- Diet must be **strictly followed**
- **High in fat**: adequate protein and limited carbohydrates
  - **Eliminates sweets**, **breads and potatoes**
  - All foods are **carefully prepared**
- Possible **side effects :** weight changes, constipation, kidney stones

Epilepsy Treatments Beyond Medication. Epilepsy Foundation. Accessed from http://www.epilepsyfoundation.org/beyond/EF_Brochure_r7.pdf
Ketogenic Diet. Accessed from http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/dietary-therapies/ketogenic-diet on May 22, 2014.

Modified Atkins Diet

- Similar to ketogenic diet in most areas except
  - **Does not start in the hospital** or with fasting
  - No restrictions on **proteins, fluids, or calories** although **fats** are strongly encouraged

Modified Atkins Diet. Accessed from http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/dietary-therapies/modified-atkins-diet on August 28, 2014.

Brain surgery

- Option for both **adults and children**
  - May be appropriate for people who have disabling **complex partial seizures** with or without secondary generalization **with drug-resistant epilepsy**
  - **Less than 10% of people** with drug-resistant epilepsy are candidates

- **Multiple types** of surgeries
  - **Removal** of a lesion, a specific area, or most of one side of the brain
  - **Splitting some connections** in the brain

Epilepsy Treatments Beyond Medication. Epilepsy Foundation. Accessed from http://www.epilepsyfoundation.org/beyond/EF_Brochure_r7.pdf
Passaro EA. Identification of Potential Epilepsy Surgery Candidates. Accessed from http://emedicine.medscape.com/article/1185635-overview on August 27, 2014.

Brain surgery

- **Results vary** by type of epilepsy and type of operation
  - Many people have fewer seizures after surgery, some become seizure-free
  - Results are not always permanent
    - Of those who are seizure-free 2 years after surgery, about 20% start having seizures again within the next 5 years
- Possible **side effects**
  - Post-operative **infection**
  - **Memory** problems
  - **Movement** problems
  - **Sensory** problems

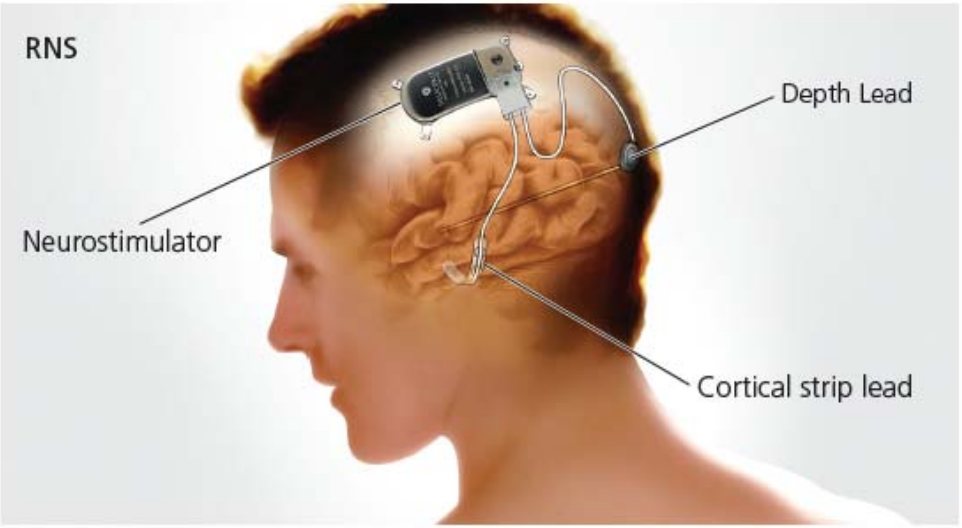
Epilepsy Treatments Beyond Medication. Epilepsy Foundation. Accessed from http://www.epilepsyfoundation.org/beyond/EF_Brochure_r7.pdf
Hirsch, LJ. Long-Term Outcome After Epilepsy Surgery: Relapsing, Remitting Disorder? Epilepsy Currents, Vol. 12, No. 4 (July/August) 2012 pp. 140-142.
Outlook After Surgery. Accessed from http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/surgery/outlook-after-surgery on August 29, 2014.
Fisher, R., Overview of Epilepsy. Epilepsy.com.

RNS®

- **Involves brain surgery** to implant a device into the skull and wires into the parts of the brain where seizures are thought to begin
- Wires send **electrical stimulation into the brain** when abnormal brain activity happens
- Surgery to implant RNS carries the **risks of brain surgery**, including infection and excessive bleeding
- **May require hospital stay** for a few days after surgery

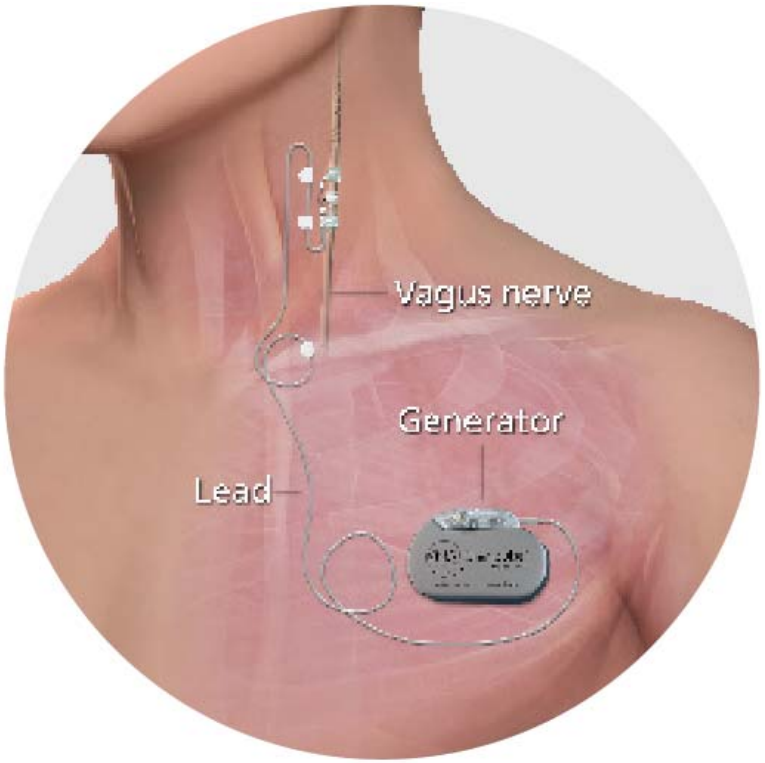
RNS®

- Clinical trials showed that RNS offered **seizure control that improved over time**
- May result in **fewer seizures**
- May result in **improvements in quality of life**
- Battery is typically **replaced every 2 to 3 ½ years** and requires head surgery



VNS Therapy®

- VNS Therapy is **NOT brain surgery**
- It is delivered by a **small device** (similar to a pacemaker) that sends **mild pulses** to the left vagus nerve in the neck
- The **vagus nerve** then sends these pulses to the **brain**
- VNS Therapy delivers these periodic pulses **all day, every day** to potentially reduce or eliminate seizures



VNS Therapy is Approved

- **As adjunctive therapy:** complements medication and other treatment options
- **To reduce the frequency and severity** of seizures
- For epilepsy that is **drug resistant**
- For **depression** that is treatment resistant

VNS Therapy Patient's Manual. Cyberonics, Inc. Houston, Texas. *US Indication.
Brief Summary of Safety Information for the VNS Therapy System (Epilepsy and Depression). Cyberonics, Inc. Houston, Texas.

Handheld patient magnet

The patient magnet

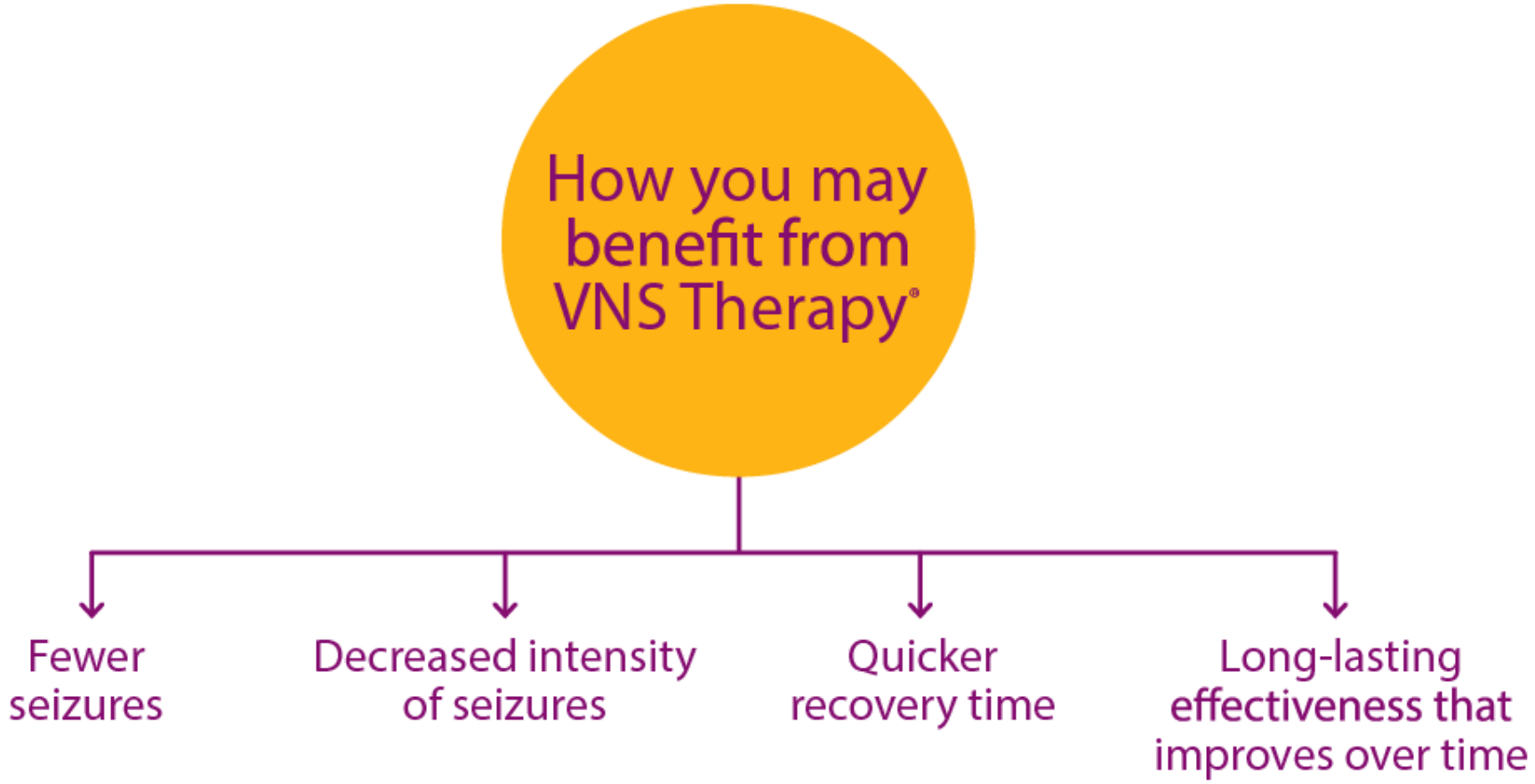
The magnet initiates an extra dose of stimulation that may…

- Shorten the seizure
- Decrease the intensity of the seizure
- Shorten the recovery period following the seizure
- Stop the seizure

Can be used by you or a friend or caregiver
Can be used before or during a seizure
Can also be used to turn device off to control side effects

Morris GL, et al. A retrospective analysis of the effects of magnet-activated stimulation in conjunction with vagus nerve stimulation therapy. Epilepsy Behav 2003;(4):740-745.
Murphy JV, et al. Vagal Nerve Stimulation in Refractory Epilepsy. Arch Pediatr Adolesc med/Vol 157, June 2003.
VNS Therapy Patient's Manual. Cyberonics, Inc.; Houston, Texas. Vonck K, et al. Vagus nerve stimulation and the postical state. Epilepsy Behav 2010; (19):182-185.
Thompson EM, et al. Vagus nerve stimulation for partial and generalized epilepsy from infancy to adolescence. J Neurosurg:Pediatrics, Vol. 10, September 2012.
Helmers SL, et al. Vagus Nerve Stimulation Therapy in Pediatri Patients with Refractory Epilepsy: Retrospective study. Jour of Child Neurology, Vol. 16, No. 11, Nov 2001.4

How you may benefit from VNS Therapy®

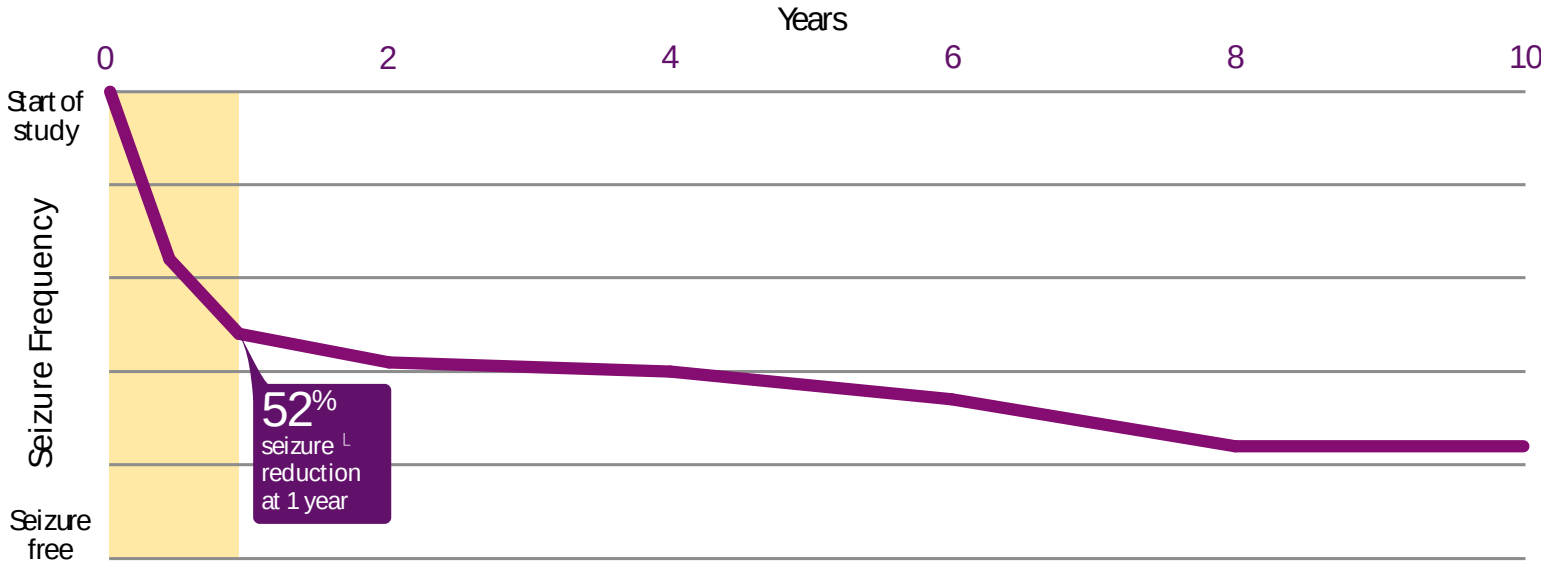


VNS Therapy Patient's Manual. Cyberonics, Inc.; Houston, Texas. Elliott RE, et al. Epilepsy & Behavior 2011:57-63, 2011.Elliott RE, et al. Neurosurgery 69:1210–1217, 2011. Thompson EM, et al. J Neurosurg Pediatr 2012;10:200-205. Klinkenberg S, et al. Dev Med Child Neurol. 2012;54(9):855-861.
Helmers SL, et al. J Child Neurol. 2001;16:843- 848. Vonck K, et al. Epilepsy Behav. 2010;19(2);182-185.
Murphy JV, et al. Arch Pediatr Adolesc Med. 2003;157(6):560-564. Elliott RE, et al. Epilepsy Behav. 2011;20(3):478-483.

Reductions in number of seizures with VNS Therapy improve over time

After 1 year with VNS Therapy,® seizures were reduced by more than 50%

As the study went on, the number of seizures continued to decrease



These are results of a 10-year study in 65 patients. Your results with VNS Therapy may be different.

Elliott RE, et al. Epilepsy & Behavior 2011;20: 478-483.

Other VNS Therapy® benefits

- Provides treatment automatically; no need to turn it on or be aware of an oncoming seizure
- Medicine may be reduced in some cases
- May improve alertness, mood, and other aspects of quality of life

VNS Therapy Patient's Manual. Cyberonics, Inc.; Houston, Texas.
Thompson EM, et al. J Neurosurg Pediatr 2012;10:200-205.
Helmers SL, et al. J Child Neurol. 2001;16:843- 848.
Vonck K, et al. Vagus nerve stimulation and the postical state. Epilepsy Behav 2010; (19):182-185.

VNS Therapy can be used with medications

VNS Therapy® can be used in addition to medicine and does not cause the following side effects:

Depression

Dizziness

Confusion

Sleepiness

Low energy

Possible side effects

- Hoarseness/changes in voice tone
- Tickling sensation in the throat or on the neck
- Coughing
- A feeling of shortness of breath

Side effects typically occur during stimulation and usually decrease over time

If you experience side effects, your physician may be able to adjust your settings and improve your comfort level

VNS Therapy Patient's Manual. Cyberonics, Inc. Houston, Texas.
Elliott RE, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: Long-term outcomes and predisctors of response. Epilepsy Behav 20 (2011) 57-63.

VNS Therapy procedure

The VNS Therapy® procedure

Simple, 1- to 2-hour procedure

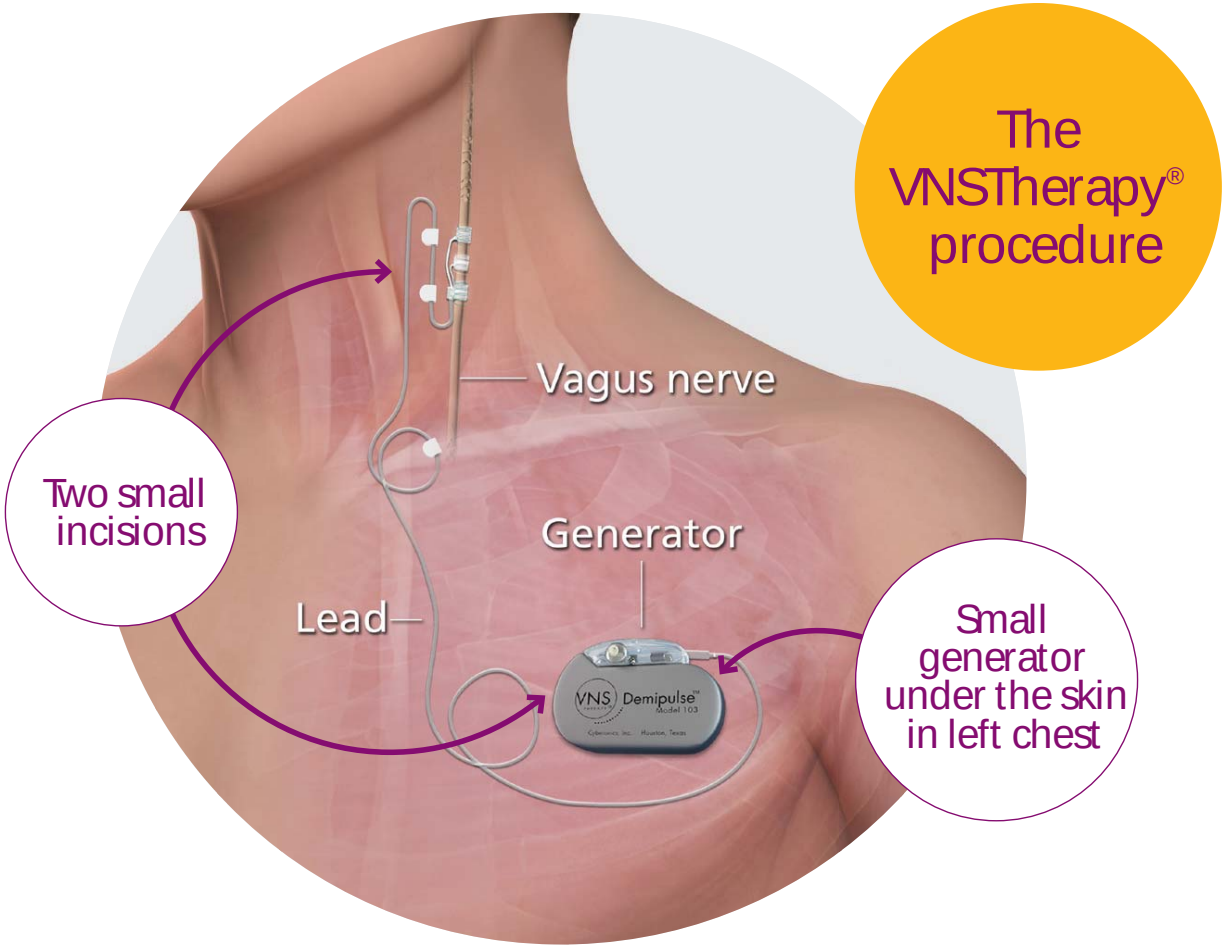
Can be done as an outpatient procedure or overnight stay in hospital

Under general anesthesia

VNS Therapy is NOT brain surgery

VNS Therapy Patient's Manual. Cyberonics, Inc. Houston, Texas.
Elliott RE, et al. Neurosurgery 69:1210-1217, 2011.

VNS Therapy procedure



- Risks of the procedure can include a small chance of infection at the incision site.

VNS Therapy is customized for you

VNS Therapy is **adjusted to your needs** by your healthcare professional

- Frequent clinic visits in the first few months to **check and adjust settings**
- Once settings are optimal, **regular follow-up visits** to monitor device and battery life
- A common dose is **30 seconds of stimulation every 5 minutes**
- Your physician will choose the proper dose to **fit your needs**

Battery replacement

Battery replacement

- 3-8 year lifetime
  Depending on VNS Therapy settings
- 1 small incision needed
- Only generator is replaced

VNS Therapy is safe

- More than 80,000 people worldwide have received VNS Therapy
- No known interactions with any medicines
- VNS Therapy can be combined with other treatments
- No increase in sudden, unexpected death in epilepsy (SUDEP)
- An animal study showed no evidence of impaired fertility or harm to the fetus due to VNS Therapy
- Pregnancies have gone to term with VNS Therapy
- MRIs are possible. Talk with your doctor first.

VNS Therapy Patient's Manual. Cyberonics, Inc. Houston, Texas. Annegers JF, et al. Epilepsia. 1998;39:206-212. Ben-Menachem E. Jour of Clin Neurophysiology 18(5):415-418. 2001. Husain MM, et al. Ann Gen Psychiatry. 2005;4:16. Houser MV, et al. Obstet Gynecol 2010;115:417–9. Danielsson et al. Brain Stimulation. 2009;2:41-9. Ben-Menachem E, et al. Lancet Neurology. Elliott RE, et al. Epilepsy Behav 20 (2011) 57-63. VNS Therapy Physician's Manual. Cyberonics, Inc. Houston, Texas. 2002;1:477-82. Data on file. Cyberonics, Inc. Houston, TX.

Next steps

Next steps/ for more information

Your physician's office or VNS Therapy® Nurse Case Manager can set up a consultation for the VNS Therapy procedure.

Talk to a VNS Therapy Nurse Case Manager directly at 1-888-867-7846.

Ask your physician how to contact a local VNS Therapeutic Consultant.

Join a monthly conference call and hear from real patients about their lives before and after VNS Therapy. The calls take place the first Tuesday of every month at 7:00 PM CST: 1-877-451-8943.

Visit www.VNSTherapy.com

Connect with us

Become part of the community

Visit www.VNSTherapy.com and click Contact Us.

Talk with a VNS Therapy Nurse Case Manager.
Ask how to connect with Epilepsy Connections Ambassadors to hear their epilepsy and VNS Therapy experiences.

Like us on Facebook and join the discussion
www.facebook.com/VNSTherapyforEpilepsy

Safety Information for VNS Therapy

INTENDED USE / INDICATIONS—UNITED STATES

Epilepsy—VNS Therapy is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures which are refractory to antiepileptic medications.

CONTRAINDICATIONS

VNS Therapy cannot be used in patients after a bilateral or left cervical vagotomy. Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with the VNS Therapy system. Diagnostic ultrasound is not included in this contraindication. Injury or damage can occur during diathermy treatment whether the VNS Therapy system is turned “ON” or “OFF.”

WARNINGS

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy System Physician’s Manual, including information that VNS Therapy may not be a cure for epilepsy. Since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, or in strenuous sports that could harm them or others. The safety and efficacy of VNS Therapy has not been established for uses outside of its approved indications. A malfunction of the VNS Therapy system could cause painful or direct current stimulation, which could result in nerve damage. Patients should use the magnet to stop stimulation if they suspect a malfunction, and contact their physician immediately for further evaluation. Removal or replacement of the VNS Therapy system requires an additional surgical procedure. Patients who have pre-existing swallowing, cardiac, or respiratory difficulties (including, but not limited to, obstructive sleep apnea and chronic pulmonary disease) should discuss with their physicians whether VNS Therapy is appropriate for them since there is the possibility that stimulation might worsen their condition. VNS Therapy may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. MRI can be safely performed; however, special equipment and procedures must be used.

PRECAUTIONS

The safety and efficacy of VNS Therapy has not been established for use during pregnancy. Patients who smoke may have an increased risk of laryngeal irritation. There is a risk of infection with the implantation surgery that may require the use of antibiotics to treat or removal of the device. The VNS Therapy system may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable devices, careful programming of each system may be necessary to optimize the patient's benefit from each device.

ADVERSE EVENTS

The most commonly reported side effects from stimulation include hoarseness (voice alteration), paresthesia (prickling feeling in the skin), dyspnea (shortness of breath), sore throat and increased coughing. Other adverse events reported during clinical studies as statistically significant are ataxia (loss of the ability to coordinate muscular movement); dyspepsia (indigestion); hypesthesia (impaired sense of touch); insomnia (inability to sleep); laryngismus (throat, larynx spasms); nausea; pain; pharyngitis (inflammation of the pharynx, throat); and vomiting. These typically occur only during stimulation, are well tolerated and noticed less as time goes on. The most commonly reported side effect from the implant procedure is infection.

*THE INFORMATION CONTAINED IN THIS SUMMARY REPRESENTS PARTIAL EXCERPTS OF IMPORTANT PRESCRIBING INFORMATION TAKEN FROM THE PRODUCT LABELING. THE INFORMATION IS NOT INTENDED TO SERVE AS A SUBSTITUTE FOR A COMPLETE AND THOROUGH UNDERSTANDING OF THE VNS THERAPY SYSTEM NOR DOES THIS INFORMATION REPRESENT FULL DISCLOSURE OF ALL PERTINENT INFORMATION CONCERNING THE USE OF THIS PRODUCT. PATIENTS SHOULD DISCUSS THE RISKS AND BENEFITS OF VNS THERAPY WITH THEIR HEALTHCARE PROVIDER. PRESCRIPTION ONLY - DEVICE RESTRICTED TO USE BY OR ON THE ORDER OF A PHYSICIAN.

VNS Therapy Physician’s Manual. Cyberonics, Inc. Houston, Texas.

Questions?

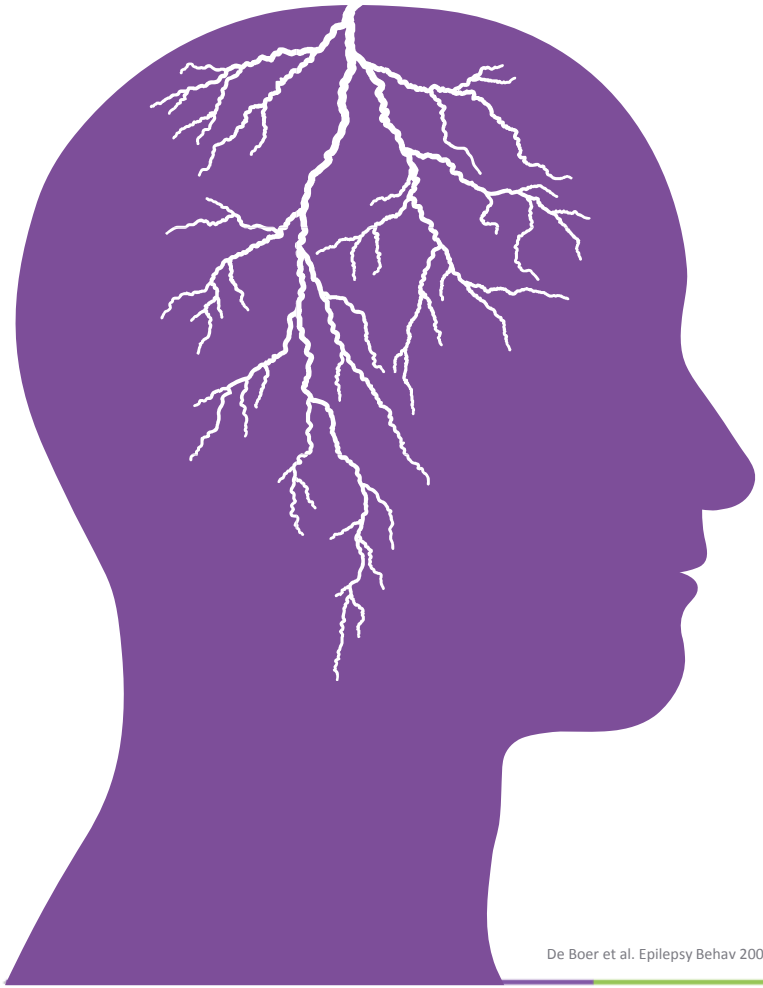
For more information, please contact Cyberonics or your healthcare provider.

Content provided by Cyberonics

Advancing the Treatment of **Drug-Resistant Epilepsy**

VNS Therapy®

Epilepsy is not a benign disease



Epilepsy is among the **most common serious neurological conditions, affecting 1 in 26 people**

Has **no geographic, social,** or **racial boundaries**

Affects **people of all ages**

Frequently associated with **comorbidities, not just seizures**

Has a **high rate of premature death** compared with the general population

De Boer et al. Epilepsy Behav 2008;12:540-546.

DinPPTPhy16U11

Mortality in epilepsy: perspective and urgency

Takes more lives than

Breast cancer

50,000 vs. 40,290 annually in US[1,2]

Every hour

5

die of epilepsy related causes[1]

Uncontrolled seizures

increased risk of premature death[3]

1. Epilepsy Foundation Stats and Facts. Accessed June 2015. 2. American Cancer Society – Key Statistics about Breast Cancer. Accessed June 2015. 3. Nevalainen O, et al. Neurology 2014;83(21):1968-1977.

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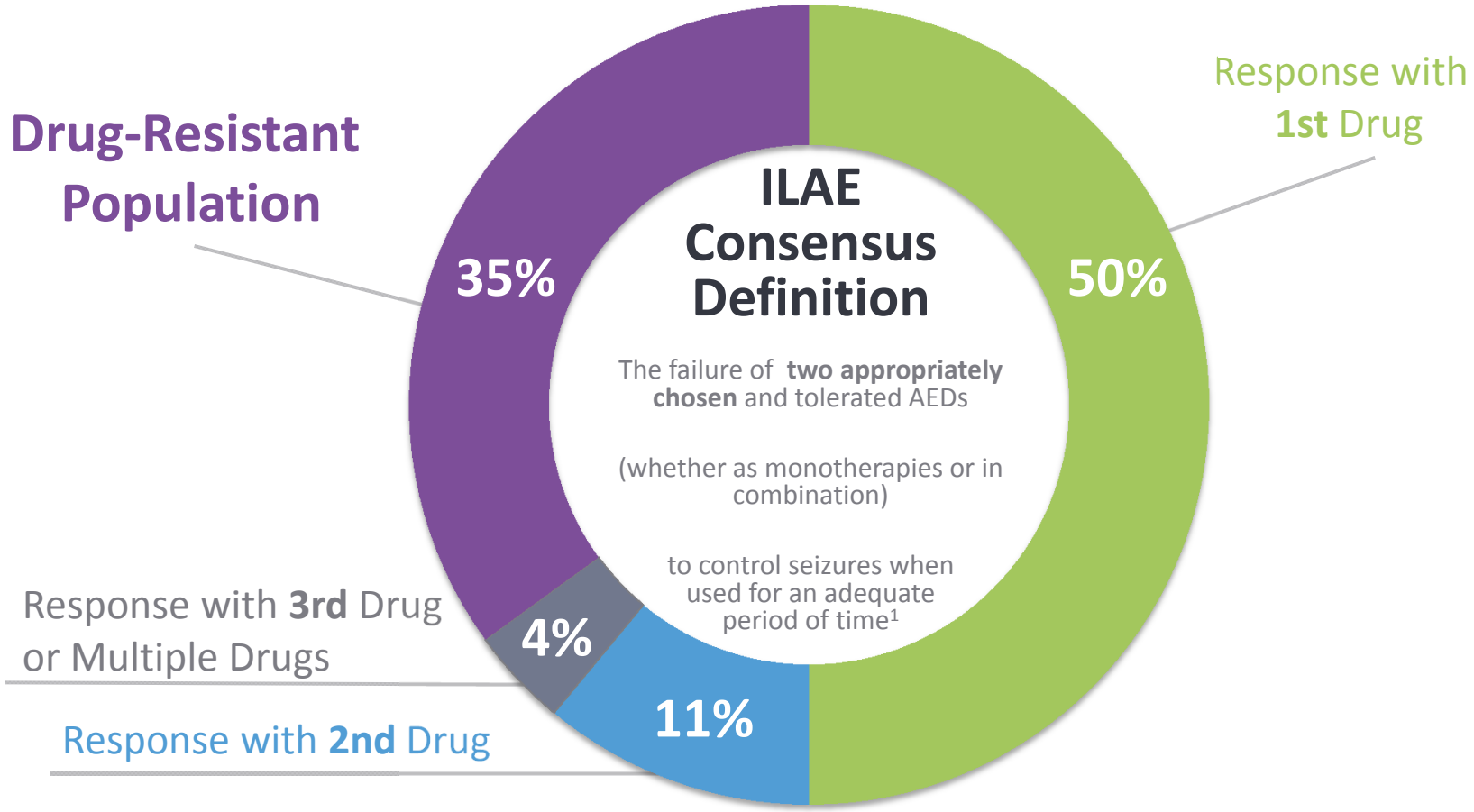
What is drug-resistant epilepsy (DRE)?



After adequate trials of **at least 2 AEDs**, overall seizure freedom rates with subsequent AED trials are dramatically decreased[2]

1. Kwan P, et al. Epilepsia 2010;51:1069-77. 2. Mohanraj R, et al. Eur J Neurol 2006;13:277-282.

DinPPTPhy16U11

Consequences of drug-resistant epilepsy extend beyond seizures

Seizure-related injuries[1,3]

Increased healthcare utilization[9-11]

Increased mortality and **morbidity**[1,6-8]

Depression, **anxiety** and **sleep disturbance**[1-4]

Cognitive and **memory impairment**[1,3,5]

Adverse effects with **long-term AED use**[1-4]

Impaired ability to

- **Obtain education**
- **Work**
- **Drive**
- **Establish families**
- **Develop** and **maintain social relations**[2,3]

Impact beyond patient (family, caregivers, etc.)[2]

1. Schmidt D. Epilepsy Res 2002;50:21-32. **2.** Wheless JW. Epilepsy Behav 2006;8:756-64. **3.** Fisher RS, et al. Epilepsy Res 2000;41:39-51. **4.** Gilliam F. Neurology 2002;58:S9-S20.
5. Meador KJ. Neurology 2002;58(suppl 5):S21-S26. **6.** Lhatoo SD, et al. Postgrad Med J 1999;75:706-709. **7.** Annegers JF, et al. Epilepsia 1998;39:206-212. **8.** Van Ness PC. Arch Neurol 2002;59:732-735.
9. Labiner DM, et al. Neurology 2010;74:1566-1574. **10.** Helmers SL, et al. Epilepsy Behav 2010;18:437-44. **11.** Faught E, et al. Epilepsia 2009;50:501-509.

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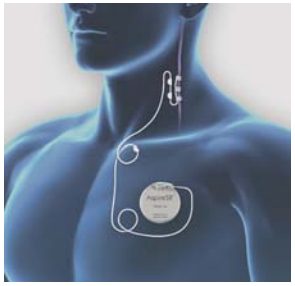
Treatment options for drug-resistant epilepsy

Comprehensive Epilepsy Evaluation

VNS Therapy



Brain Surgery

Resection

Corpus Callosotomy

Multiple Subpial Transsections

Stereotactic Laser Ablation

RNS

Diet

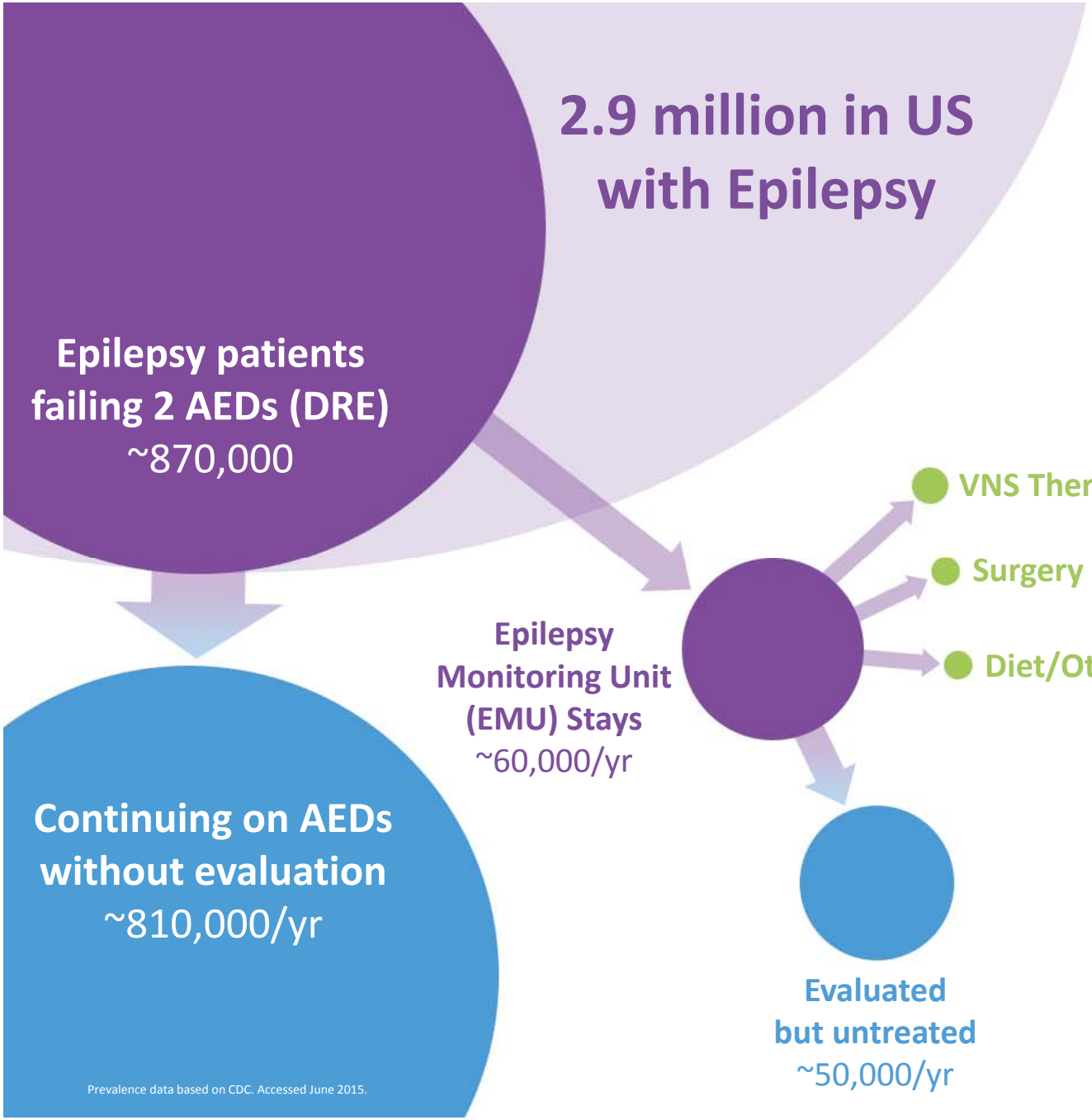
Ketogenic

Modified Atkins

Low glycemic index

Other

Other pharmacologics



Treatment gap for drug-resistant epilepsy

Only 1-2% of DRE patients receive treatment each year

VNS Therapy

ADDRESSING THE TREATMENT GOALS FOR DRUG-RESISTANT EPILEPSY

Treatment goals and strategies shift for DRE

Newly Diagnosed Epilepsy

Treatment Goals

- No seizures
- No side effects

+

Drug-Resistant Epilepsy

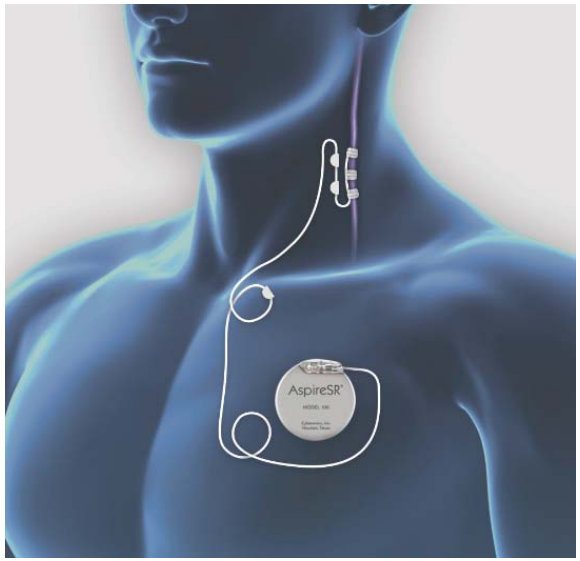
Treatment Goals

- Optimize long-term seizure control
- Maximize quality of life
- Minimize side effects
- Maximize adherence
- Decrease seizure severity/postictal period

Kwan P, et al. Epilepsia 2009;50(Suppl. 8):57–62. Gilliam F. Neurology 2002;58:s9-s19. Faught E, et al. Epilepsia 2009;50(3):501-509.

Introduction to VNS Therapy

- **Controls seizures** by sending mild pulses to the left vagus nerve in the neck at regular intervals all day, every day
- **Short outpatient procedure**, typically 1-2 hours



Indication

Approved in the US in **1997** for use as an **adjunctive** therapy in reducing the frequency of seizures

- in adults and adolescents over 12 years of age
- with partial onset seizures that are refractory to antiepileptic medications

VNS Therapy Physician's Manual, Cyberonics, Inc. Houston ,TX.

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VNS Therapy is the most established device solution for DRE

>85,000

patients treated[1]

>25 years

worldwide patient experience[1]

>1,000

peer-reviewed publications on VNS Therapy

Assessed 3 times by AAN

Evidence confirmed VNS Therapy for epilepsy is both **effective** and **safe**[2-4]

1. Data on File, Cyberonics, Inc. Houston, TX. 2. Fisher RS, et al. Neurology 1997;49:293-297. 3. Fisher RS, Handforth A. Neurology 1999;53:666-9. 4. Morris GL, et al. Neurology 2013;81:1453-9.

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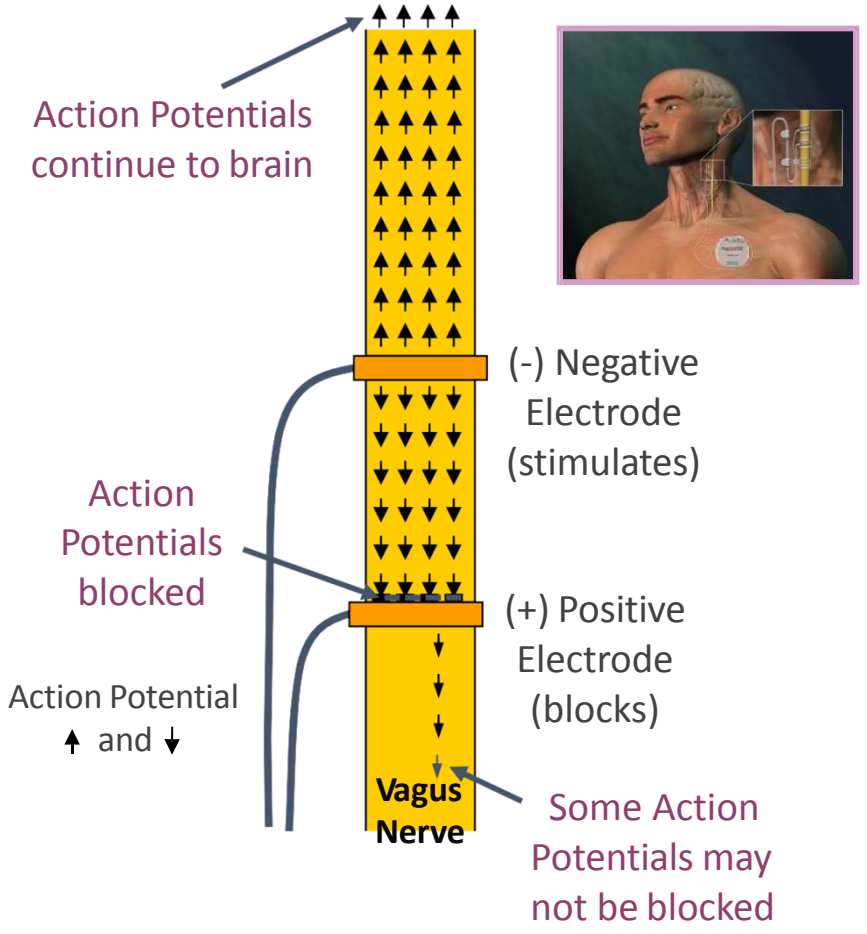
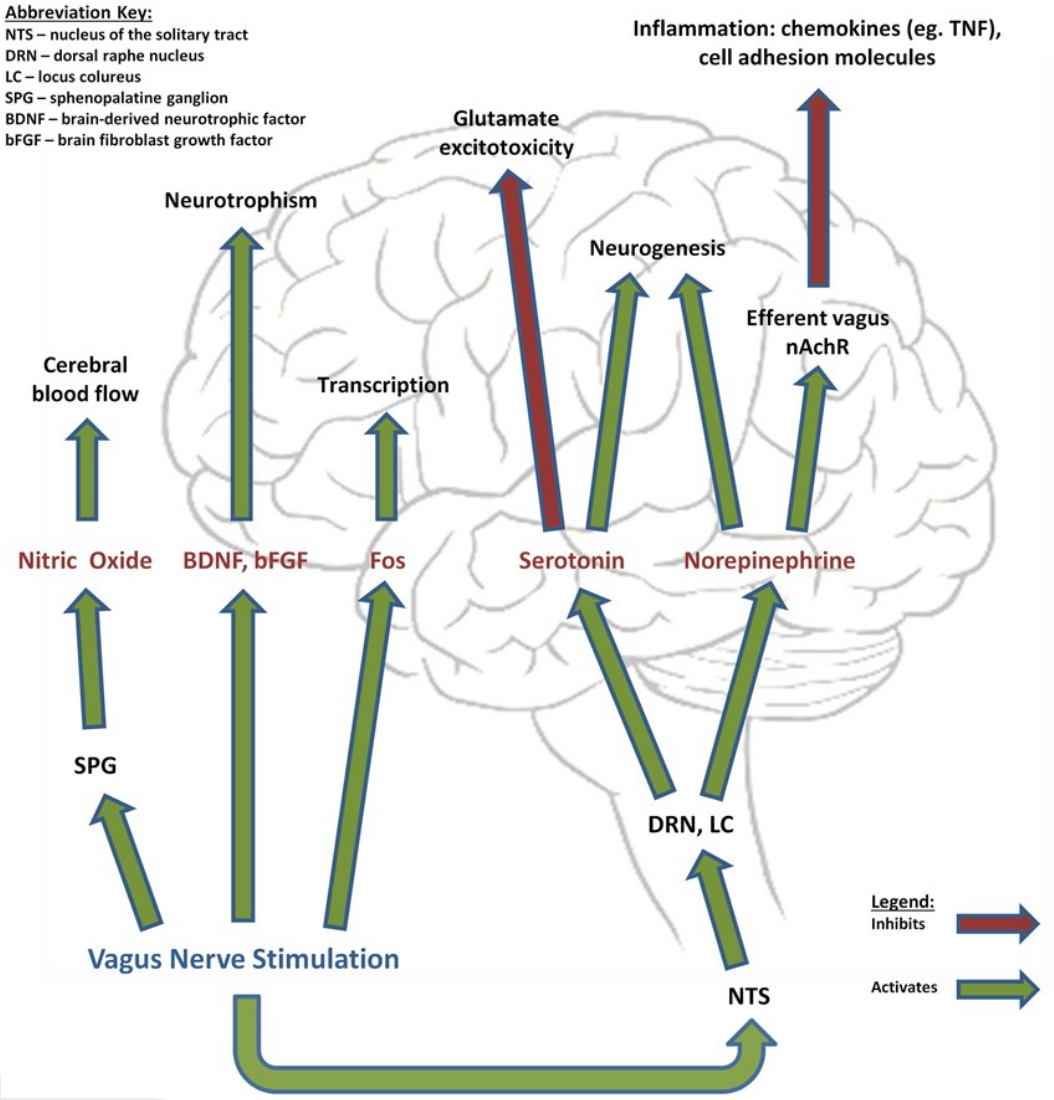
Action potential propagation

Negative electrode **generates action potentials** that **travel afferently** via sensory fibers

Efferently traveling action potentials **are mostly blocked** by positive electrode to minimize side effects



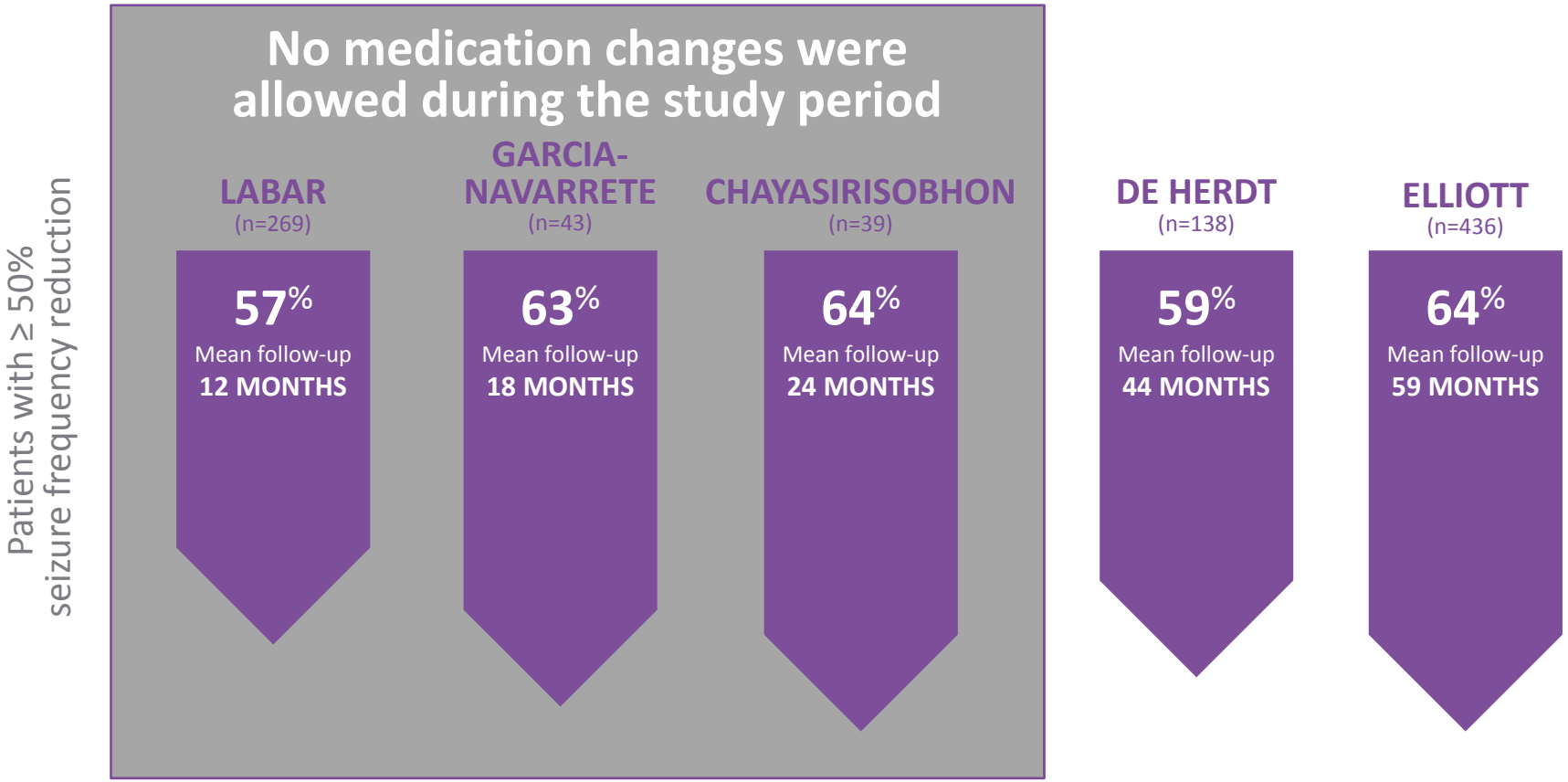
VNS Therapy impacts multiple structures and functions



- Neurotransmitter Expression[1-7]
- Cerebral blood flow[8,9]
- Neurotrophism[10]
- Neurogenesis[10]
- Excitotoxicity[10]
- Inflammation[10]

1. Roosevelt RW, et al. Brain Res 2006;1119(1):124-32. 2. Hassert DL, et al. Behavioral Neuroscience 2004;118(1):79-88. 3. Woodbury DM and Woodbury JW. Epilepsia 1990;31 (Suppl. 2):S7-S19.
4. Hammond BM, et al. Brain Research 1992;583:300-3. 5. Ben-Menachem E, et al. Epilepsy Res 1995;20:221-7. 6. Marrosu F, et al. Epilepsy Res 2003;55:59-70. 7. Krahl S, et al. Epilepsia. 1998;39:709-714. 8. Henry TR, et al. Epilepsia. 2004;45(9):1064-1070. 9. Vonck K, et al. Seizure 2008; 17(8):699-706. 10. Cai et al. Front Neurol 2014;5:107.

Long-term effectiveness confirmed across multiple studies



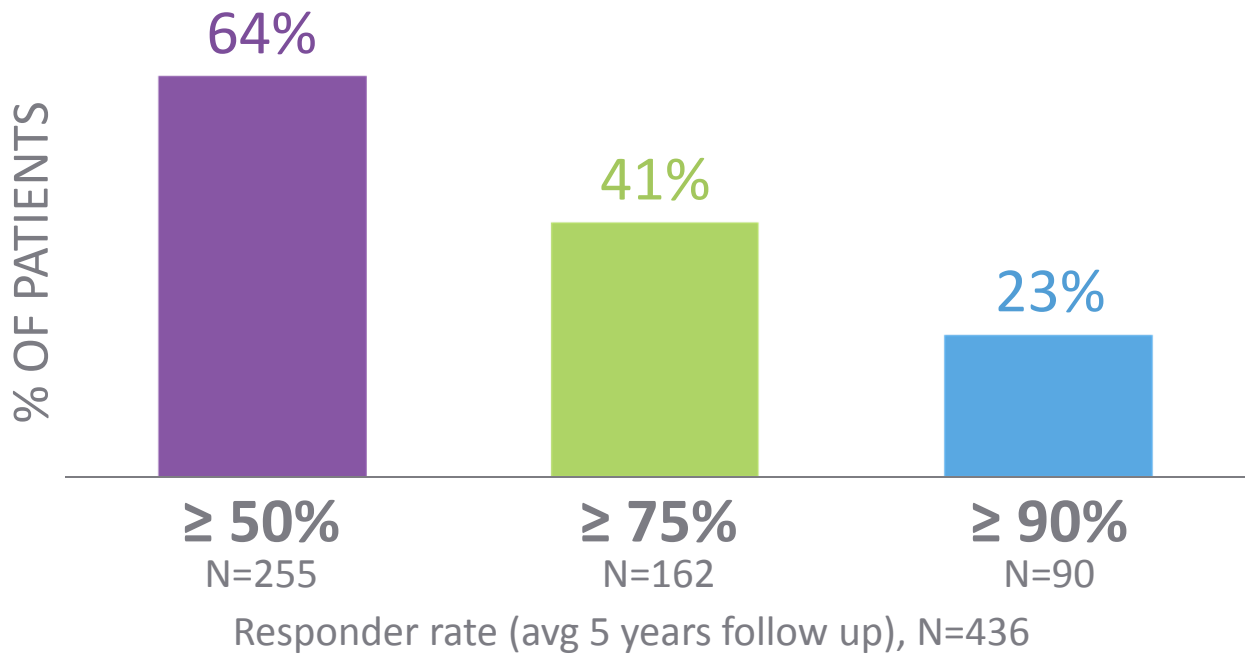
1. Labar DR. Seizure 2004;13:392-8. 2. Garcia-Navarrete E, et al. Seizure. 2013;22(1):9-13. 3. Chayasirisobhon S, et al. J Neurol Neurophysiol 2015;6:1. **4.** De Herdt V, et al. Eur J Paediatr Neurol 2007;11:261-9.
5. Elliott RE, et al. Epilepsy Behav 2011;20(1):57-63.

DinPPTPhy16U11

Elliott NYU study: Full cohort responder rates

Patient characteristics:

- **2.7** AEDs at baseline (mean)
- **5.6** AEDs failed (mean)
- **19.2** years mean duration of epilepsy
- **29%** prior brain or epilepsy surgery



Elliott RE, et al. Epilepsy Behav 2011;20:57-63.

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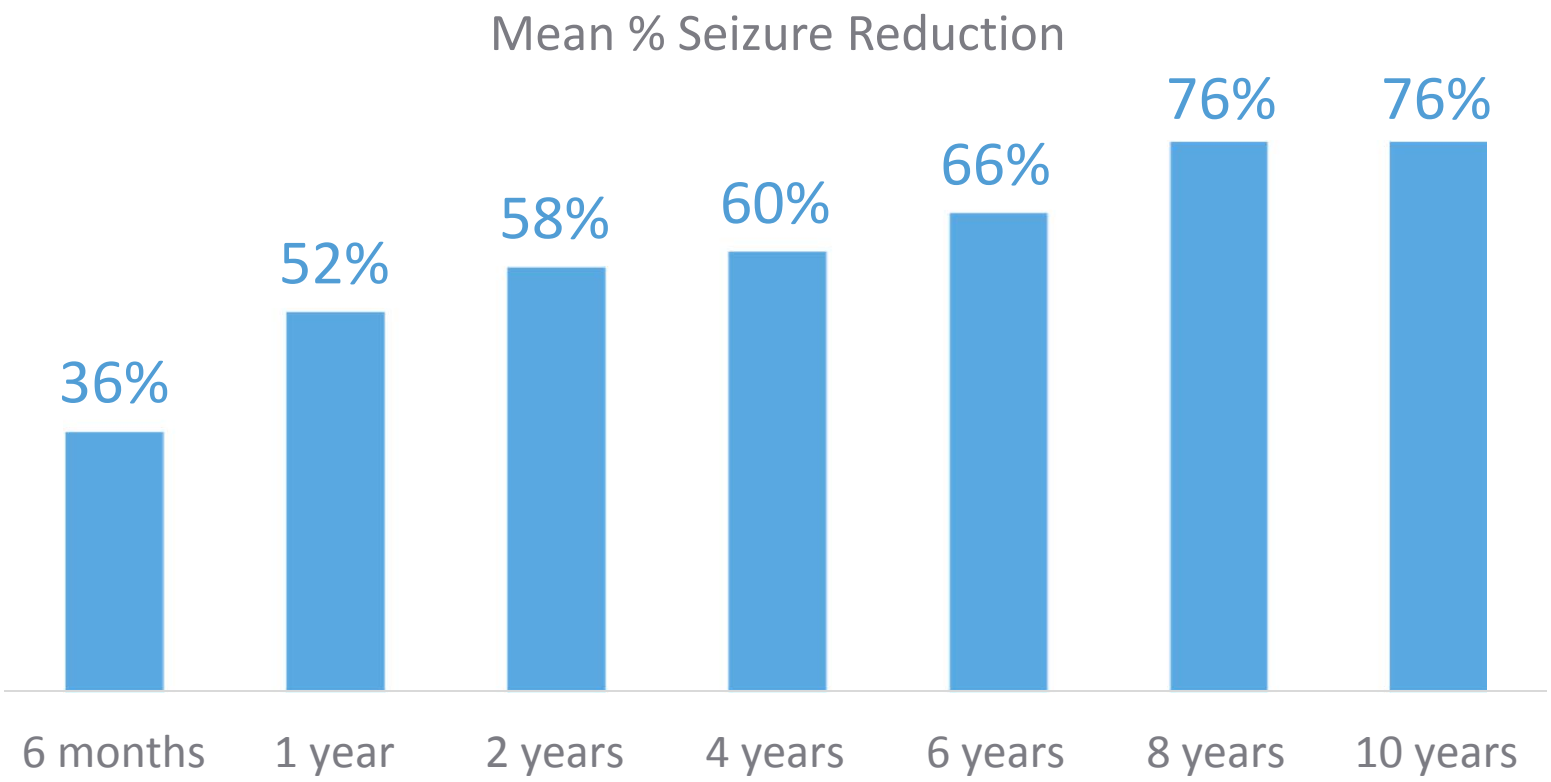
Seizure reduction that continues to improve over time



Seizure frequency was **significantly reduced** from baseline at each of the recorded intervals ($p<0.01$); N=65

Elliott RE, et al. Epilepsy Behav 2011;20(3):478-483.

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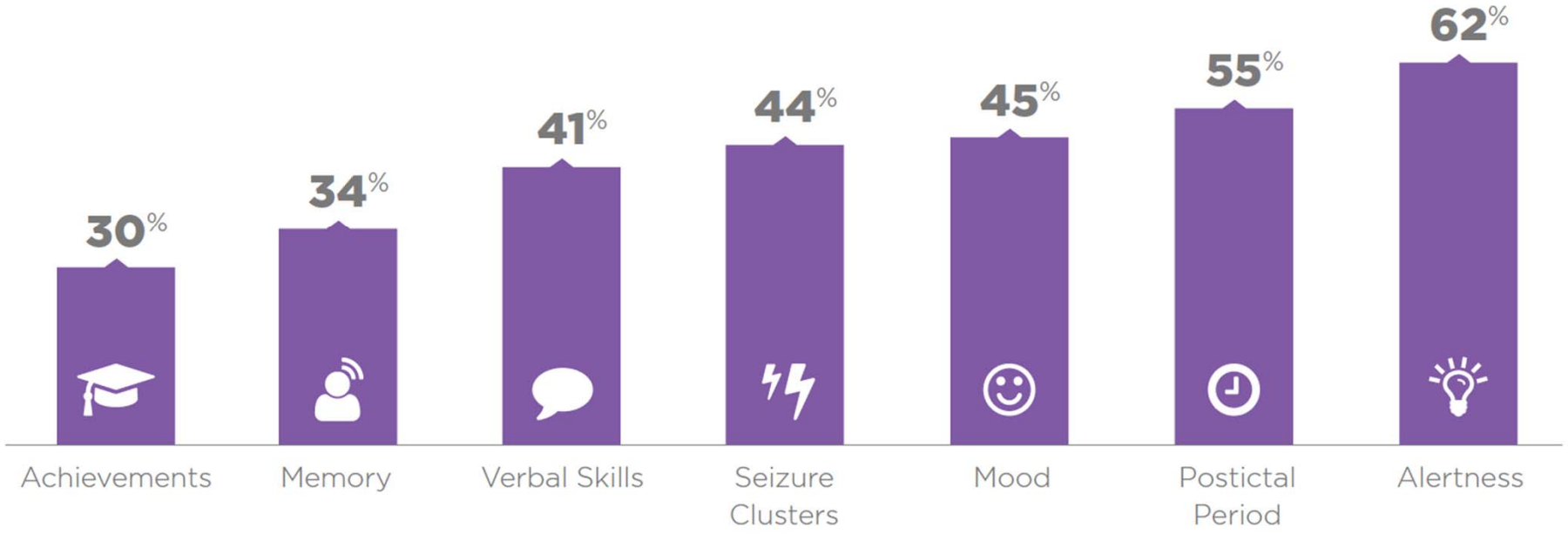
Quality of life improvements
Independent of seizure control

Quality of Life Improvement from
Patient Outcome Registry



Improvement was defined as patient being "better" or "much better" at 12 months (N=2,229)

Data on File, Cyberonics, Inc. Houston, TX.

PuLsE Trial

The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: The PuLsE (Open Prospective Randomized Long-term Effectiveness) trial

*Philippe Ryvlin, †Frank G. Gilliam, ‡Dang K. Nguyen, §Gabriella Colicchio, ¶Alfonso Iudice, #Paolo Tinuper, **Nelia Zamponi, ††Umberto Aguglia, ‡‡Louis Wagner, §§Lorella Minotti, ¶¶Hermann Stefan, ##Paul Boon, ***Mark Sadler, †††Paolo Benna, ‡‡‡Pradheep Raman, and §§§Emilio Perucca

Study

Prospective, long-term, open-label, randomized, parallel-group study of VNS Therapy vs Best Medical Practice (BMP) in 112 patients with DRE

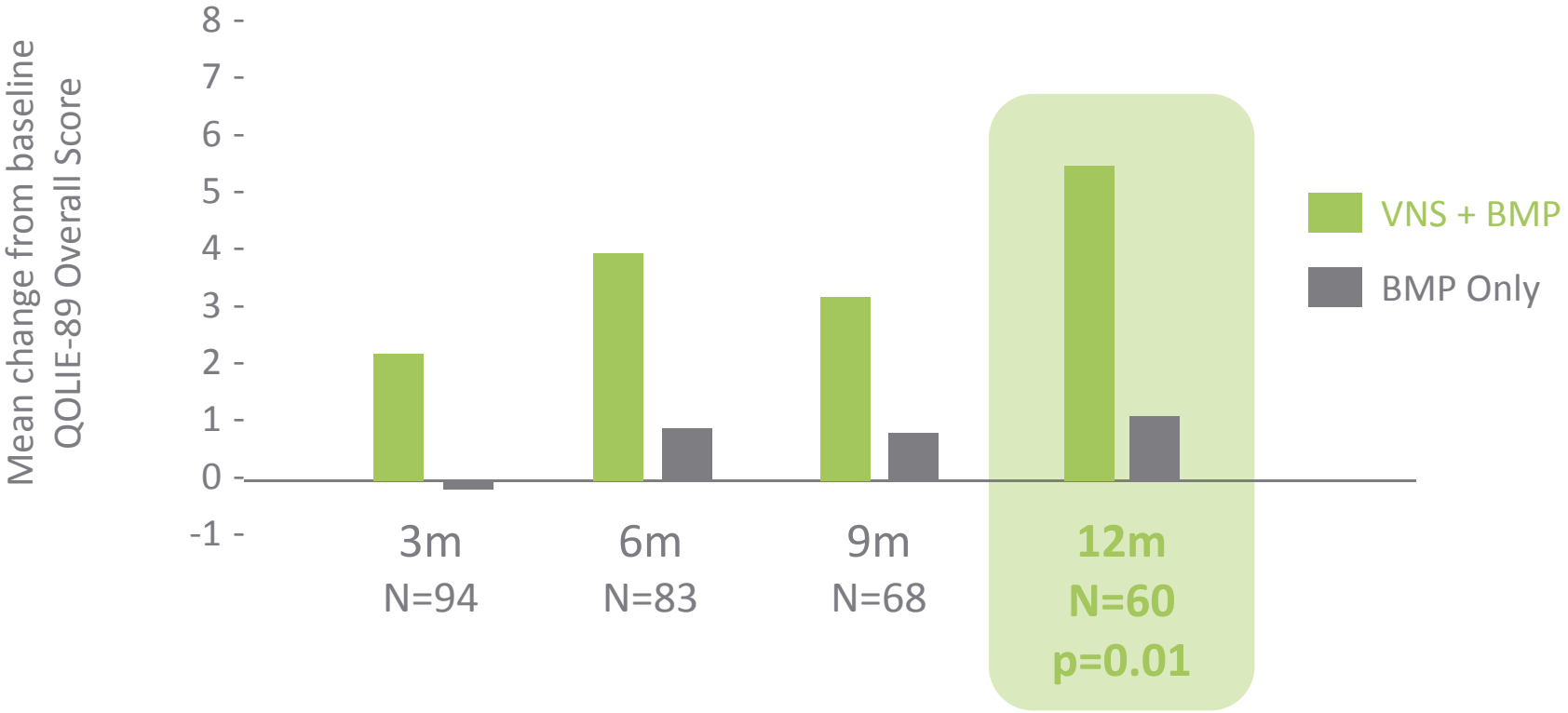
Outcome

VNS Therapy + Best Medical Practice (BMP) resulted in a **significant improvement** in quality of life (QOL) compared with BMP alone

Ryvlin P, et al. Epilepsia 2014; 55(6):893–900.

Superior quality of life with VNS Therapy vs AEDs alone

VNS Therapy + Best Medical Practice (BMP) provides significant improvement in quality of life compared with BMP alone at 12 months



Ryvlin P, et al. Epilepsia 2014; 55(6):893–900.

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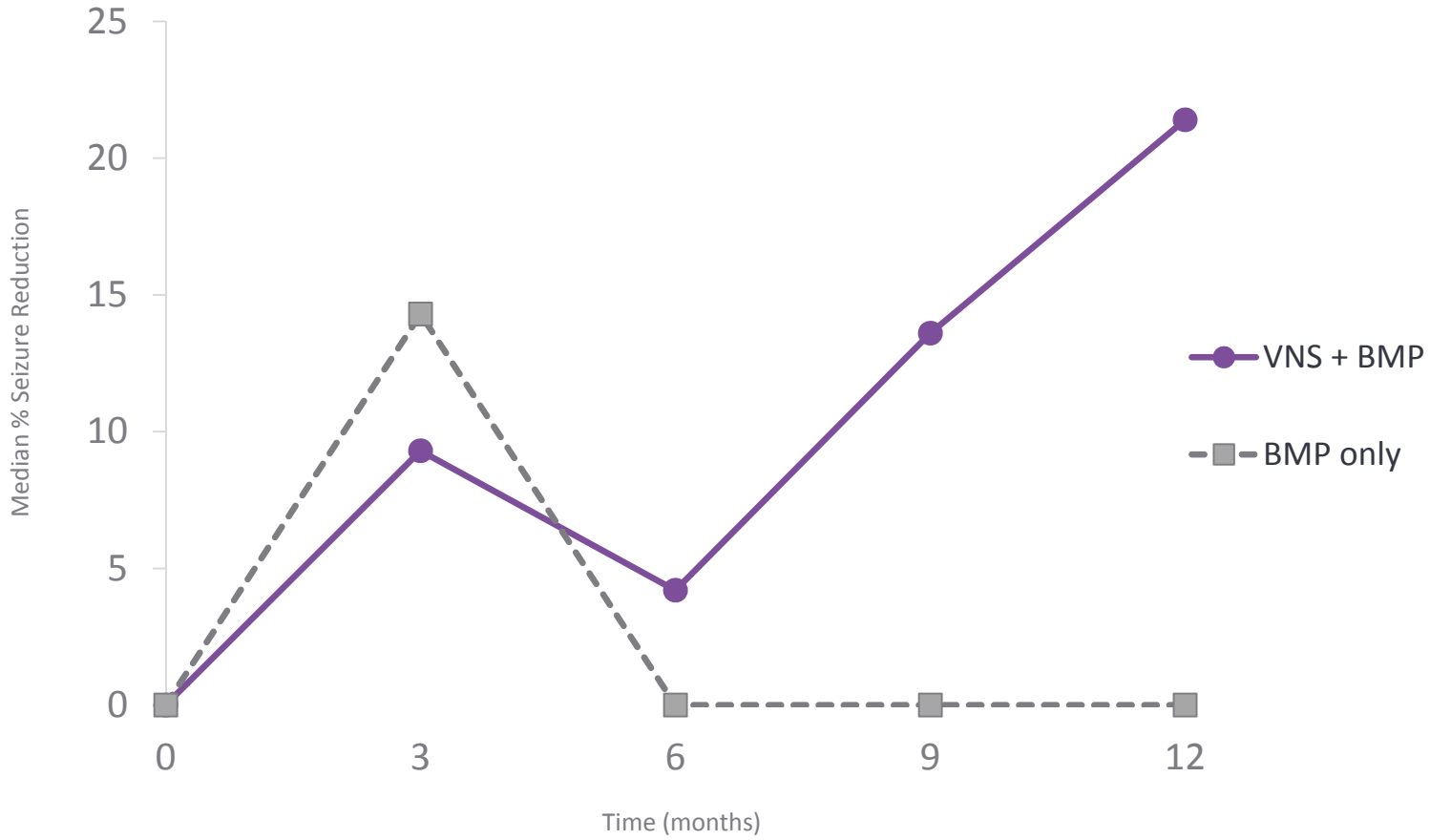
No "Honeymoon Effect" with VNS Therapy

Effectiveness increases over time



Ryvlin P, et al. Epilepsia 2014; 55(6):893–900.

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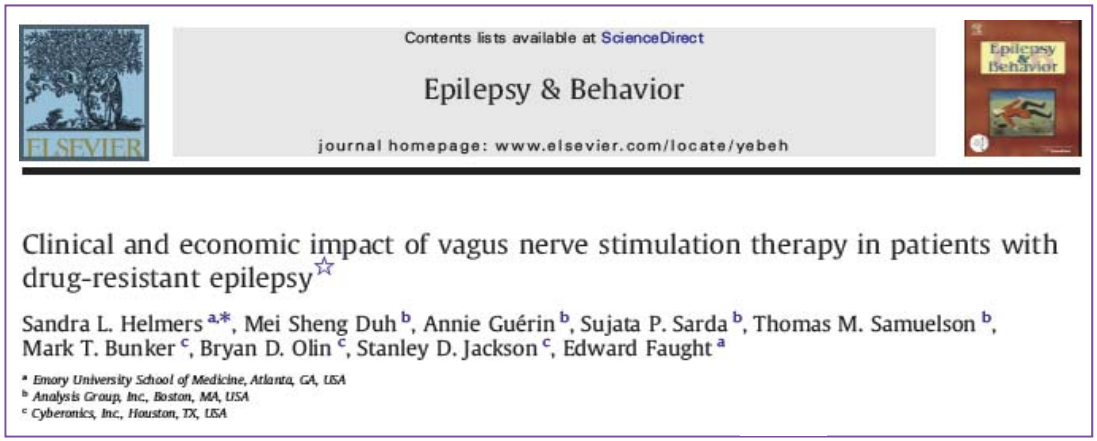
Healthcare Utilization & Cost



Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy☆

Sandra L. Helmers [a,*], Mei Sheng Duh [b], Annie Guérin [b], Sujata P. Sarda [b], Thomas M. Samuelson [b], Mark T. Bunker [c], Bryan D. Olin [c], Stanley D. Jackson [c], Edward Faught [a]

[a] Emory University School of Medicine, Atlanta, GA, USA
[b] Analysis Group, Inc., Boston, MA, USA
[c] Cyberonics, Inc., Houston, TX, USA

Study

Long-term medical and economic benefits of VNS Therapy in DRE

Retrospective, pre–post analysis using multistate Medicaid data from January 1997–June 2009

Outcome

Lower use of healthcare resources

Lower occurrence of epilepsy-related comorbidities

Lower total healthcare cost, a net cost savings after 1.5 years

Helmers SL, et al. Epilepsy Behav 2011;22:370-5.

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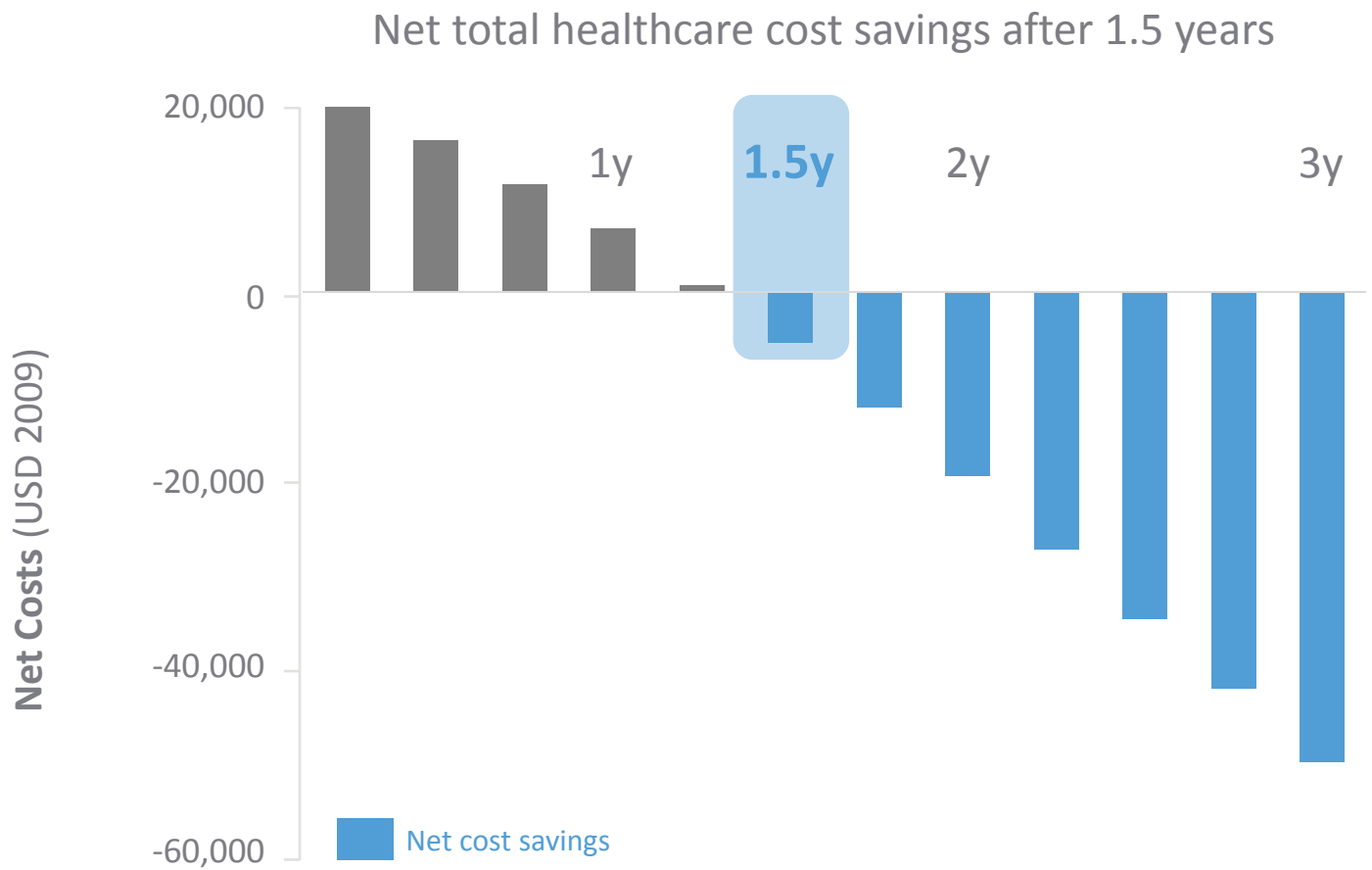
Significant total healthcare cost savings



*Negative net costs indicate lower costs in the Post-VNS period relative to the mean quarterly cost in the Pre-VNS period. (N=1,655)

Adapted from Helmers SL, et al. Epilepsy Behav 2011;22:370-5.

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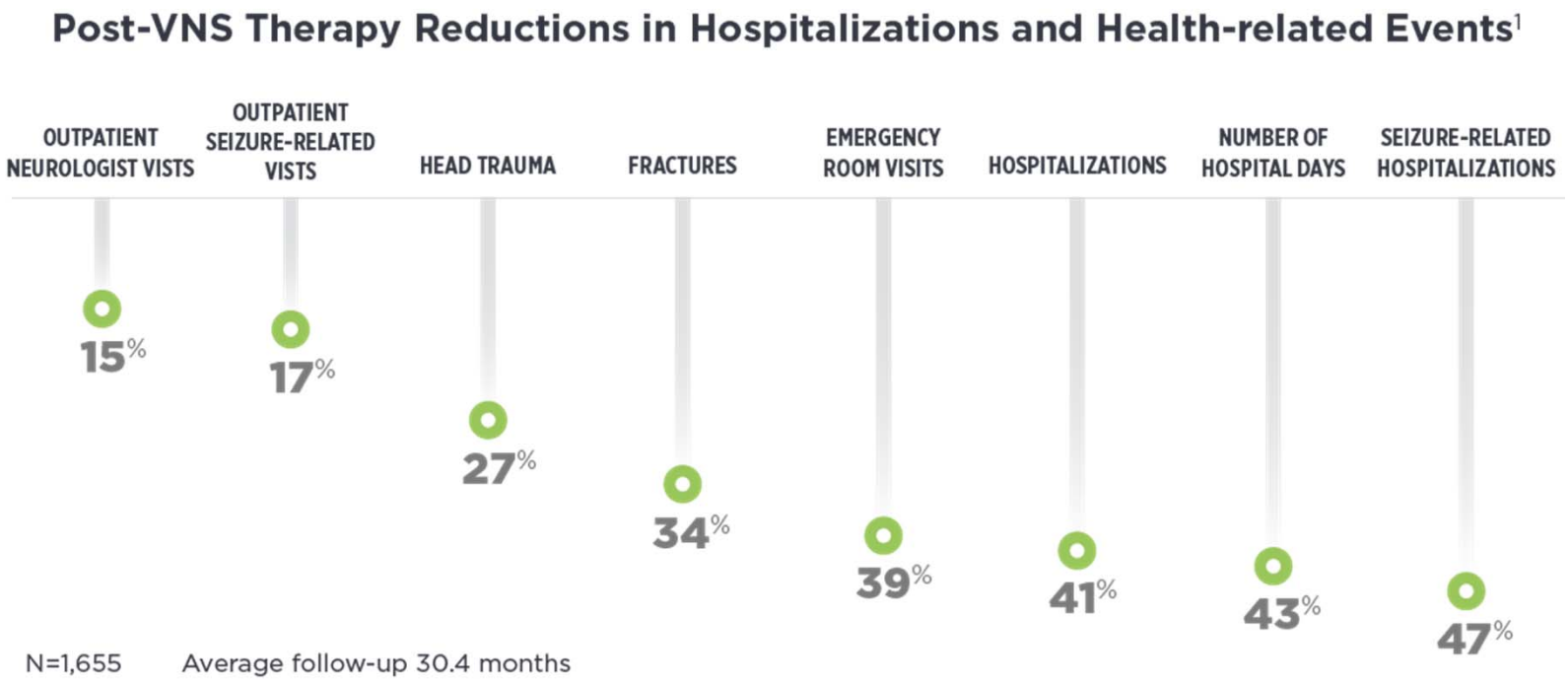
Resource utilization and epilepsy-related clinical events were significantly reduced



1. Adapted from Helmers SL, et al. Epilepsy Behav 2011;22:370-5.

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Positive impact on SUDEP rates

After 2 years of VNS Therapy, SUDEP rates are:

Significantly lower compared to the first 2 years of VNS Therapy

(5.5 per 1000 vs 1.7 per 1000, *p=0.048*)[1]

67%

lower than rate of SUDEP in people with severe epilepsy

(1.7 per 1000 after 2 years of VNS Therapy[1] vs 5.1 per 1000 for people with severe epilepsy[2])

n=1,819 followed, 3,176.3 person years post-implant

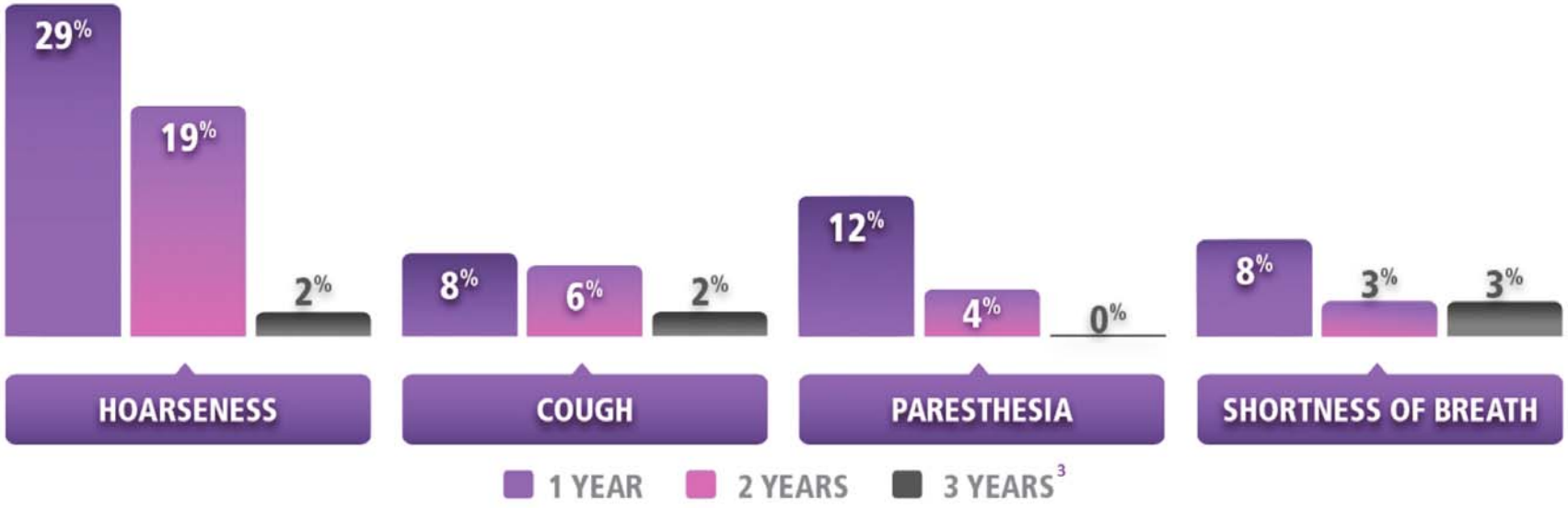
1. Annegers JF, et al. Epilepsia 2000;41:549-553. **2.** Morris GL, et al. Neurology 2013;81:1453-9.

Nonpharmacological side effect profile

None of the common systemic CNS side effects related to drugs

Most side effects associated with VNS Therapy

- Occur only during stimulation and generally diminish over time[1-3]
- May be diminished or eliminated by the adjustment of parameter settings[2]
- May be controlled by use of the magnet[4]



1. Ben-Menachem E, et al. Neurology 1999;52(6):1265-1267. 2. Ben-Menachem E. J Clin Neurophysiol 2001;18:415. 3. Morris GL, et al. Neurology 1999;53:1731-5. 4. Schacter SC. Neurology 2002;59(suppl 4):S15-S20.

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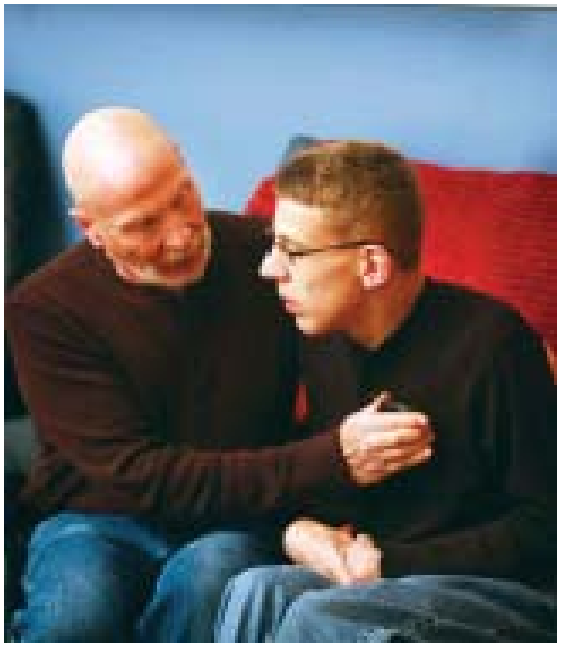
On-demand magnet stimulation is a unique benefit of VNS Therapy



Benefits of on-demand magnet stimulation

Offers more control for patients and their families

Initiates on demand stimulation

- ❑ May abort or decrease severity of seizures[1]
- ❑ May improve postictal period[2]

Stops stimulation

- ❑ Acutely manage side effects

1. Majkowska-Zwolińska et al 2012, Major and Thiele 2008, Khurana et al 2007, McHugh et al 2007, Morris 2003, Murphy et al 2003, Boon et al 2001, Wang et al, 2009, Hammond et al, 1992. **2.**Murphy et al 2003.

DinPPTPhy16U11

Unmet needs and missed treatment opportunities

I have nocturnal seizures

I don't have enough time to apply my magnet before my seizure

I can't apply my magnet

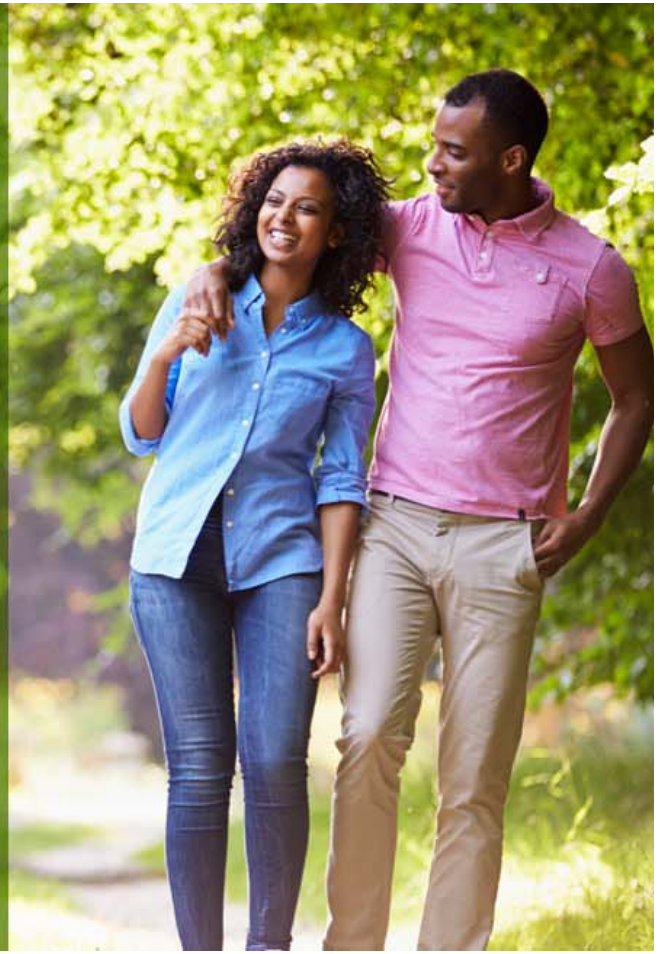
I don't have an aura

Data on File, Cyberonics, Inc. Houston, TX.

DinPPTPhy16U11

Introducing AspireSR®

The **first and only** VNS Therapy® that provides responsive stimulation to heart rate increases that may be associated with seizures.



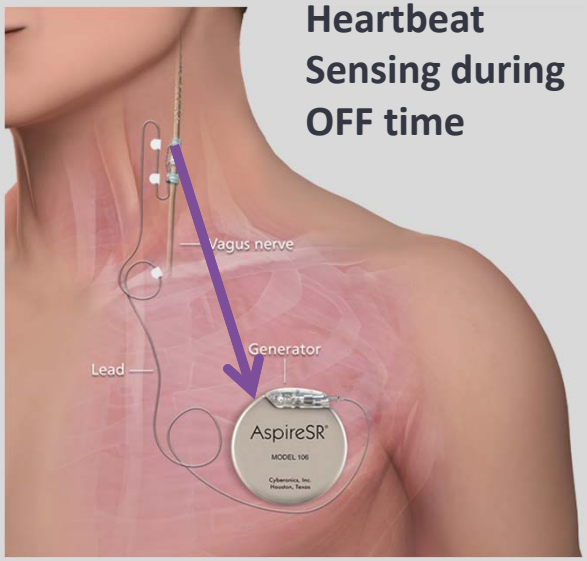
Sometimes the best medicine isn't just another medicine

VNS Therapy Physician's Manual, Cyberonics, Inc. Houston, TX.

AspireSR - 2015 FDA Approval

82% of patients with epilepsy experience **rapid heart rate increase** associated with a seizure[1]

HOW AspireSR WORKS



Heartbeat Sensing during OFF time

The AutoStim Mode feature:[2]

- Detects rapid heart rate rise
- Delivers automatic stimulation
- Has customizable parameters to meet patients' needs
- Works in conjunction with normal and magnet mode

1. Eggleston KS, et al. Seizure 2014;23(7):496-505. 2. VNS Therapy Physician's Manual, Cyberonics, Inc. Houston ,TX.

DinPPTPhy16U11

AspireSR patient considerations

AspireSR may be used for **any patient** with DRE who is a candidate for VNS Therapy

AutoStim is an optional feature that can be enabled or disabled at any time

The **AutoStim Mode feature** may not provide the same clinical benefit for patients:

- Patients with clinically meaningful arrhythmias currently being managed by devices or treatments that interfere with normal intrinsic heart rate responses (e.g., pacemaker dependency, implantable defibrillator, beta adrenergic blocker medications)

- Patients whose heart rate does not increase commensurate with increased activity or metabolic demand (chronotropic incompetence)

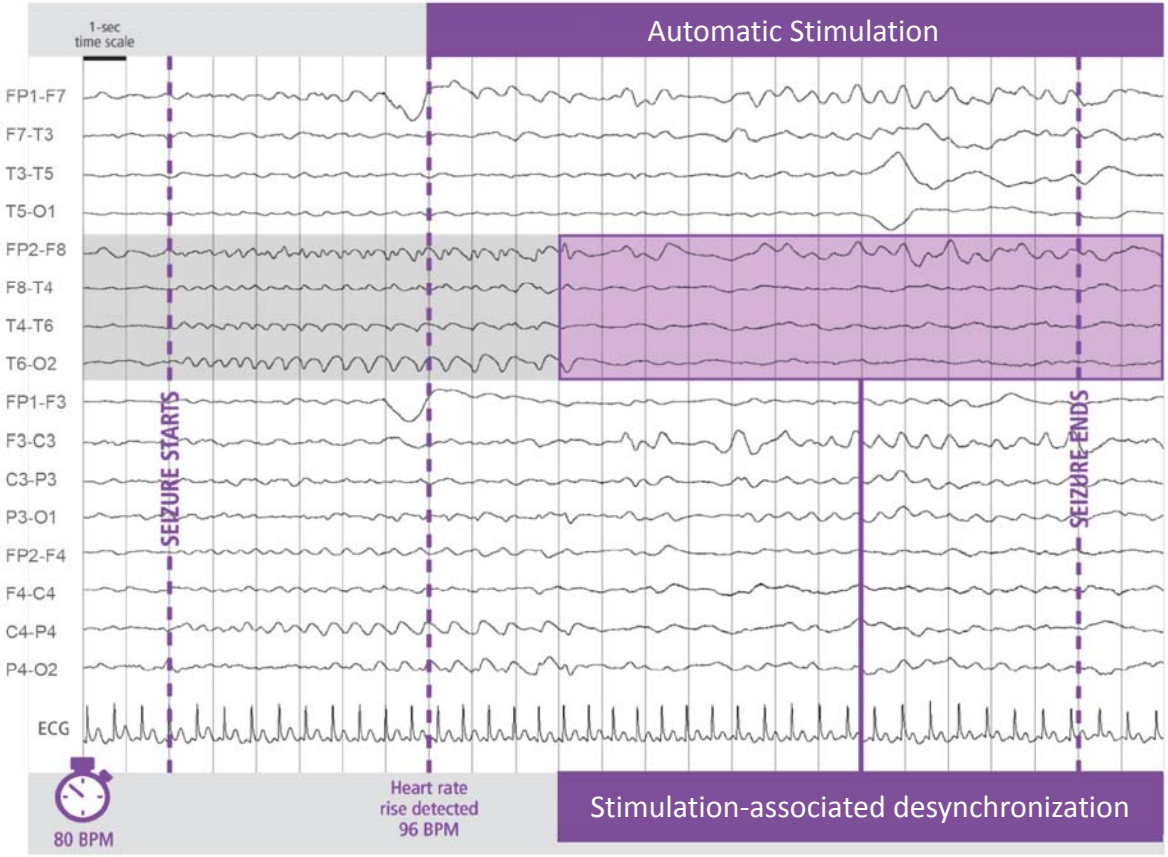
VNS Therapy Physician's Manual, Cyberonics, Inc. Houston, TX.

DinPPTPhy16U11

Seizure cessation during automatic stimulation was observed in AspireSR clinical trials

Stimulation-associated desynchronization of focal seizure*

20% Threshold for AutoStim



Over 60%

of seizures treated ended during automatic stimulation

(28/46 treated seizures from 14 patients)

*Single study patient example. Individual results may vary.

Data on File, Cyberonics, Inc. Houston, TX.

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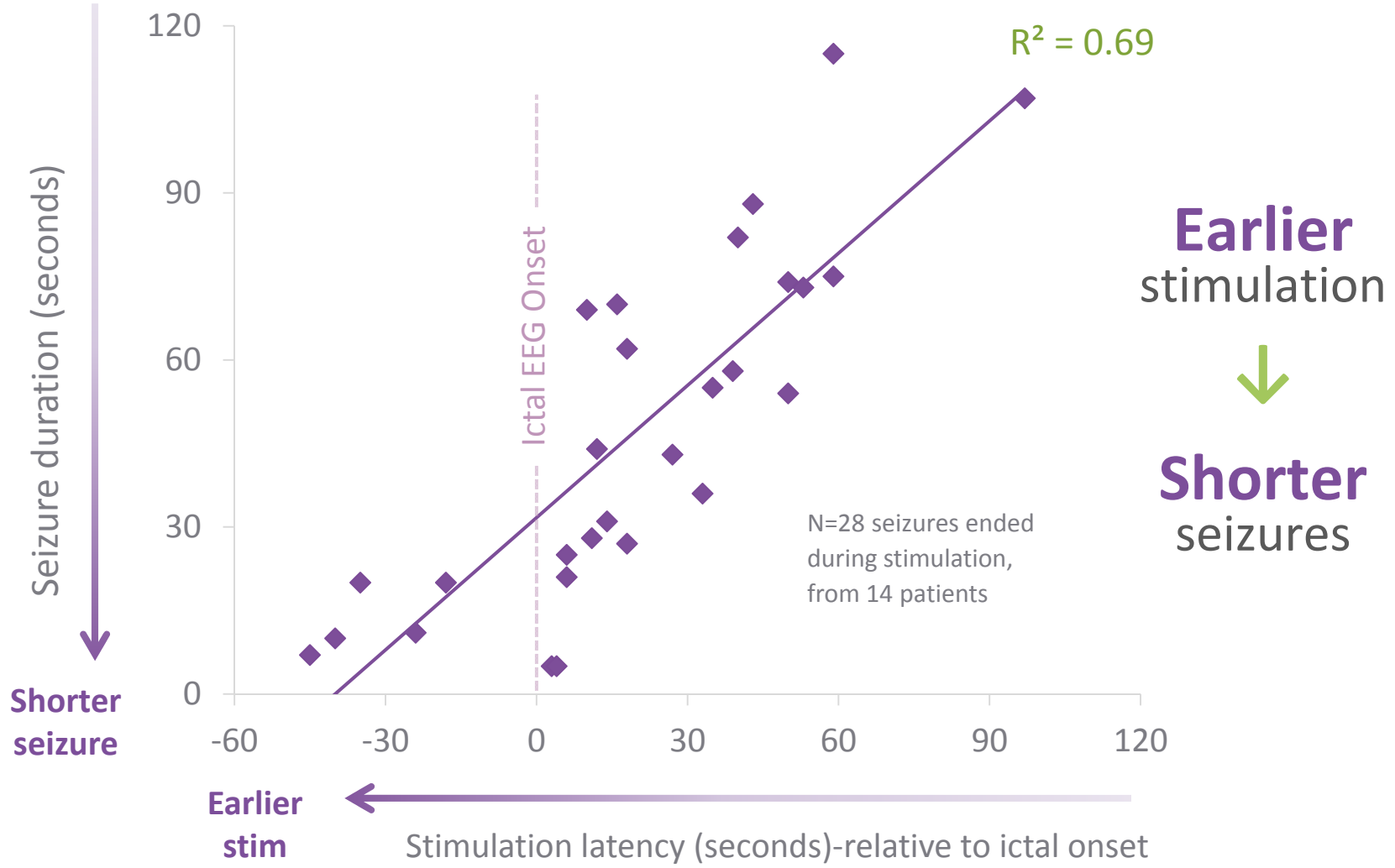
Earlier stimulation correlated with shorter seizures



Data on File, Cyberonics, Inc. Houston, TX.

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Clinical observations during 3-5 day EMU stay

- Only AutoStim Enabled
- Mean Output Current = 0.74 mA

Seizure Cessation

> 60% of seizures treated (n=46) ended during automatic stimulation

Reduced Severity

Significant reduction in **complex partial seizure severity** compared to baseline ($p<0.001$) using National Hospital Seizure Severity Scale (NHS3)

Importance of stimulating at or near seizure onset

The **closer** stimulation was to seizure onset, the **shorter** the seizure duration

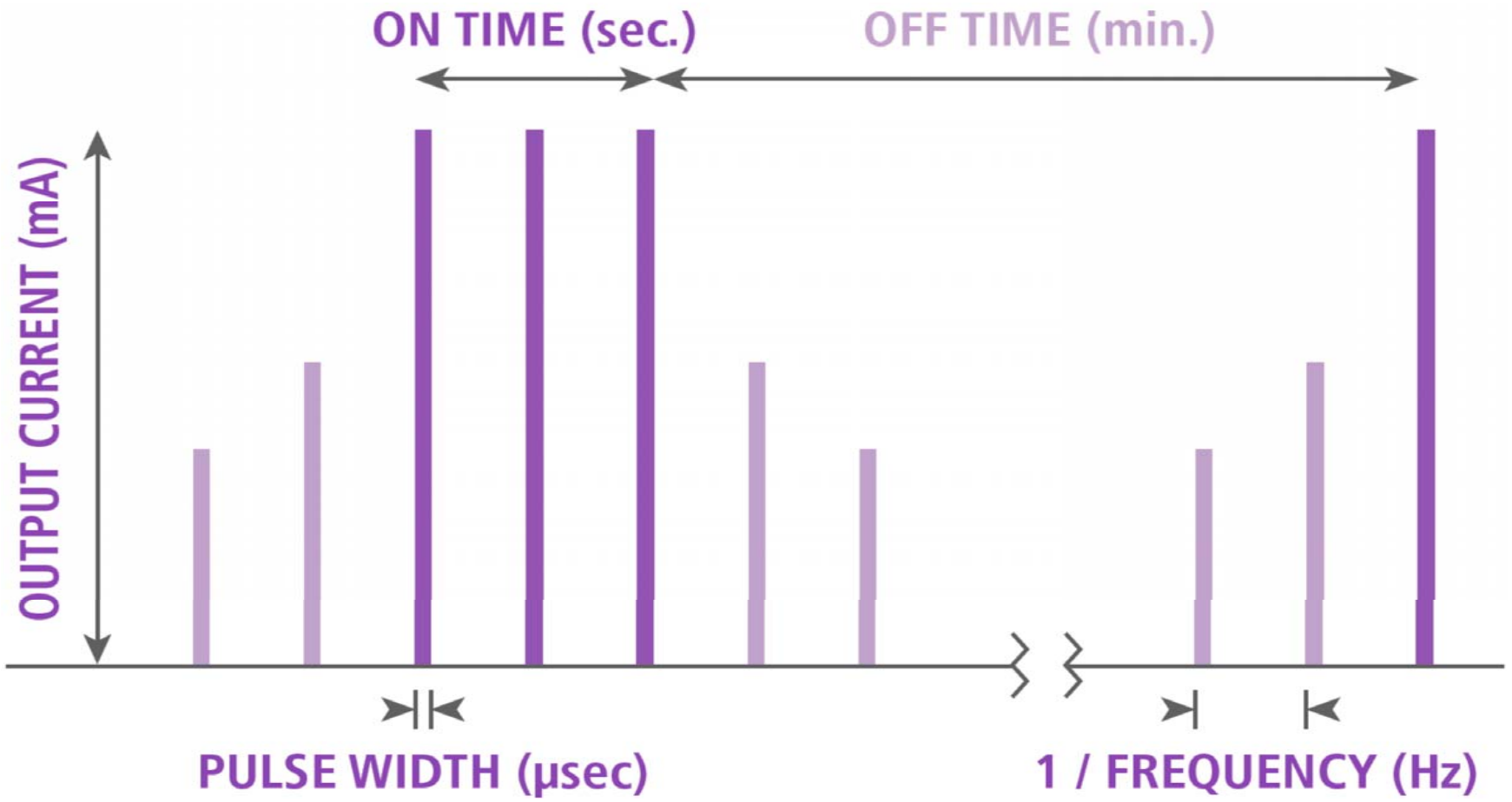
Data on File, Cyberonics, Inc. Houston, TX.

DinPPTPhy16U11

Practical Applications

DOSING
REIMBURSEMENT/RVU
MRI
PATIENT EDUCATION

Repetitive pulses of stimulation are delivered during On-Time



VNS Therapy Dosing Guidelines, Cyberonics, Inc. Houston, TX.

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Simple approach to dosing VNS Therapy

	Objectives
Phase 1: Output Current Increase Output Current in 0.25 mA steps to therapeutic range (1.5 - 2.25 mA)[1,2] as quickly as tolerable	Generate a compound action potential on the vagus nerve by creating a charge
Phase 2: Duty cycle Increase duty cycle over time and assess clinical outcome	Increase the amount of time stimulation is being delivered in a 24-hour period

Continue to optimize dose to therapeutic effect or tolerability

1. Helmers SL, et al. Acta Neurol Scand 2012;126(5):336-43. **2.** Heck C, et al. Neurology 2002;59(6 Suppl 4):S31-7.Adapted from VNS Therapy Dosing Guidelines, Cyberonics, Inc. Houston TX.

VNS Therapy reimbursement codes

2016 Medicare Fees and Relative Value Units

CPT Code	Description	Total Non-Facility RVU	2016 Rates (National Average)
95970	Interrogation without changing any stimulation parameters	1.93	$69.15
95971[1]	Interrogation with a change to any stimulation parameter; simple [3,5]	1.42	$50.88
95974[2]	Interrogation with a change to any stimulation parameter for sessions up to 60 minutes; complex[4,5]	5.87	$210.31
95975	Interrogation with a change to any stimulation parameter for each additional 30 minutes after the initial 60 minutes	3.16	$113.22

[1] Oct. 2012, CPT Assistant Q&A pg. 15, Medicine: Neurostimulators, Analysis-Programming; 95971 includes cranial nerve stimulator pulse generator/transmitter

[2] 2013 AMA CPT Professional Edition, pg. 539; For 95974, use modifier 52 if less than 31 minutes in duration

[3] Simple: Three or fewer parameters must be changed in order to report simple programming

[4] Complex: More than three parameters must be changed in order to report complex programming

[5] Oct. 2012, CPT Assistant Q&A pg. 15, Medicine: Neurostimulators, Analysis-Programming; Assessing changes in more than one clinical feature also counts as one parameter for these purposes

3T and 1.5T MRI Guidelines for VNS Therapy

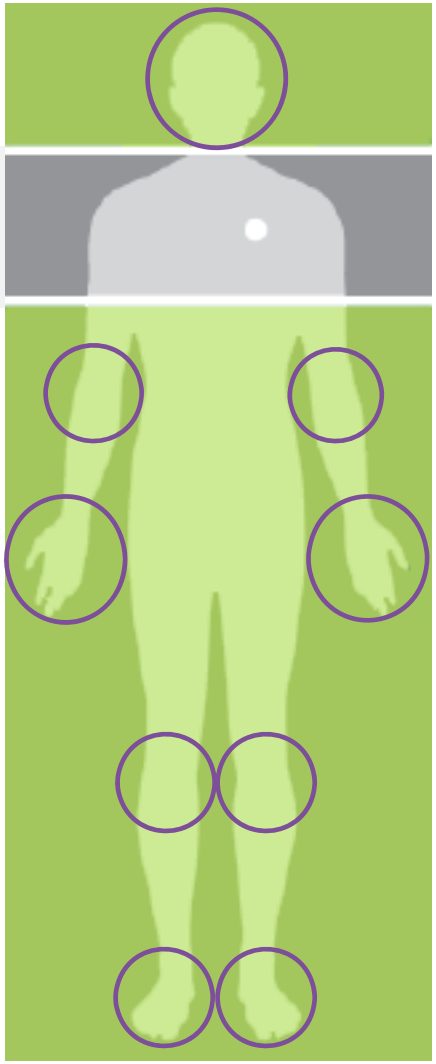
Performing MRI is safe provided that specified guidelines are followed

VNS Therapy System
The VNS Therapy system (generator and lead), usually located between C7 and T8 vertebrae, must not be exposed to the radio frequency (RF) field

Safe Zone
with local Transmit/Receive Coil

MR Exclusion Zone

Local Transmit/Receive coil commercially available



Note: Imaging techniques such as x-ray, computed tomography, and ultrasound are safe to perform in the MR Exclusion Zone

VNS Therapy Physician's Manual, Cyberonics, Inc. Houston, TX.

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MRI Guidelines for partial implants

	Complete VNS Therapy system OR Suspected lead break OR Lead only *>2 cm remaining* 	Lead only *≤2 cm remaining** 
Allowable imaging zones	**See graphic on previous page**	**Full body**
RF coil type	**Head or local ONLY**	**Any**
RF coil mode	**Transmit/receive ONLY**	**Any**
Static magnetic field	3T or 1.5T	3T or 1.5T
MRI configuration	Closed-bore	Closed-bore
MRI operating mode	Normal	Normal
Spatial gradient field	≤720 gauss/cm	≤720 gauss/cm
Head-averaged SAR	≤3.2 W/kg	≤3.2 W/kg

*Equivalent to clipping the lead at the anchor tether.

For more information about performing MRI on patients with VNS Therapy, please see the VNS Therapy System Physician's Manual, available at www.VNSTherapy.com

VNS Therapy Physician's Manual, Cyberonics, Inc. Houston, TX.

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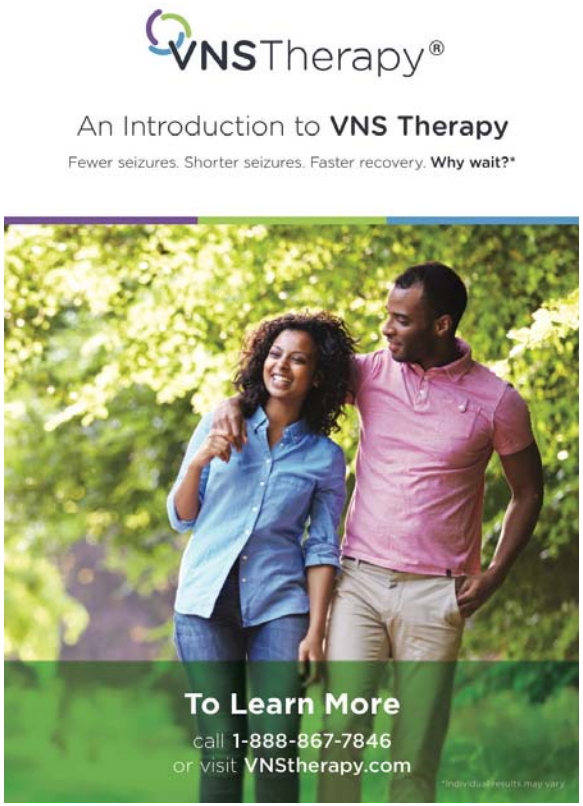
VNS Therapy Patient Education Resources

Patient Introduction Brochure with DVD



Epilepsy Connections Patient Ambassador Program

- One-on-one phone call or email with someone who has VNS Therapy or cares for someone with VNS Therapy

VNS Therapy Patient Teleconference

- First Tuesday of every month, 7:00 pm CST, 1-877-451-8943
- Hear from patients and a physician
- Ask questions anonymously or just listen to the discussion

LivaNova Staff

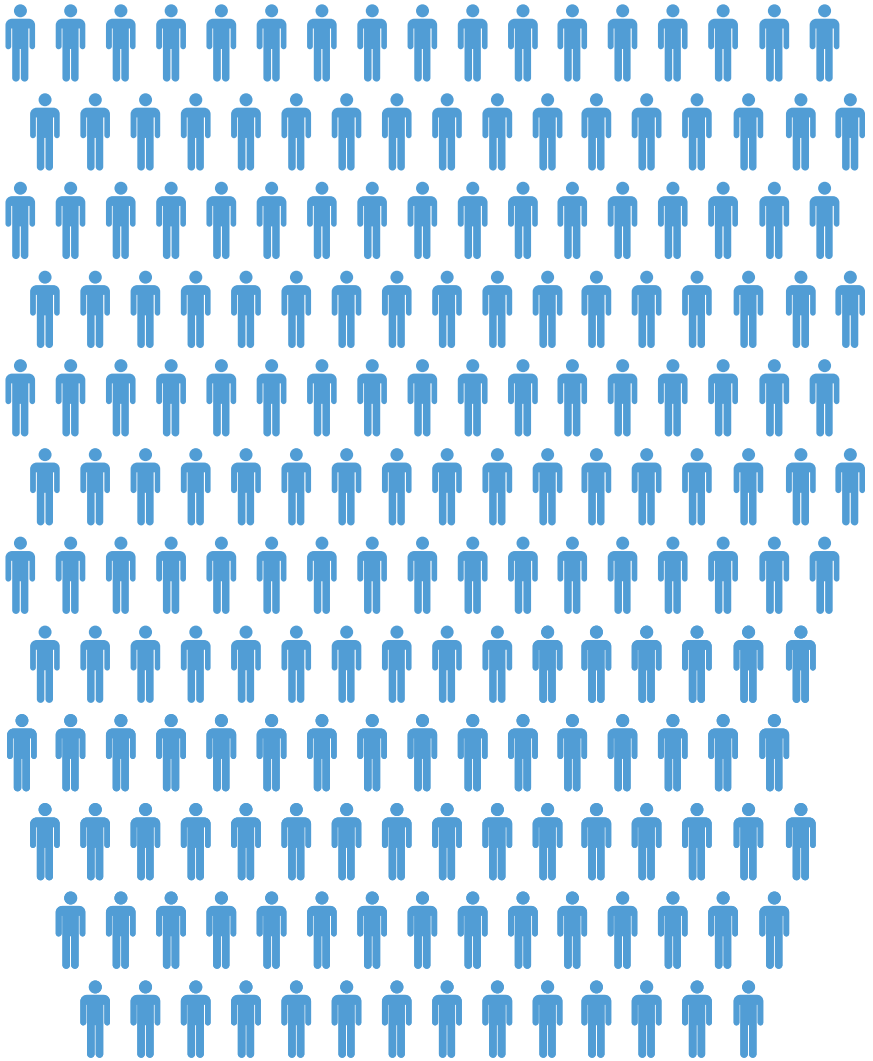
- Nurse Case Managers
- Clinical Specialists
- Therapeutic Consultants

Who will you help tomorrow?

By the time we return to work tomorrow…

DRE patients in the US will experience nearly **200** catastrophic life events

- **77** ER visits
- **35** fractures, head traumas or status epilepticus
- **17** hospitalizations
- **51** deaths



Adapted from Helmers SL, et al. Epilepsy Behav 2011;22:370-5. Incidence per 12 hours.

DinPPTPhy16U11

VNS Therapy addresses the needs of patients with DRE

Seizure reduction that continues to improve over time[1]

Decreased seizure severity/postictal period[4,5]

Quality of life improvements, independent of seizure control[2]

Nonpharmacological side effects that typically diminish over time[6,7]

Decreased healthcare utilization and costs[3]

Maximal adherence

AspireSR: The first and only VNS Therapy that provides responsive stimulation to heart rate increases that may be associated with seizures[8]

1. Elliott RE, et al. Epilepsy Behav 2011;20(3):478-483. 2.Klinkenberg S, et al. Clin Neurol Neurosurg 2012;114(4):336-340. 3. Helmers SL, et al. Epilepsy Behav 2011;22(2):370-375. 4. Tubbs RS, et al. J Neurosurg 2005;102(Suppl 2):213-217. 5. Vonck K, et al. Epilepsy Behav 2010;19(2):182-185. 6. Morris GL III, Mueller WM. Neurology 1999;53(7):1731- 1735. 7. Ben-Menachem E. J Clin Neurophysiol 2001;18(5):415-418. 8. VNS Therapy Physician's Manual, Cyberonics, Inc. Houston, TX.

Thank you

QUESTIONS?

IMPORTANT SAFETY INFORMATION

Brief Summary of Safety Information for the VNS Therapy® System [Epilepsy Indication] (June 2015)

1. INTENDED USE / INDICATIONS

Epilepsy (US)–The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to antiepileptic medications.

2. CONTRAINDICATIONS

Vagotomy–The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy.

Diathermy–Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

3. WARNINGS – GENERAL

Physicians should inform patients about all potential risks and adverse events discussed in the physician's manuals. This document is not intended to serve as a substitute for the complete physician's manuals.

The safety and efficacy of the VNS Therapy System have not been established for uses outside the “Intended Use/Indications” section of the physician's manuals.

The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias.

It is important to follow recommended implantation procedures and intraoperative product testing described in the Implantation Procedure part of the physician's manuals. During the intraoperative System Diagnostics (Lead Test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics (Lead Test) or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration. Dyspnea (shortness of breath) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency such as chronic obstructive pulmonary disease or asthma may be at increased risk for dyspnea.

Brief Summary of Safety Information for the VNS Therapy® System [Epilepsy Indication] (June 2015)

3. WARNINGS – GENERAL (Continued)

Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging "OFF" time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder.

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage. Patients should be instructed to use the magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation.

Patients with the VNS Therapy System, or any part of the VNS Therapy System, implanted should have MRI procedures performed only as described in the *MRI with the VNS Therapy System (US)*. Surgery will be required to remove the VNS Therapy System if a scan using a transmit RF body coil is needed.

Excessive stimulation at an excess duty cycle (that is, one that occurs when "ON" time is greater than "OFF" time) and high frequency stimulation (i.e., stimulation at ≥ 50 Hz) has resulted in degenerative nerve damage in laboratory animals.

Patients who manipulate the pulse generator and lead through the skin (Twiddler's Syndrome) may damage or disconnect the lead from the pulse generator and/or possibly cause damage to the vagus nerve.

Cardiac arrhythmia (Model 106 only)–The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias currently being managed by devices or treatments that interfere with normal intrinsic heart rate responses (e.g., pacemaker dependency, implantable defibrillator, beta adrenergic blocker medications). Patients also should not have a history of chronotropic incompetence [commonly seen in patients with sustained bradycardia (heart rate < 50 bpm)].

Pre-surgical Surface Assessment (Model 106 only)–For anticipated use of the AutoStim feature, it is important to follow the recommended pre-surgical surface assessment described in the Implantation Procedure to determine a location for the pulse generator to reside in which it can accurately detect heart beats.

4. WARNINGS – EPILEPSY

The VNS Therapy System should only be prescribed and monitored by physicians who have specific training and expertise in the management of seizures and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

The VNS Therapy System is not curative. Physicians should warn patients that the VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others.

Sudden unexplained death in epilepsy (SUDEP): Through August 1996, 10 sudden and unexplained deaths (definite, probable, and possible) were recorded among the 1,000 patients implanted and treated with the VNS Therapy device. During this period, these patients had accumulated 2,017 patient-years of exposure. Some of these deaths could represent seizure-related deaths in which the seizure was not observed, at night, for example. This number represents an incidence of 5.0 definite, probable, and possible SUDEP deaths per 1,000 patient-years. Although this rate exceeds that expected in a healthy (nonepileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving vagus nerve stimulation, ranging from 1.3 SUDEP deaths for the general population of patients with epilepsy, to 3.5 (for definite and probable) for a recently studied antiepileptic drug (AED) clinical trial population similar to the VNS Therapy System clinical cohort, to 9.3 for patients with medically intractable epilepsy who were epilepsy surgery candidates.

Brief Summary of Safety Information for the VNS Therapy® System [Epilepsy Indication] (June 2015)

5. PRECAUTIONS – GENERAL

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy physician's manuals.

Prescribing physicians should be experienced in the diagnosis and treatment of epilepsy and should be familiar with the programming and use of the VNS Therapy System.

Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System.

The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. VNS should be used during pregnancy only if clearly needed.

The VNS Therapy System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy System is indicated for use only in stimulating the **left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve**.

It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure.

The VNS Therapy System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillatory therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device.

Reversal of lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that leads with dual connector pins are correctly inserted (white marker band to + connection) into the pulse generator's lead receptacles.

The patient can use a neck brace for the first week to help ensure proper lead stabilization.

Do not program the VNS Therapy System to an "ON" or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.

For Models 100, 101, 102 and 102R do not use frequencies of 5 Hz or below for long-term stimulation.

Resetting the pulse generator disables or turns the device OFF (output current = 0 mA). For Model 100, 101, 102 and 102R, resetting the pulse generator will result in device history loss.

Patients who smoke may have an increased risk of laryngeal irritation.

Unintended Stimulation (Model 106 only)–Because the device senses changes in heart rate, false positive detection may cause unintended stimulation. Examples of instances where the heart rate may increase include exercise, physical activity, and normal autonomic changes in heart rate, both awake and asleep, etc. Adjustments to the AutoStim feature's detection threshold should be considered; which may include turning the feature OFF.

Device Placement (Model 106 only)–The physical location of the device critically affects the feature's ability to properly sense heart beats. Care must be taken to follow the implant location selection process outlined in the Implantation Procedure.

Battery Drain (Model 106 only)–Talk to your patient about use of the AutoStim feature since use of the feature will result in faster battery drain and the potential for more frequent device replacements. The physician's manual describes the impacts to the battery life. The patient should return to their physician at appropriate intervals to further evaluate whether they are receiving benefit from the current AutoStim settings.

Brief Summary of Safety Information for the VNS Therapy® System [Epilepsy Indication] (June 2015)

6. ENVIRONMENTAL AND MEDICAL THERAPY HAZARDS

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a pulse generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

VNS Therapy System operation **should always be checked** by performing device diagnostics after any of the procedures mentioned in the physician's manuals.

For clear imaging, patients may need to be specially positioned for mammography procedures, because of the location of the pulse generator in the chest.

Therapeutic radiation may damage the pulse generator's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately.

External defibrillation may damage the pulse generator.

Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the pulse generator.

Magnetic resonance imaging (MRI) should not be performed with a magnetic resonance body coil in the transmit mode. The heat induced in the lead by an MRI body scan can cause injury. Additionally, in vitro tests have shown that an intact lead without an implanted pulse generator presents substantially the same hazards as a full VNS Therapy System. If an MRI should be done, use only a transmit-and-receive type of head coil or local coil. MRI compatibility was demonstrated using 1.5T and 3.0T MR systems. Consider other imaging modalities when appropriate. Procedures in which the radio frequency (RF) is transmitted by the body coil should not be done on a patient who has the VNS Therapy System. Thus, protocols must not be used that utilize local coils that are RF receive-only, with RF-transmit performed by the body coil. Note that some RF head coils are receive-only, and that most other local coils, such as knee and spinal coils, are also RF-receive only. **These coils must not be used in patients with the VNS Therapy System**. See *MRI with the VNS Therapy System*(U.S. version) for details or further instructions for special cases such as lead breaks or partially explanted VNS Therapy systems.

Extracorporeal shockwave lithotripsy may damage the pulse generator. If therapeutic ultrasound therapy is required, avoid positioning the area of the body where the pulse generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the pulse generator output to 0 mA for the treatment, and then after therapy, reprogram the pulse generator to the original parameters.

If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit), either the pulse generator should be set to 0 mA or function of the pulse generator should be monitored during initial stages of treatment.

Routine therapeutic ultrasound could damage the pulse generator and may be inadvertently concentrated by the device, causing harm to the patient.

For complete information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, refer to the physician's manuals.

7. ADVERSE EVENTS – EPILEPSY

Adverse events reported during clinical studies as statistically significant are listed below in alphabetical order: ataxia (loss of the ability to coordinate muscular movement); dyspepsia (indigestion); dyspnea (difficulty breathing, shortness of breath); hypesthesia (impaired sense of touch); increased coughing; infection; insomnia (inability to sleep); laryngismus (throat, larynx spasms); nausea; pain; paresthesia (prickling of the skin); pharyngitis (inflammation of the pharynx, throat); voice alteration (hoarseness); vomiting.

The information contained in this Brief Summary for Physicians represents partial excerpts of important prescribing information taken from the physician's manuals. (Copies of VNS Therapy physician's and patient's manuals are posted at www.cyberonics.com.) The information is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the physician's manuals for the VNS Therapy System and its component parts nor does this information represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

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www.VNSTherapy.com

VNS Therapy®

CYBERONICS, INC.
100 Cyberonics Boulevard
Houston, Texas 77058
Tel: +1.800.332.1375
Fax: +1.281.218.9332

CYBERONICS EUROPE BVBA
Vuurberg - Airport Plaza Building C Kyoto
Leonardo Da Vincilaan 19
1831 Diegem, Belgium
Tel: +32.2.720.95.93
Fax: +32.2.720.60.53

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