

# Advances in the Treatment of Acute Coronary Syndromes

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# Cardiovascular Disease

## Continu

- ◆ In 2007
  - More than 16.3 million people in the United States had coronary heart disease
  - 671,000 patients were discharged from the hospital with a primary diagnosis of ACS
  - An additional 195,000 silent myocardial events occur each year
- ◆ Approximately 785,000 people experienced a new cardiac event and approximately 470,000 had a recurrent event in 2010

Cardiovascular Risk Factors



Atherosclerosis



Coronary Heart Disease



Atherothrombosis

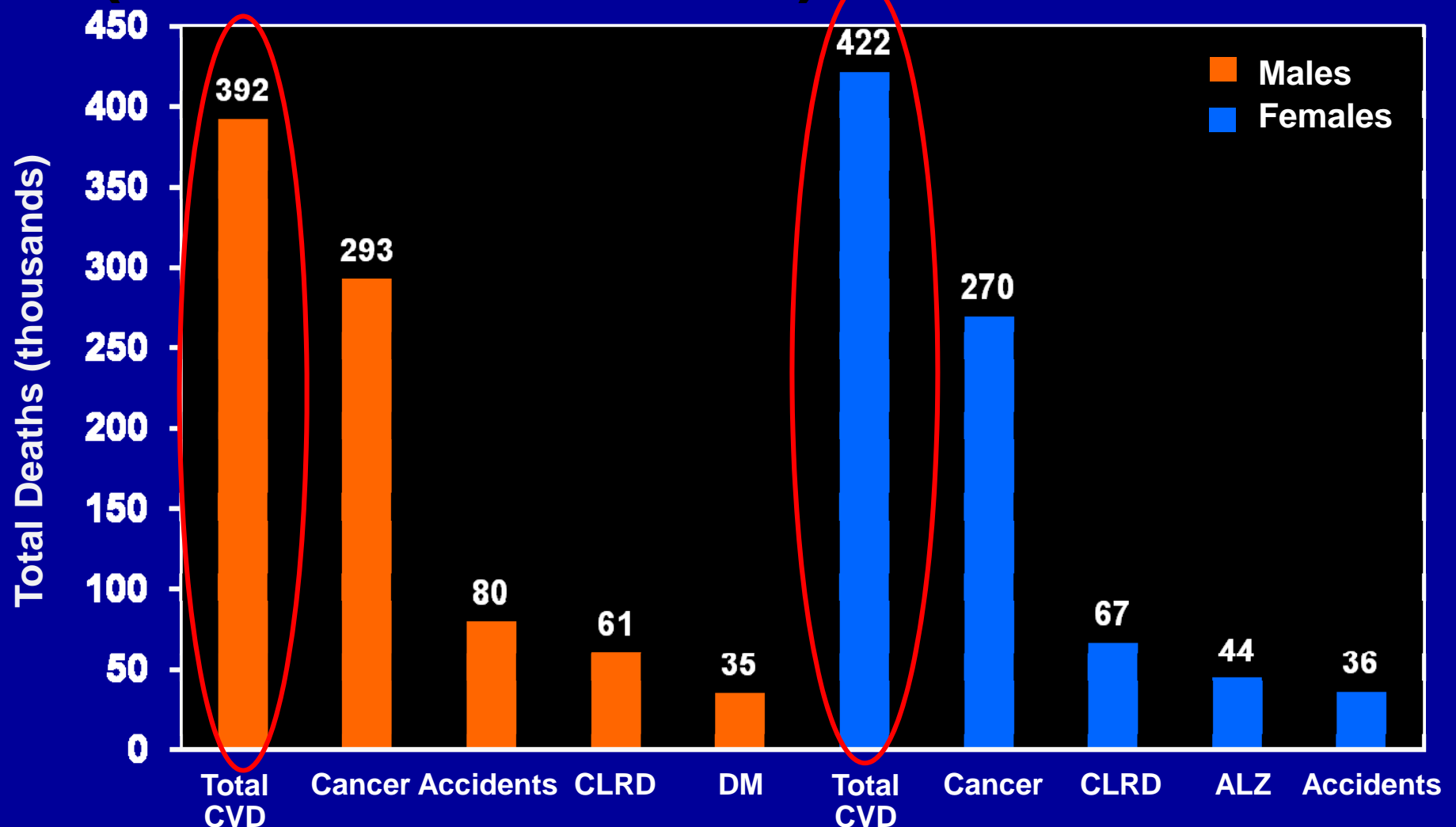


Acute Coronary Syndrome



Sudden Cardiac Death

# Major Causes of Death (United States 2007)<sup>1</sup>



1. Numbers shown are the primary data rounded to the nearest whole number

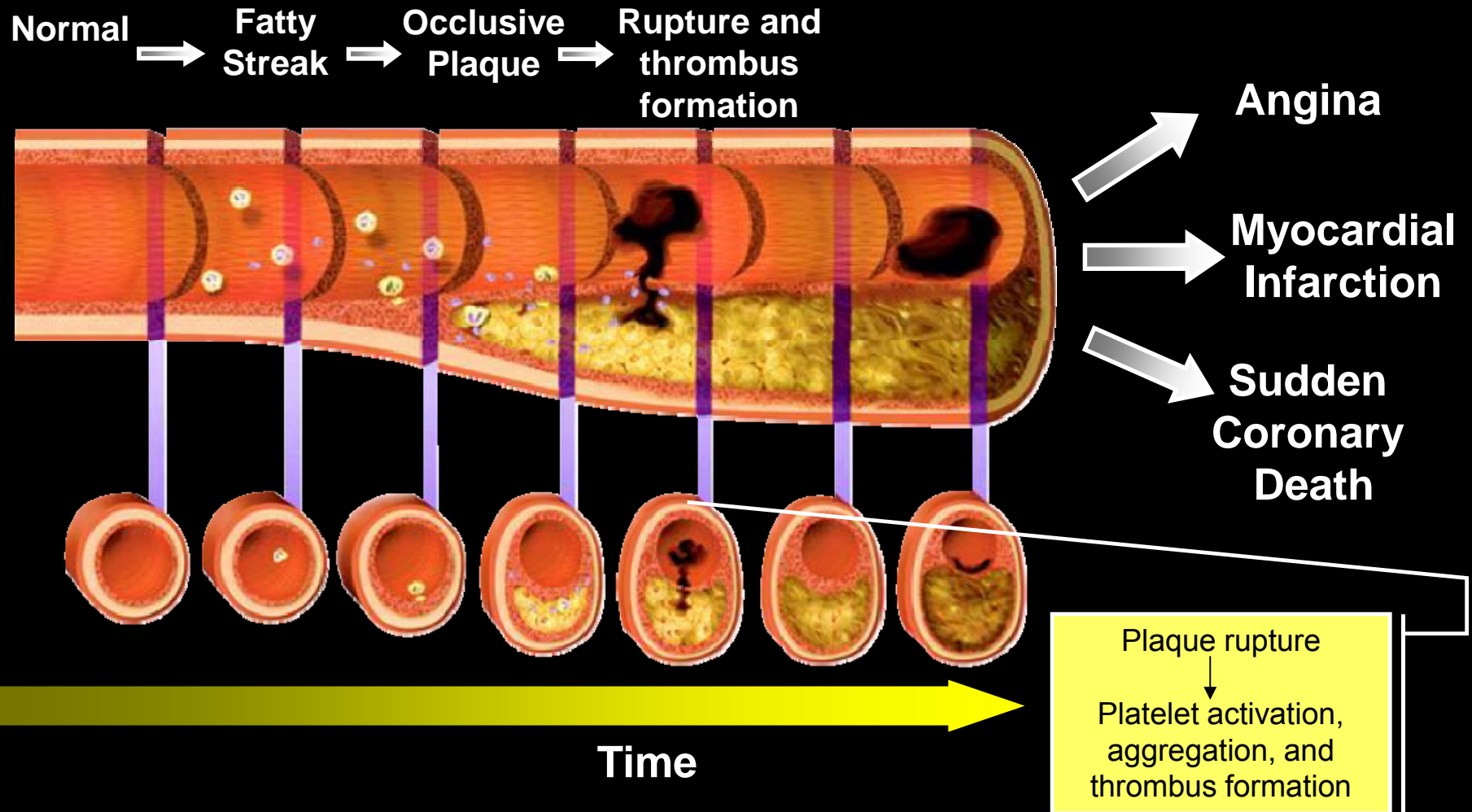
Roger VL et al. *Circulation* 2011;123:e000-e000

ALZ=Alzheimer's Disease; CLRD=Chronic Lower Respiratory Disease; CVD=Cardiovascular Disease; DM=Diabetes Mellitus

# Acute Coronary Syndrome

- ◆ Atherosclerosis is a generalized disease process that affects arteries throughout the body
- ◆ Atherothrombosis is characterized by a sudden atherosclerotic plaque disruption and the formation of a platelet-rich thrombus
- ◆ Plaque rupture leads to ACS

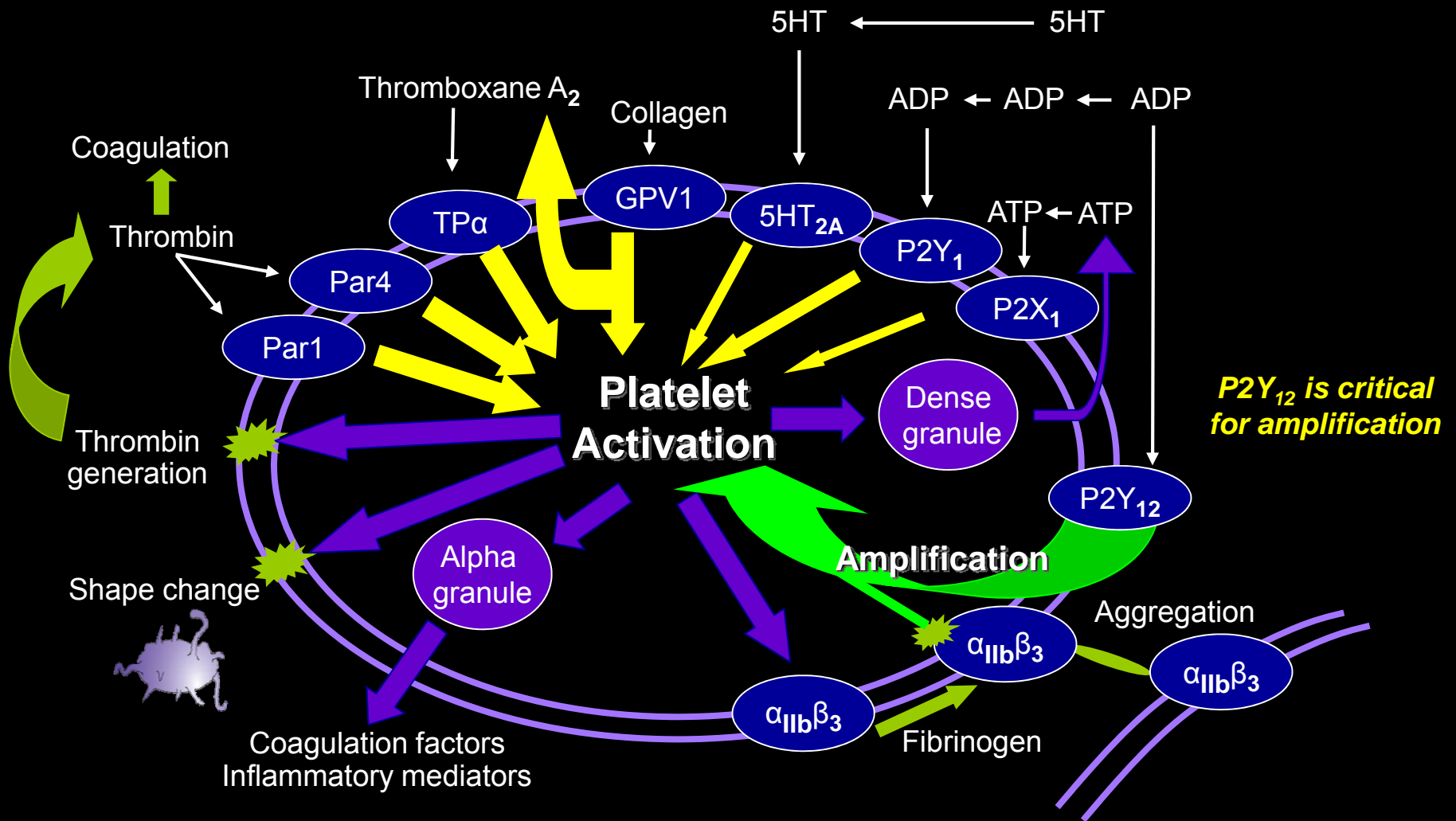
# Progression of Atherosclerosis



# Stable vs Vulnerable Plaque

- Fibrous cap
- Normal endothelium
- Lipid core  
stable/regressed
- Normal Smooth  
muscle cells
- Thin cap
- Inflamed endothelium,  
fissures,ulcers
- Lipid core growth, foam  
cells present
- Activated Smooth  
muscle cells,  
macrophages, T-lymph

# Platelet Activation

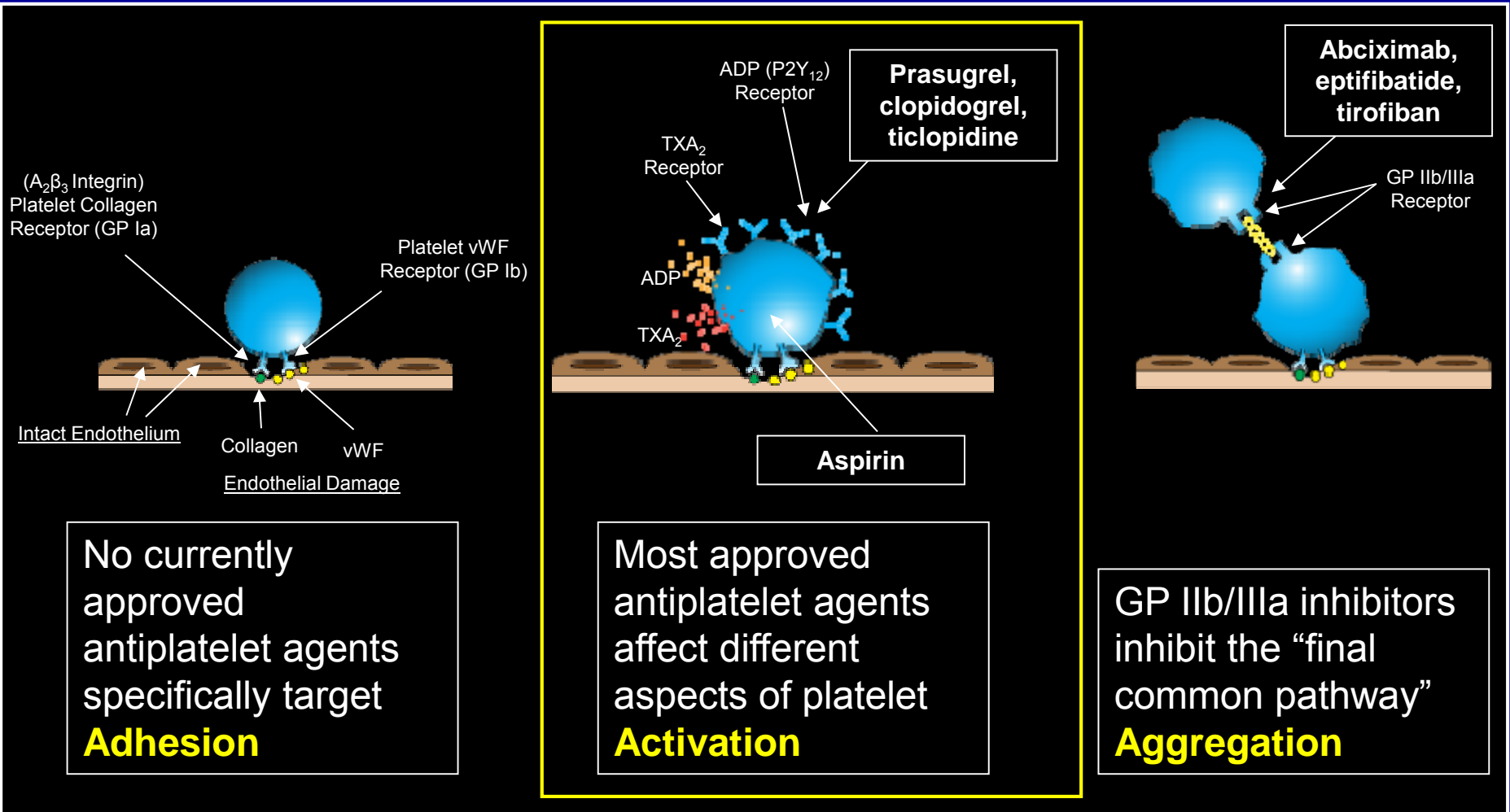


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Reprinted from Storey RF. *Curr Pharm Des* 2006;12:1255-1259

5HT=5-hydroxytryptamine; ADP=Adenosine Diphosphate; ATP=Adenosine Triphosphate; GP=Glycoprotein; PAR=Protease Activated Receptor; TP=Thromboxane A<sub>2</sub> Receptor

# Platelet-mediated



Meadows TA and Bhatt DL. *Circulation Res* 2007;100:1261-1275

ADP=Adenosine Diphosphate; GP=Glycoprotein; TX=Thromboxane; vWF= von Willebrand Factor

# Acute Coronary Syndrome

- ◆ ACS refers to several related conditions that have similar clinical symptoms consistent with acute myocardial ischemia
  - Unstable angina
  - NSTEMI
  - STEMI
- ◆ Common pathophysiology of plaque disruption or erosion
- ◆ Conditions are differentiated clinically by electrocardiogram and biomarkers

# Causes of UA/NSTEMI\*

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- Thrombus or thromboembolism, usually arising on disrupted or eroded plaque
  - Occlusive thrombus, usually with collateral vessels†
  - Subtotally occlusive thrombus on pre-existing plaque
  - Distal microvascular thromboembolism from plaque-associated thrombus
  - Thromboembolism from plaque erosion
- Non-plaque-associated coronary thromboembolism
- Dynamic obstruction (coronary spasm‡ or vasoconstriction) of epicardial and/or microvascular vessels
- Progressive mechanical obstruction to coronary flow
- Coronary arterial inflammation
- Secondary UA
- Coronary artery dissection§

# Hospitalizations in the U.S. Due to ACS

**Acute Coronary Syndromes\***

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graph TD; A[Acute Coronary Syndromes*] --> B[1.57 Million]; B --> C[UA/NSTEMI†]; B --> D[STEMI]; C --- E[1.24 million]; D --- F[0.33 million]
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**1.57 Million**

**UA/NSTEMI†**

**1.24 million**

**STEMI**

**0.33 million**

# Classical symptoms

- Pain
- Pressure
- Squeezing
- Burning
- Weight
- Indigestion
- “Sharp”
- Ache

# Symptom Location

- Midline Chest
- Pectoral
- Epigastrium
- Posterior Thorax
- Arms
- Shoulders
- Neck/Throat
- Jaw
- Teeth

# Other Features

- Dyspnea
- Nausea/Emesis
- Diaphoresis
- Radiation
- Pre-syncope
- Impending doom
- Muscle Weakness
- Levine sign

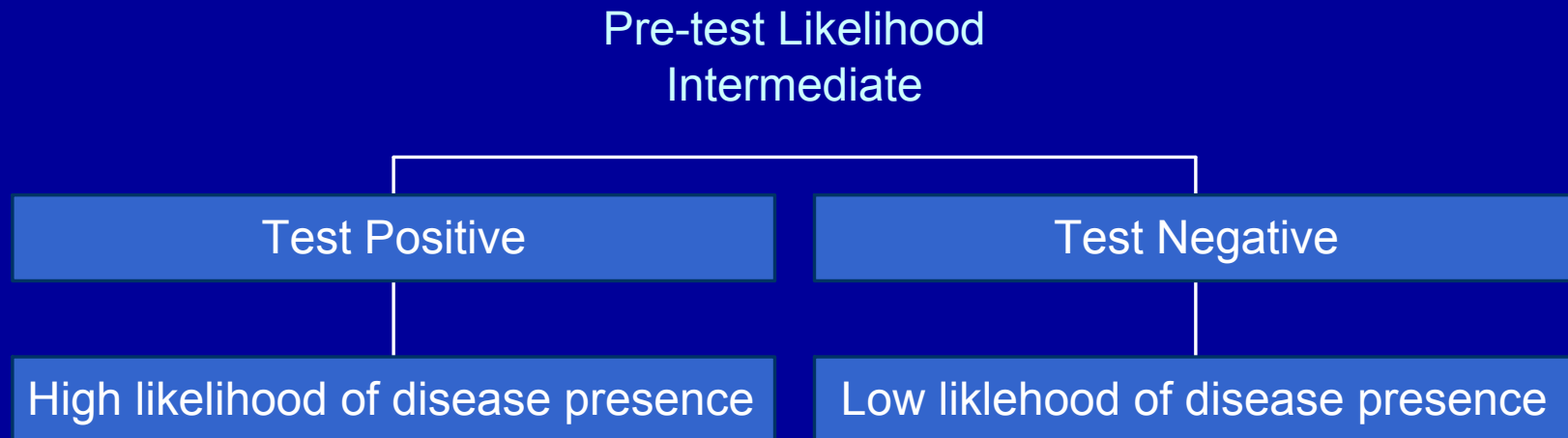
# Atypical Presenters

- Diabetics
- Elderly
- Female
- Sedentary
- Acute co-morbidities (sepsis, ARF)

# Electrocardiography During Symptoms

- ST Depression
- ST Elevation
- T-Wave inversion, biphasic

# Stress Testing Useful in Intermediate Probability



# Stress Testing Less Useful

- Low Likelihood Pretest: Is the abnormal test a false positive?
- High Likelihood Pretest: Is the normal stress test a false negative?

# Choices of Stress Tests

- Walking Preferred: Prognostic Value associated with capacity on treadmill, Symptoms on TM, Exercise-induced VT or Hypotension
- Pharmacologic Nuclear: LBBB, Paced, prior MI, COPD
- Dobutamine Echo: Pre-menopausal , younger, concomitant valve disease, LVH

# ASA Therapy

- Angina, Death or MI reduced 30%
- Stroke reduction
- Low doses effective

# Thienopyridines

- CURE Trial: 20% reduction in CV death, CVA, or MI among ACS patients
- CHARISMA: no difference in asymptomatic chronic patients with risk factors, but 15% reduction among those with symptomatic atherosclerosis
- Reduced death or MI 30% if pre-treated before PCI

# Thienopyridines-2

- 3% risk of bleeding with asa/clop combination
- Drug-resistance to clopidogrel exists, requires activation, delayed onset of effects
- 5 days to reverse effects

# Thienopyridines-3

- Prasugrel in ACS (TRITON) 13,608 pts
- 19% reduction in VC death, NF-MI, CVA composite
- Stent thrombosis reduced 52% (sub-group)
- 0.5% absolute increase in major bleeding, 0.3% fatal bleeding
- Prior stroke, age>75, weight<60KG

# Glycoprotein IIb-IIIa Inhibitors

- CAPTURE: Abcix in ACS/PCI patients had 30% reduction in MI or ischemia
- PRISM: Tirofib in ACS patients had 32% reduction in death, MI or Ischemia
- PURSUIT: Integrilin in NSTEMI patients had 10% reduction in death or MI

# Unfractionated Heparin (UFH)

- 50% reduction in MI among ACS patients using heparin+ASA vs ASA alone (Theroux et al)
- Meta-Analysis of 6 trials showed 33% reduction in death or MI

# Low Molecular Weight Heparin (LMWH)

- FRISC: LMWH+ASA showed 63% reduction in death or MI vs ASA alone
- ESSENCE: LMWH showed 20 % reduction in death, MI or angina vs UFH
- TIMI-11B: 15% reduction in death, MI or Revasc vs UFH but increased minor bleeding rates

# Invasive Strategy

- Balloon-era trials inconclusive (TIMI-3B), early cath/CABG (VANQUISH)
- RITA-3 (2002): Early invasive strategy showed 34% reduction in death, NFMI, or refractory angina
- Mehta Meta-analysis of 7 trials (2006): 18% reduction in death or MI with early invasive strategy using “all the tricks”

## 2009 ACC/AHA STEMI and 2009 ACC/AHA/SCAI PCI Guidelines: Recommendations for the Use of Prasugrel (part 1 of 2)

<b>Class I STEMI Recommendations</b>	<b>Class and Level of Evidence</b>
A loading dose of prasugrel 60 mg is recommended for STEMI patients for whom PCI is planned and should be given as soon as possible for primary PCI	I B
For STEMI patients undergoing non-primary PCI, and if the patient did not receive fibrinolytic therapy and PCI is planned, it is recommended that a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI once the coronary anatomy is known	I B
In patients receiving a stent (BMS or DES) during PCI for ACS, prasugrel 10 mg daily should be given for at least 12 months	I B
If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered	I C
In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect at least 7 days in patients receiving prasugrel unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding	I C

Kushner et al. *J Am Coll Cardiol* 2009;54:2205-2241

ACC=American College of Cardiology; ACS=Acute Coronary Syndrome; AHA=American Heart Association; BMS=Bare-metal Stent; CABG=Coronary Artery Bypass Graft; DES=Drug-eluting Stent; PCI=Percutaneous Coronary Intervention; SCAI=Society for Cardiovascular Angiography and Interventions; STEMI=ST-Elevation Myocardial Infarction

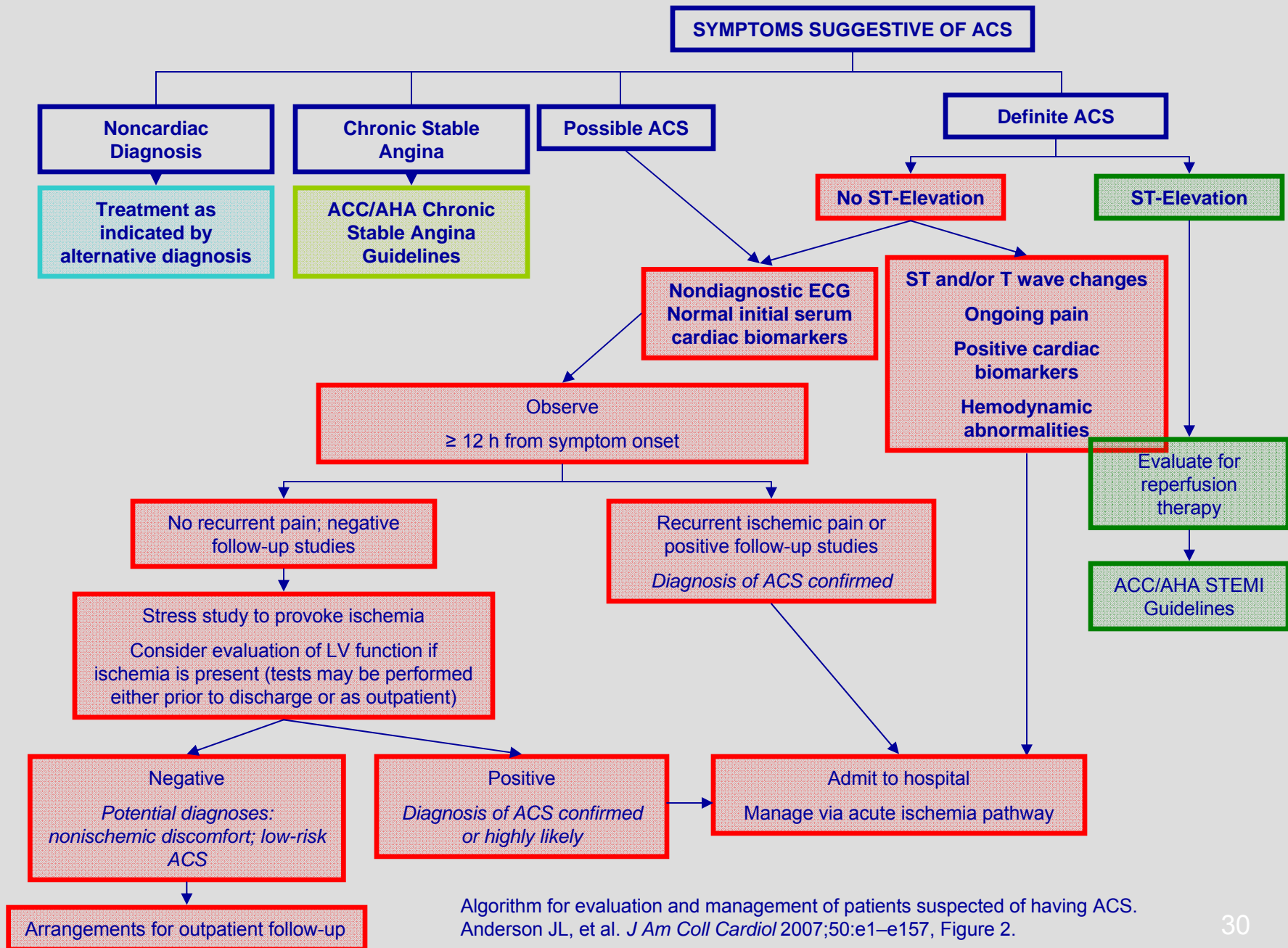
## 2009 ACC/AHA STEMI and 2009 ACC/AHA/SCAI PCI Guidelines: Recommendations for the Use of Prasugrel (part 2 of 2)

<b>Class I PCI Recommendations for UA/NSTEMI patients</b>	<b>Class and Level of Evidence</b>
Patients with definite or likely UA/NSTEMI selected for an invasive approach should receive dual-antiplatelet therapy. Aspirin should be initiated on presentation. Prasugrel (at the time of PCI) is recommended as a second antiplatelet agent	I B

<b>Class IIb and III STEMI Recommendations</b>	<b>Class and Level of Evidence</b>
Continuation of prasugrel beyond 15 months may be considered in patients undergoing drug-eluting stent placement (IIb C)	IIb C
In patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual antiplatelet therapy regimen (III C)	III C

Kushner et al. *J Am Coll Cardiol* 2009;54:2205-2241

ACC=American College of Cardiology; AHA=American Heart Association; PCI=Percutaneous Coronary Intervention; SCAI=Society for Cardiovascular Angiography and Interventions; STEMI=ST-Elevation Myocardial Infarction; UA=Unstable Angina; NSTEMI=Non-ST-Elevation Myocardial Infarction



Algorithm for evaluation and management of patients suspected of having ACS. Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Figure 2.