Epidemiology of Acute Coronary Syndromes in the US

Single most frequent cause of death
- 1 of every 7 deaths
- 151,863 deaths from ACS

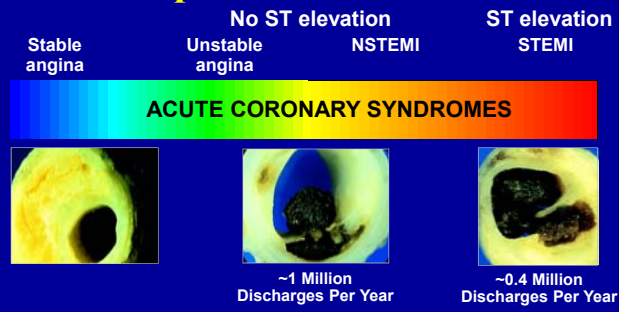
Incidence
- Each year, 1.0 million Americans will have a new or recurrent coronary event

Prevalence
- 20 million Americans have a history of MI, angina, or both

Costs
- 204.8 billion dollars a year in direct and indirect costs

CHD = coronary heart disease; MI = myocardial infarction.
American Heart Association. *Heart Disease and Stroke Statistics—2018 Update;* 2018.

Spectrum of CAD



Abbreviations: CAD, coronary artery disease; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Figures reproduced with permission from Davies MJ. *Heart.* 2000;83:361-366.
Rosamond W, et al. American Heart Association Statistics Committee and Stroke Statistics Committee. Heart Disease and Stroke Statistics 2008 Update [published online ahead of print December 17, 2007]. *Circulation*. doi:10.1161/CIRCULATIONAHA.107.187998.

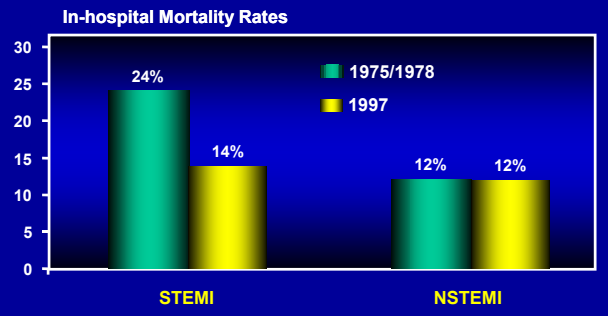
Clinical Assessment

Evaluation and Diagnosis

- Patients presenting with chest pain
  - Detailed symptom history
  - Focused physical examination
  - 12 Lead ECG (within 10 minutes of presentation)
  - Directed risk-factor assessment
- Estimate the probability of significant ischemic heart disease (low, intermediate, high)
- Estimate the risk of major vascular events if ischemic heart disease is present

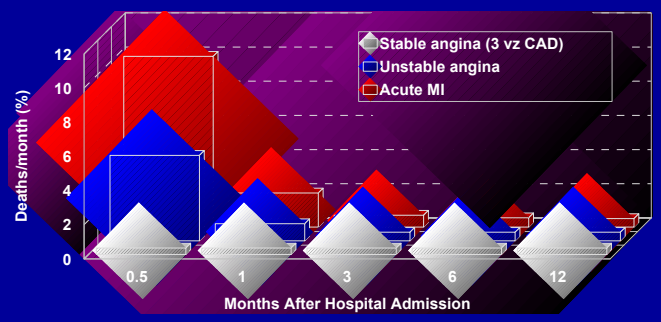
Fihn SD et al. *J Am Coll Cardiol.* 2012;60:1-40.

Hospital Mortality of NSTEMI vs STEMI



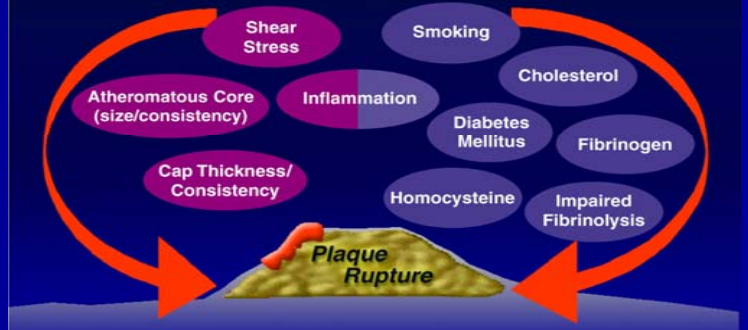
Furman MI, et al. *JACC* 2001; 37(6): 1571-80.

Time Dependent Risk of Coronary Syndromes



Outcome of 21,761 patients grouped by ischemic heart disease diagnosis on admission
Duke Database AHCPR Unstable Angina Guidelines

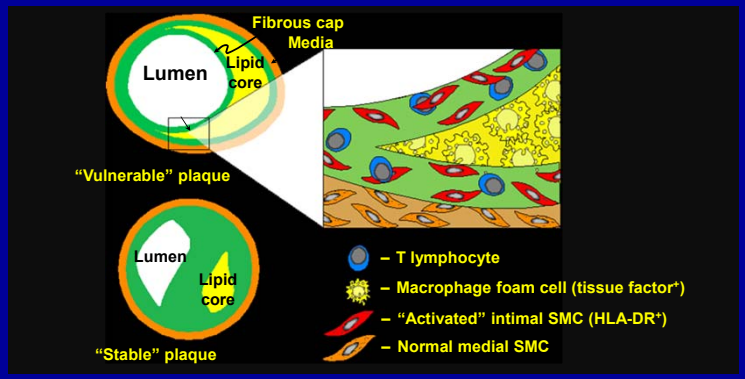
Risk Factors for Plaque Rupture



Adapted from Fuster, et al. *N Engl J Med.* 1992;326:310-318 and Falk, et al. *Circulation.* 1995;92:657-671.

STRIVE™

Characteristics of Plaques Prone to Rupture



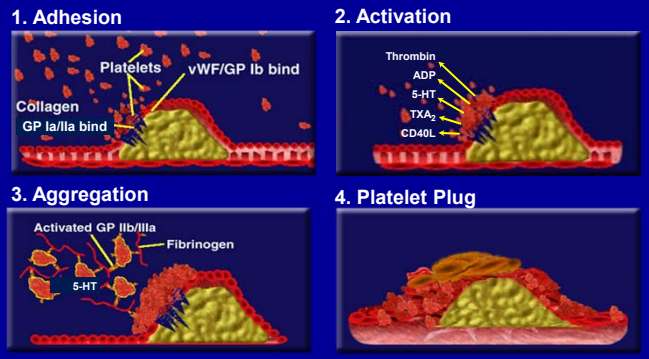
Libby P. *Circulation.* 1995;91:2844-2850.

The Role of Antiplatelet Therapy in Unstable Angina and Non-Q-wave MI

- Platelets play a key role in thrombus formation associated with rupture of unstable atherosclerotic plaques
- Angioscopic findings show that unstable angina is associated with the formation of a platelet-rich thrombus
- Anti-platelet therapy is recognized as the foundation of immediate and long-term ACS management

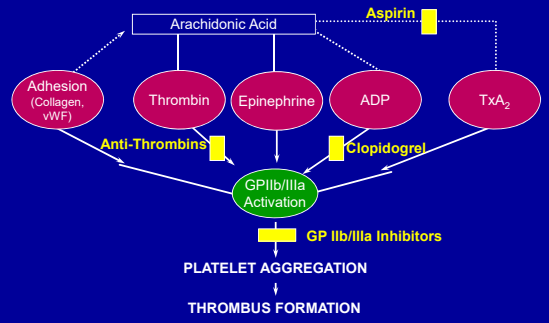
Théroux P et al *Circulation* 1998; 97:1195–1206

Formation of the Platelet Plug

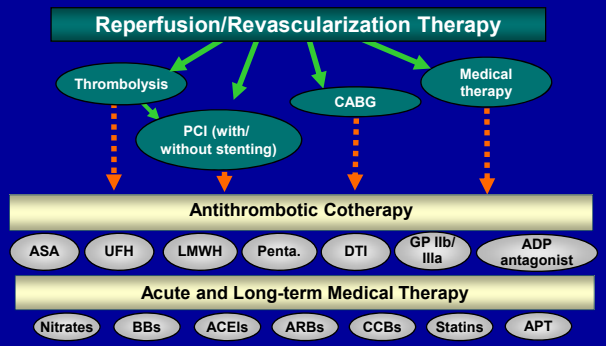


vWF = von Willebrand factor; GP = glycoprotein; ADP = adenosine diphosphate; 5-HT = 5-hydroxytryptamine (serotonin); TXA_2 = thromboxane A_2.
Adapted from Schafer AI. *Am J Med*. 1996;101:199-209.

Platelet Activation Mechanisms

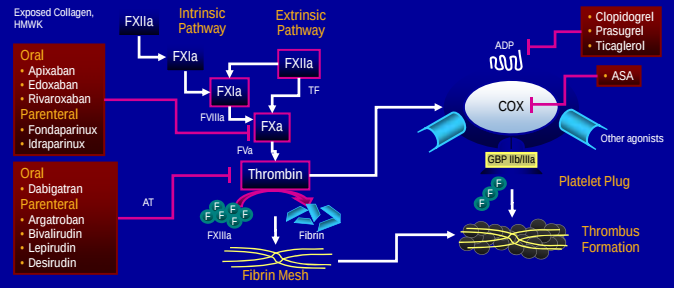


ACS Treatment Strategies



PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; ASA = aspirin; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; Penta. = pentasaccharide; DTI = direct thrombin inhibitors; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitors; ADP antagonist = adenosine diphosphate antagonist; BBs = beta blockers; ACEI = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CCBs = calcium channel blockers; APT = antiplatelet therapy

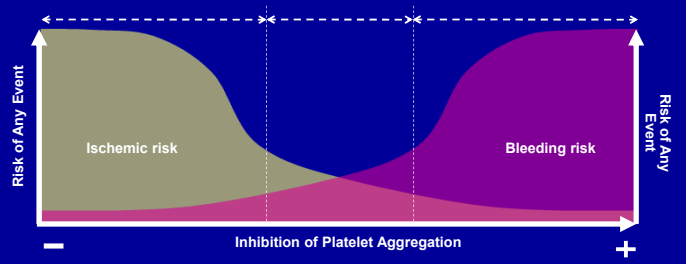
Antithrombotic and Antiplatelet Agents



ADP = adenosine diphosphate; ASA = aspirin; AT =; COX = cyclo-oxygenase; HMWK = high-molecular-weight kininogen; TF = tissue factor.
Adapted from Cannon CP, Stecker EC. Am J Manag Care. 2010;16:S291-S297; Ghebrehiwet B, et al. Front Immunol. 2011;2,pii:58; Patrono C, et al. Eur Heart J. 2011;32:2922-2932; Selwyn AP. Am J Cardiol. 2003;91:3H-11H; Turpie AG. Eur Heart J. 2008;29:155-165.

Optimizing Antiplatelet Therapy

Balancing Safety and Efficacy



ACS = acute coronary syndrome; CKD = chronic kidney disease; DM = diabetes mellitus

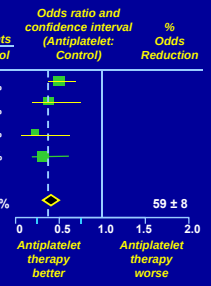
Ferreiro JL et al. *Thromb Haemost.* 2010;103:1128-1135. *Courtesy of Stephen Wiviott, MD.*

Acute Coronary Syndromes

Results of Trials Comparing Aspirin vs. Placebo in Unstable Angina

In Death and Nonfatal MI

Trial Name	N	Follow-up	Therapy (mg)	Events/Patients Study	Events/Patients Control
Lewis	1266	3 months	ASA325	5.0%	10.1%
Cairns	278	24 months	ASA1200	12.2%	25.9%
Theroux	239	6 days	ASA650	3.3%	13.6%
RISC	796	3 months	ASA75	6.5%	17.1%
Crude Total	3048			5.9%	13.6%



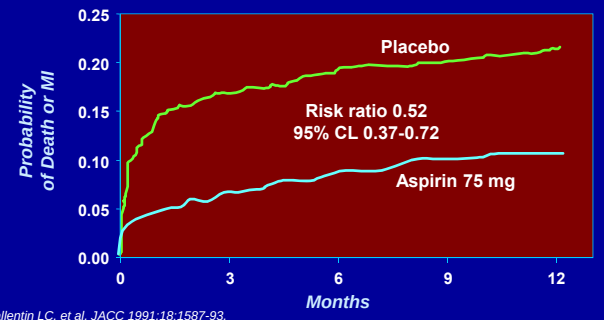
Treatment Effect, 2P <0.001

X^2 for heterogeneity, 8.0. P=0.03

White HD. In: Topol EJ, ed. Comprehensive Cardiovascular Medicine. Philadelphia, PA: Lipponcott-Raven; 1998: chap 18.

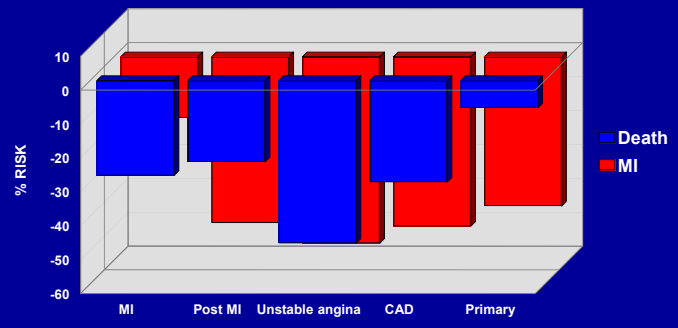
Acute Coronary Syndromes

Long-Term Efficacy of Aspirin in Reducing Death or MI in Patients with Unstable Angina



Wallentin LC, et al. JACC 1991;18:1587-93.

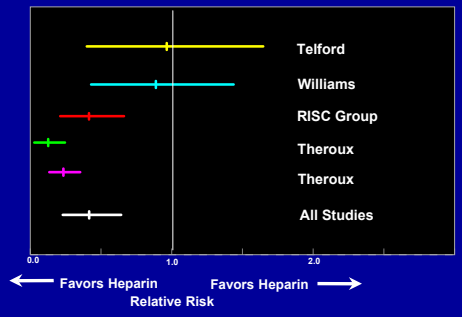
Aspirin as a Therapeutic Agent in Cardiovascular Disease



AHA Special Report Circulation 1993;87:659 86 Studies 670,000 patient years

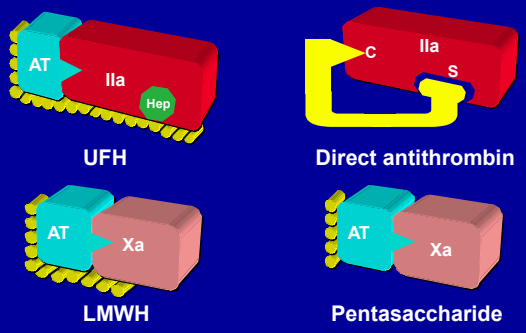
Intravenous Heparin for Unstable Angina

Meta-Analysis 5 Trials 1,845 Subjects



AHCPR Unstable Angina Guideline 1994

Anti-Thrombotic Therapy in ACS Rx

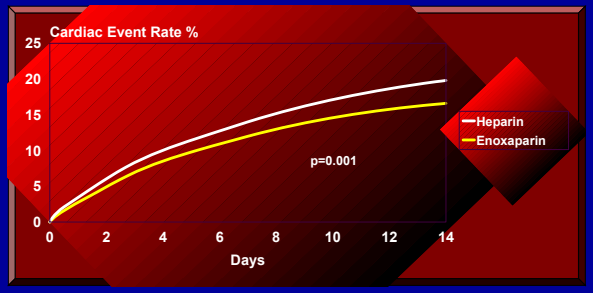


Konkle BA, Schafer AI. In: Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Braunwald's Heart Disease*. 7th ed. Vol 2. Philadelphia: Elsevier Saunders; 2005:2067-2092.

= saccharide unit.

Low Molecular Weight Heparin for Unstable Angina

ESSENCE Trial



3100 patients with unstable angina or NonQ MI
Enoxaparin 1.0 mg/kg bid vs Heparin PTT 60-90, both plus aspirin

Unfractionated Heparin and LMWH in ACS Without ST Elevation: a Meta-Analysis

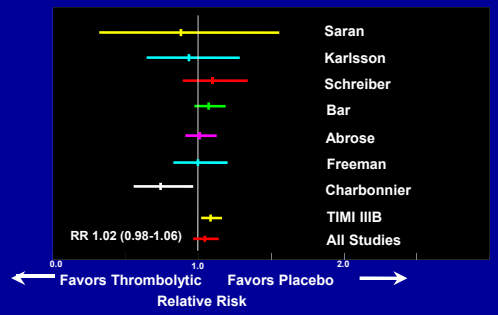
Death or MI at up to 7 days	RR	95% CI	P
UH or LMWH vs Placebo	0.53	0.38-0.73	0.0001
UH vs LMWH	0.88	0.69-1.12	0.34

12 trials: 17,157 patients

Lancet 2000; 355: 193642

Intravenous Thrombolytics for ACS

Meta-Analysis 8 Trials 9,000 Subjects



AHCPR Unstable Angina Guideline 1994

Glycoprotein IIb/IIIa Antagonists in Acute Coronary Syndromes

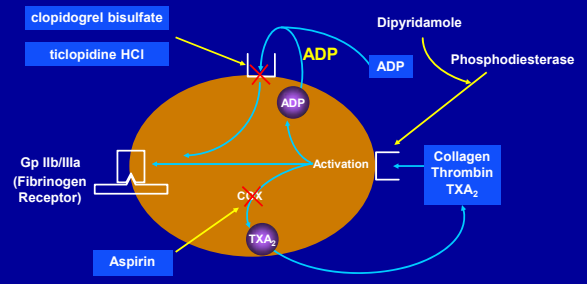
	Placebo vs GP	RR, (95% CI)	P value
Death or MI / 30 day	11.8 vs 10.8	0.91 (0.84-0.98)	0.015
Death / 30 day	3.7 vs 3.4	0.91 (0.81-1.03)	0.14
Major Bleeding	1.4 vs 2.4	1.62 (1.36-1.94)	0.0001

No PCI/CABG Patients: 8.8% vs 8.4%, RR 0.95 (0.86-1.05) p=NS
PCI/CABG Patients: 6.6% vs 14.9%, RR 0.89 (0.0.80-0.98, P=0.001

6 trials of IV gp IIb/IIIa receptor antagonists in ACS, n=31,402
PRISM, PRISM PLUS, PARAGON A, PURSUIT, PARAGON B, GUSTO-IV
Lancet 2002;359: 189-198

Oral Antiplatelet Agents

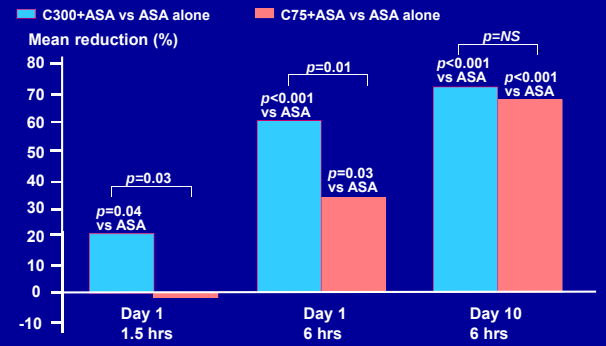
Different Mechanisms of Action



ADP = adenosine diphosphate, TXA2 = thromboxane A2, COX = cyclooxygenase.
Schafer AI. Am J Med. 1996;101:199–209.

Rapid and Synergistic Effect of Clopidogrel on top of ASA (Healthy Volunteers)

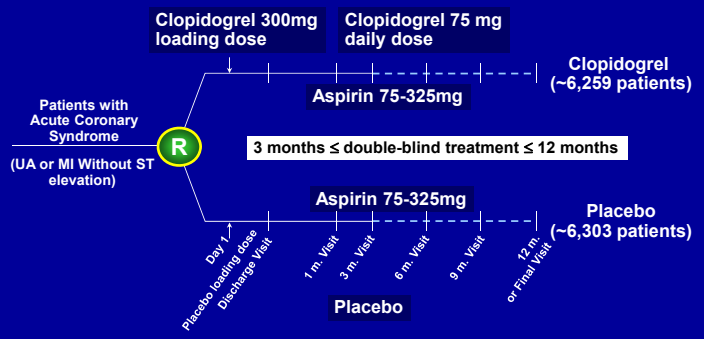
Mean reduction of platelet deposition compared with ASA alone



n=18 for all comparisons

Cadroy Y et al *Circulation* 2000;101:2823–2828

CURE: Patient Randomization

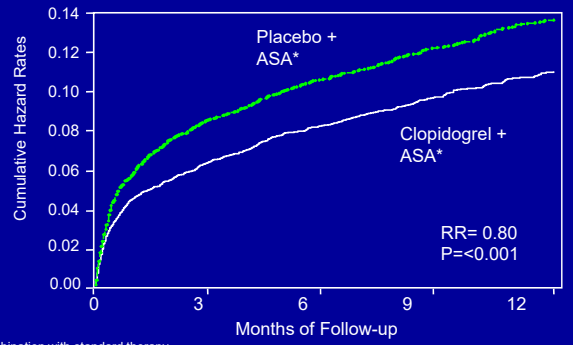


R=Randomization

CURE Steering Committee. NEJM. 2001;345:494-502

CURE Primary Endpoint:

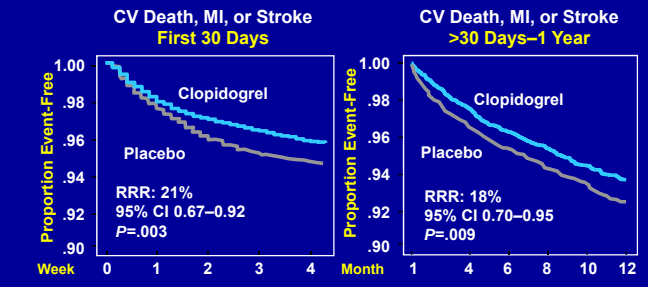
CV Death/MI/Stroke



* In combination with standard therapy

CURE Steering Committee. NEJM. 2001;345:494-502.

CURE Study: Event-Free Survival



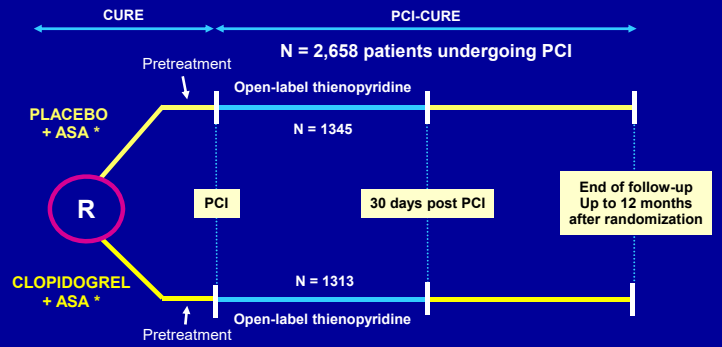
No. at Risk						
Clopidogrel	6259	6145	6070	6026	5990	
Placebo	6303	6159	6048	5993	5965	

No. at Risk						
Clopidogrel	5981	5481	4742	4004	3180	2418
Placebo	5954	5390	4639	3929	3159	2388

RRR = relative risk reduction.

Adapted with permission from Yusuf S, et al. *Circulation*. 2003;107:966-972.

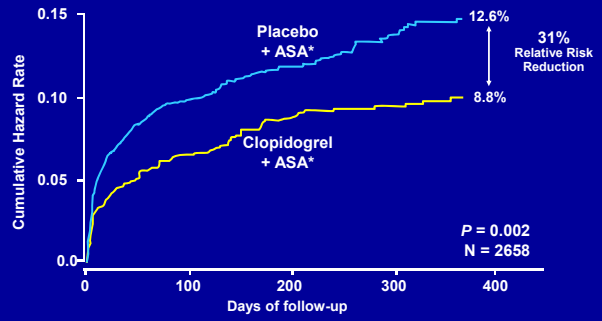
PCI-CURE Study Design



* In addition to other standard therapies.

Mehta et al for the CURE Investigators. *Lancet*. 2001;358:527-533.

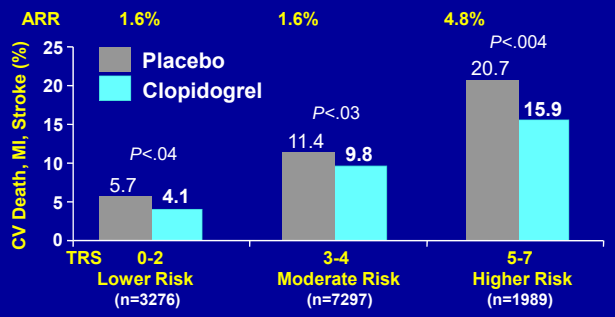
PCI-CURE Results



* In addition to other standard therapies.

Mehta et al for the CURE Investigators. *Lancet.* 2001;358:527-533.

CURE Study: Benefit of Clopidogrel Stratified by TIMI Risk Score (TRS)



ARR = adjusted risk reduction.

Adapted with permission from Budaj A, et al. *Circulation*. 2002;106:1622-1626.

CURE Results: Bleeding

Endpoint	Aspirin + Placebo (n=6303)	Aspirin + clopidogrel (n=6259)	Relative risk	p value
Major bleeding	2.7%	3.7%	1.34	0.001
Life-threatening bleeding	1.8%	2.2%	1.15	N/A
Fatal bleeding	0.2%	0.1%	0.5	N/A
Minor bleeding	2.4%	5.1%	1.78	<0.001
Transfusions	2.2%	2.8%	1.28	0.03

CURE Steering Committee. NEJM. 2001;345:494-502.

Major/Life-Threatening Bleeds within 7 Days of CABG Surgery

	Placebo	Clopid	RR	p
Stopped ≤ 5 days prior to CABG	N = 476	N = 436		
Pts with Maj/LT Bleeds	6.3%	9.6%	1.53	0.06
Stopped > 5 days prior to CABG	N = 454	N = 456		
Pts with Maj/LT Bleeds	5.3%	4.4%	0.83	0.53

ISAR-REACT: Trial Design

2159 low- to intermediate-risk patients undergoing elective PCI with stent placement

Clopidogrel* (600-mg loading dose)

325-500 mg Aspirin

Randomized

Abciximab + 70 U/kg heparin (n = 1079)

Clopidogrel 150 mg/d until discharge, then 75 mg/d for 4 wk*

End Points:

- **Primary** 30-day death/MI/urgent target-vessel revascularization
- **Secondary** 30-day bleeding complications

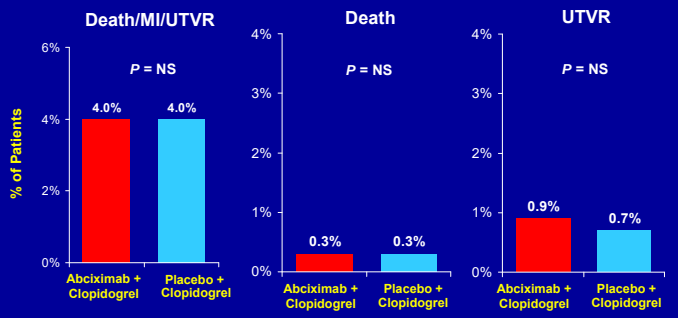
Placebo + 140 U/kg heparin (n = 1080)

Clopidogrel 150 mg/d until discharge, then 75 mg/d for 4 wk*

*In addition to aspirin.

Kastrati A, et al. *N Engl J Med*. 2004;350:232-238.

ISAR-REACT Primary End Point: 30-Day Death/MI/UTVR



UTVR = urgent target-vessel revascularization.

Adapted with permission from Kastrati A, et al. *N Engl J Med*. 2004;350:232-238.

High Risk ACS After Clopidogrel 600 mg Loading Dose: ISAR-REACT 2

30 Day Outcomes

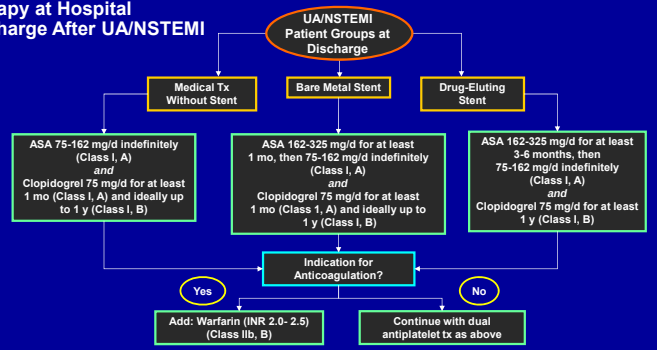
End point	Abciximab (%)	Placebo (%)	RR (95% CI)
Death/MI/ urgent TVR*	8.9	11.9	0.75 (0.58–0.97)
Death	1.1	1.6	0.69 (0.32–1.47)
MI	8.1	10.5	0.77 (0.59–1.02)
Urgent TVR	1.0	1.2	0.83 (0.36–1.92)

*Primary end point

Kastrati A et al. *JAMA* 2006; available at: http://www.jama.com.

ACC/AHA UA/NSTEMI Guideline Revision

Long-term Antithrombotic Therapy at Hospital Discharge After UA/NSTEMI



Reproduced with permission from Anderson JL, et al. *J Am Coll Cardiol*. 2007;50:652-726.

CURRENT-OASIS 7
Clopidogrel Results

Patients with UA/NSTEMI/STEMI planned for early invasive strategy
(ie, intended for PCI as early as possible within 72 hours)

Randomized

Clopidogrel Standard-Dose Group
Clopidogrel 300 mg LD (+ placebo) day 1 followed by 75 mg (+ placebo) from days 2 to 7; 75 mg from days 8 to 30

Clopidogrel High-Dose Group
Clopidogrel 600 mg LD day 1 followed by 150 mg from days 2 to 7; 75 mg from days 8 to 30

	Standard (%)	Double (%)	HR (95% CI)	*P* Value
CV death/MI/Stroke				
Overall (N = 25,086)	4.4	4.2	0.94 (0.83-1.06)	0.30
PCI (n = 17,263)	4.5	3.9	0.86 (0.74-0.99)	0.039
No PCI (n = 7,855)	4.2	4.9	1.17 (0.92-1.40)	0.14

Mehta SR, et al. N Engl J Med. 2010;363:930-942; Mehta SR, et al. Lancet. 2010;376:1233-1243; Mehta SR, et al. CURRENT-OASIS 7 presentation. www.clinicaltrialresults.org. Accessed February 16, 2012.

P_2Y_{12} Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, not limited by metabolism	Active drug
Onset of Effect^	2-4 hours	30 minutes	30 minutes
Duration of Effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

^ 50% inhibition of platelet aggregation

Hamm CW et al. Eur Heart J. 2011;32:2999-3054

TRITON-TIMI 38
Study Design

ACS (STEMI or UA/NSTEMI) and Planned PCI

ASA — N = 13,600

Double-blind

Clopidogrel
300 mg LD/75 mg MD

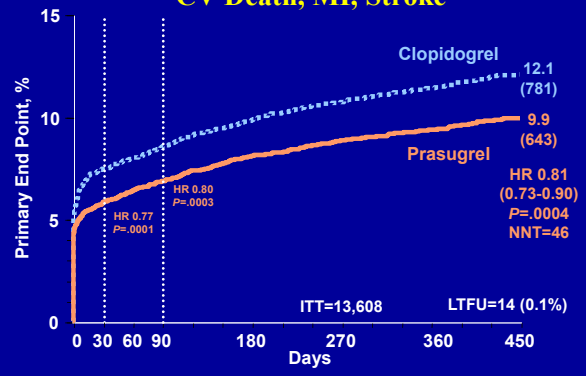
Prasugrel
60 mg LD/10 mg MD

Median duration of therapy – 12 months

1o endpoint: CV death, MI, stroke
2o endpoints: CV death, MI, stroke, rehospitalization for recurrent ischemia, UTVR, ST

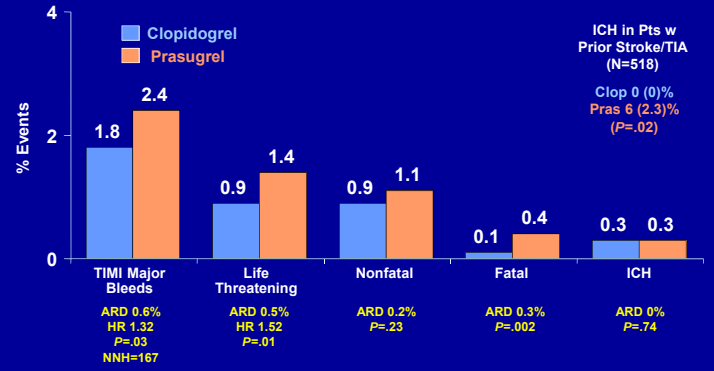
MD = maintenance dose; TRITON-TIMI 38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction; UTVR = urgent target-vessel revascularization.
Wiviott SD, et al. Am Heart J. 2006;152:627-635. Wiviott SD, et al. N Engl J Med. 2007;357:2001-2015.

TRITON-TIMI 38 Primary End Point: CV Death, MI, Stroke



Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.

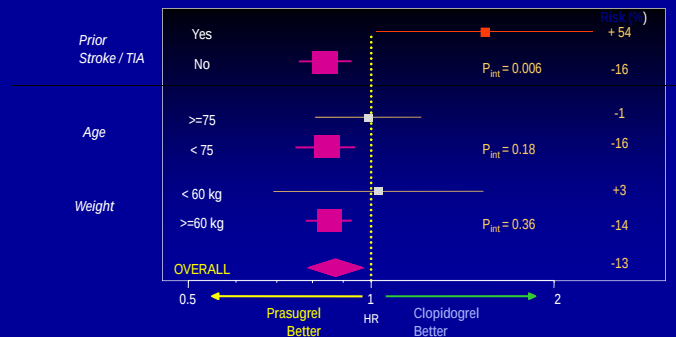
TRITON-TIMI 38: Bleeding Events—Safety Cohort (N=13,457)



Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.

TRITON TIMI 38: *Net Clinical Benefit*

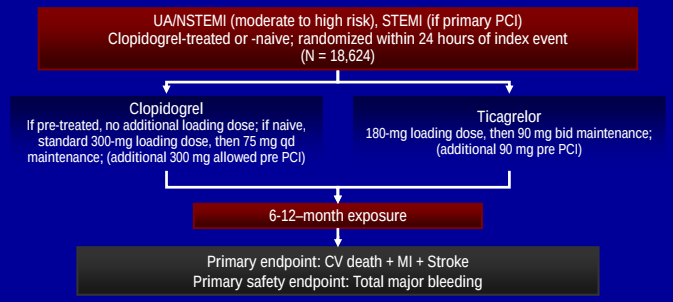
Prasugrel vs Clopidogrel Subgroups; Post-hoc Analysis



Wiviott SD et al. N Engl J Med. 2007;357:2001-2015

PLATO

Study Design

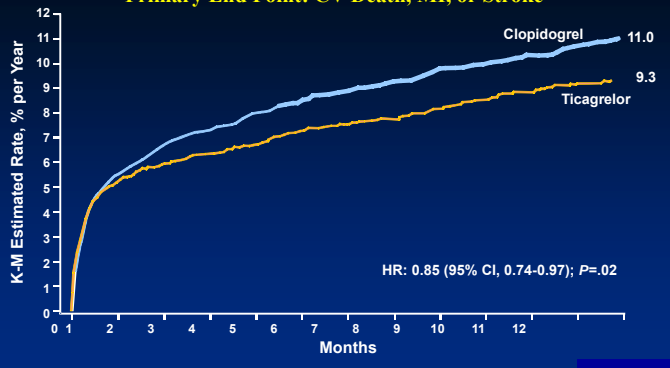


Bid = twice daily; qd = once daily; PLATO = Study of Platelet Inhibition and Patent Outcomes.

Wallentin L, et al. N Engl J Med. 2009;361:1045-1057. Wallentin L. PLATO presentation. www.clinicaltrialresults.org. Accessed February 16, 2012.

PLATO

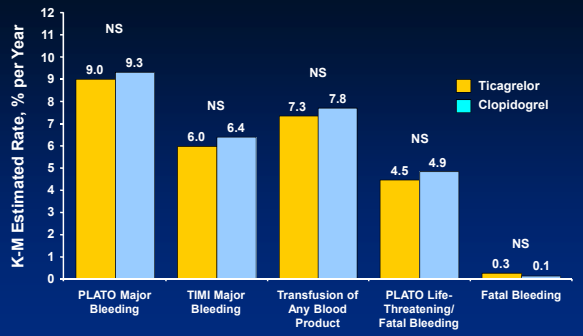
Primary End Point: CV Death, MI, or Stroke



Wallentin L, et al. N Engl J Med. 2009;361:1045-1057; Wallentin L. PLATO presentation. www.cliniciantrialresults.org. Accessed February 18, 2012.

STRIVE

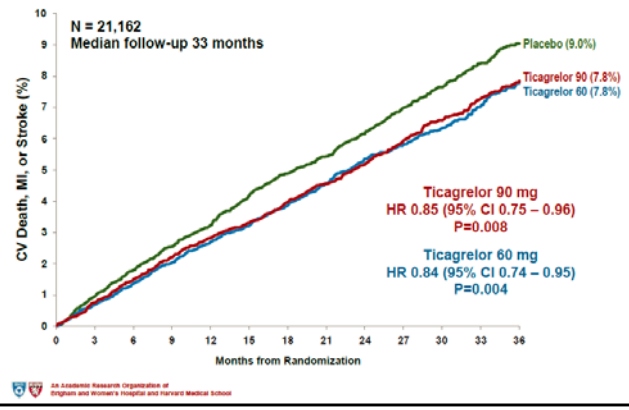
PLATO: Total Major Bleeding



Major bleeding and major or minor bleeding according to TIMI criteria refer to nonadjudicated events analyzed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.

STRIVE

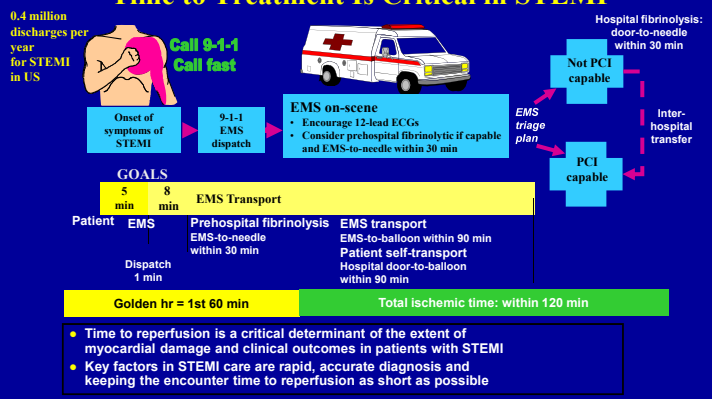
Primary Endpoint



Highlights of Recent Antiplatelet Trials

- Clopidogrel
  - Double-dose (600 mg load, 150 mg qd x 1 week) in setting of PCI decreases non-fatal MI and stent thrombosis
- Prasugrel
  - ↓early and late ischemic events compared with clopidogrel
  - ↓ stent thrombosis
  - Especially large benefit in patients with diabetes and in the STEMI population
- Ticagrelor
  - ↓ early and late ischemic events compared with clopidogrel
  - ↓ stent thrombosis
  - ↓ mortality compared with clopidogrel

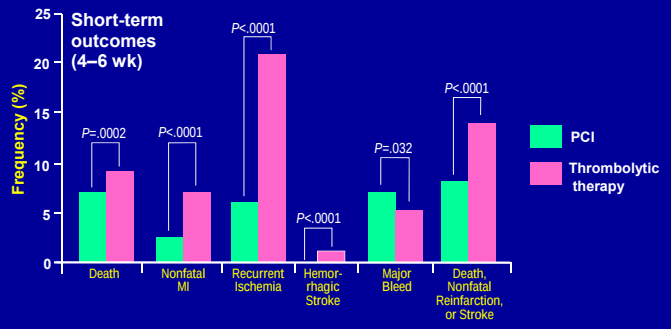
Time to Treatment Is Critical in STEMI



- Time to reperfusion is a critical determinant of the extent of myocardial damage and clinical outcomes in patients with STEMI
- Key factors in STEMI care are rapid, accurate diagnosis and keeping the encounter time to reperfusion as short as possible

Figure adapted with permission from Antman EM, et al. *J Am Coll Cardiol.* 2008;51(2):210-247.

Primary PCI vs Thrombolysis in STEMI: Quantitative Analysis (23 RCTs, N=7739)



Adapted with permission from Keeley EC, et al. *Lancet*. 2003;361:13-20.

Early Invasive vs Initial Conservative Strategy

General Considerations in UA/NSTEMI

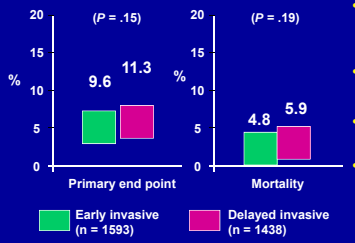
EARLY INVASIVE STRATEGY GENERALLY PREFERRED	INITIAL CONSERVATIVE STRATEGY GENERALLY PREFERRED OR REASONABLE
• Recurrent angina at rest or with low level activities despite intensive medical therapy • Elevated cardiac biomarkers (TnT or TnI) • New or presumably new ST-depression • Signs or symptoms of heart failure or new or worsening mitral regurgitation • High-risk findings from noninvasive testing • Hemodynamic instability • Sustained ventricular tachycardia • PCI within 6 mo; prior CABG • High risk score (e.g. GRACE, TIMI) • Mild to moderate renal dysfunction • Diabetes mellitus • Reduced left ventricular function (LVEF <40%)	• Low risk score (e.g. GRACE, TIMI) • Patient or physician preference in the absence of high-risk features

CABG = coronary artery bypass graft surgery; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction; TnI = troponin I; TnT = troponin T

Anderson et al. J Am Coll Cardiol 2012;61:e1-e171

TIMACS: Timing in NSTEMI

Trial design: Patients with NSTEMI were randomized to an early (within 24 hours) or delayed (after 36 hours) invasive strategy. Clinical outcomes were compared at 6 months.



Results

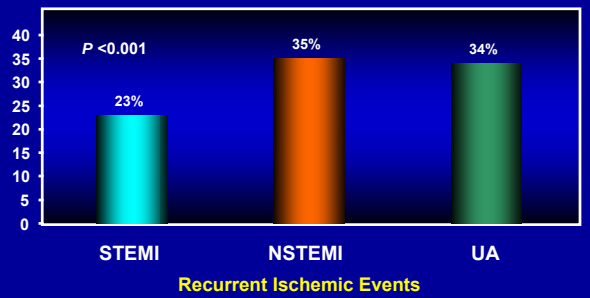
- No difference in primary outcome (death, MI, stroke) between the two arms (HR, 0.85; 95% CI, 0.68-1.06; *P* = .15), except in high-risk patients (GRACE risk score >140) (HR, 0.65; 95% CI, 0.48-0.89; *P* = .005)
- Death, MI, refractory ischemia ↓ in early invasive arm (*P* = .003), due to ↓ in refractory ischemia (*P* <.001); death (*P* = .19), stroke (*P* = .74) similar
- Major bleeding was similar (*P* = .55)

Conclusions

- An early invasive strategy (within 24 hours) is not associated with harm compared with a delayed invasive strategy (after 36 hours) in patients with NSTEMI, and may be beneficial in high-risk patients
- Significant reduction in refractory ischemia with an early invasive strategy

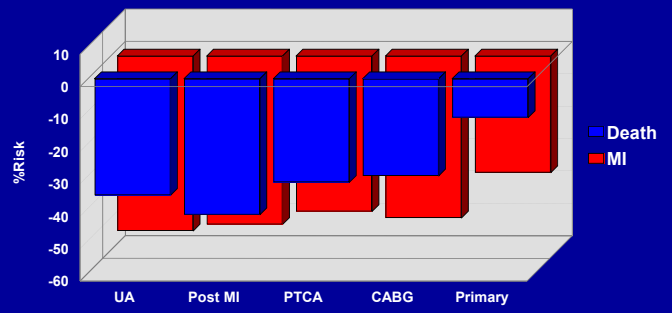
Mehta SR, et al. *N Engl J Med*. 2009;360(21):2165-2175.

Continued Risk of Recurrent Ischemic Events During First Year



*** Symptoms of ischemia, ST-segment deviations, definite T-wave inversion, and/or new hypotension, pulmonary edema, or cardiac murmur. GUSTO-IIb Data**
Armstrong PW, et al. 1998 *Circulation*.; 98:1860-1868.

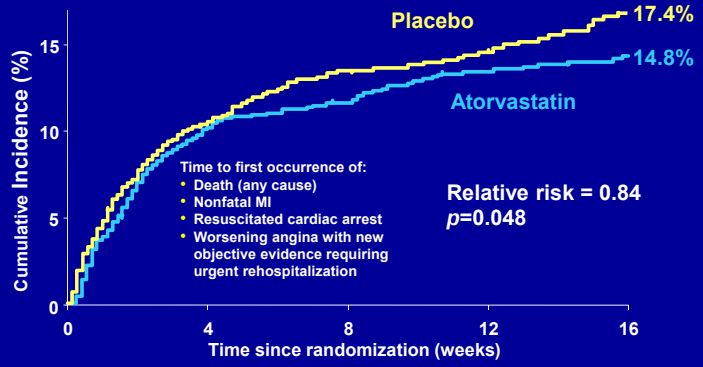
Statins as a Therapeutic Agent in Cardiovascular Disease



12 Trials 186,800 patient-years follow-up

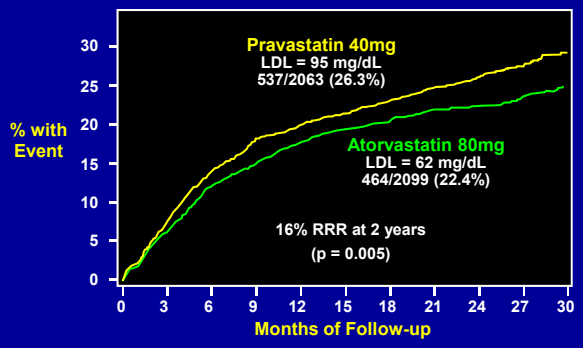
NEJM 1995;333:1301 Lancet 1994;344:1383 Circulation 1995;91:2528

MIRACL: Primary Composite Endpoint



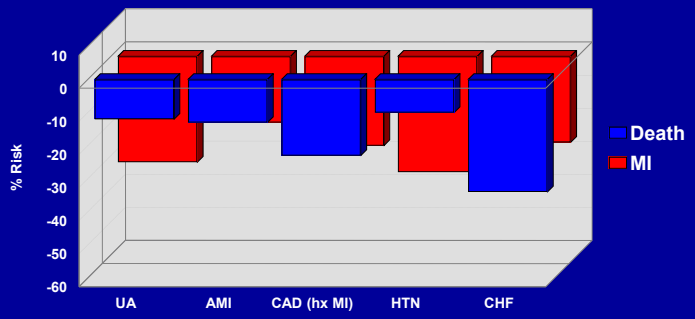
MIRACL: 3086 with ACS, TC < 270, within 1-4 days Atorvastatin 80 mg vs Placebo (LDL B 124 P135 A 72)
Schwartz JAMA;285:1711-1718

PROVE-IT TIMI 22 Results: All-Cause Death or Major CV Events Post ACS



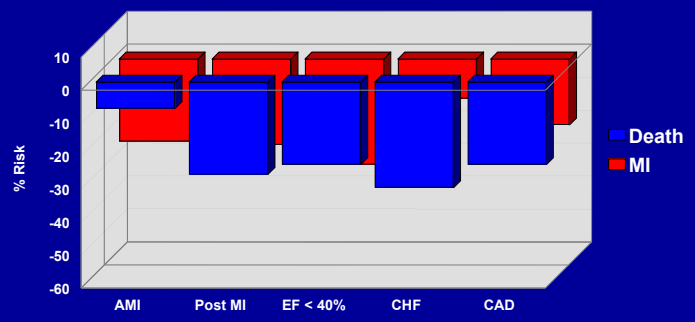
Cannon NEJM 2004;350:1495-1504

Beta-Blockers as a Therapeutic Agent in Cardiovascular Disease



Yusuf Circ 1990;82:II-117 48 Trials 260,000 patient years

ACE Inhibitors as a Therapeutic Agent in Cardiovascular Disease



Circulation 1994;90:2056 HOPE 42 Trials 332,000 patient years f/u

ACC/AHA UA/NSTEMI Guideline Revision

Secondary Prevention: Recommendations

- Aspirin and/or ADP RA
- β-blockers
- ACE inhibitors/ARBs
- Aldosterone blockade (EF <40)
- Lipid management
  - High intensity statin therapy regardless of baseline LDL-C initiated prior to discharge
- Encouraging consumption of omega-3 fatty acids for risk reduction reasonable

Updated from Anderson JL, et al. *J Am Coll Cardiol*. 2007;50(7):e1-e157.

ACC/AHA UA/NSTEMI Guideline Revision

Secondary Prevention: Additional Recommendations

- BP control
  - <130/80 mm Hg
- Diabetes management: HbA_{1c} <7%, SGLT2 inhibitors or GLP-1 agonists
- Smoking cessation/no environmental smoke exposure
  - Education, referral programs, drug therapy
- Physical activity (30-60 min, 7 d/wk; min 5 d/wk)
- Cardiac rehabilitation
- Weight management
  - BMI 18.5-24.9 kg/m^2
  - Waist circumference: men, <40 in; women, <35 in
- Discharge education/referral
- Stepped-care approach to musculoskeletal pain management
- Annual influenza immunization
- HRT, antioxidant vitamin supplements (C, E, beta carotene) and folic acid not recommended

Updated Anderson JL, et al. *J Am Coll Cardiol*. 2007;50(7):e1-e157.

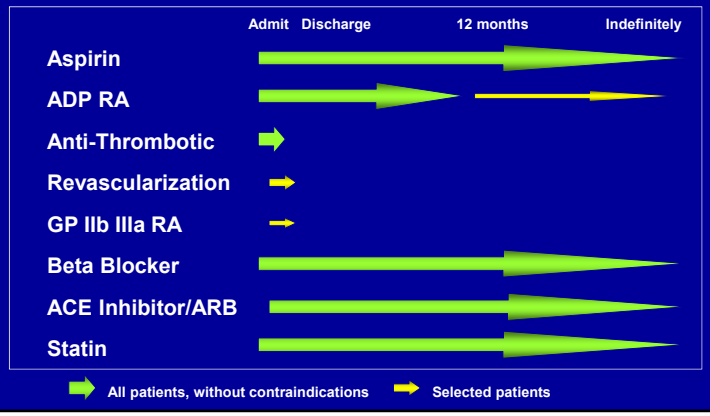
Cumulative Impact of Five Simple Cardiovascular Protective Medications

	Relative-risk	1yr CV event rate
None	- -	20%
Aspirin	↓ 25%	15%
ADP RA	↓ 20%	12%
Beta blocker	↓ 25%	9.0%
ACE inhibitor	↓ 25%	6.8%
Statin	↓ 30%	4.7%
Statin LDL <70	↓ 16%	4.0%

Cumulative risk reduction if all five medications are used: 80%
Absolute risk reduction: 16.0%, NNT = 6

CV event = CV death, MI, or stroke

Evidence Based ACS Management



Conclusions

- Large number of patients are impacted by ACS and these are high risk patients
- Antiplatelet therapy with aspirin and ADP RA and anti-thrombotic Rx, are the foundation of immediate ACS management; early invasive management improves outcomes. Rapid reperfusion in STEMI is critical
- Combination cardiovascular protective medications used long-term can dramatically reduce risk after ACS (aspirin, ADP RA, beta blockers, ACE inhibitors, and high intensity statin therapy)