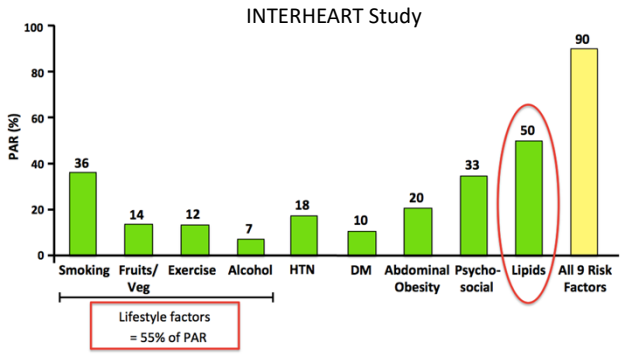
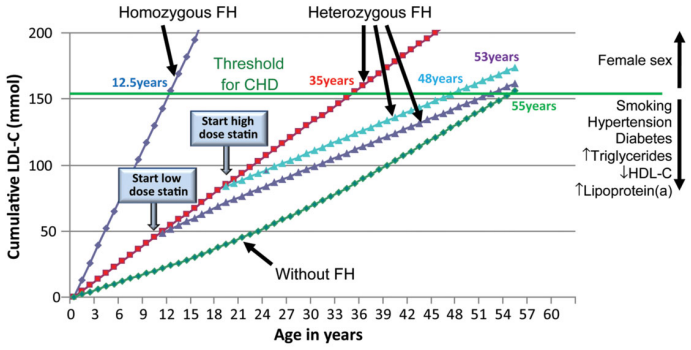
How Should My Approach to Hypercholesterolemia Change?

Importance of Hypercholesterolemia



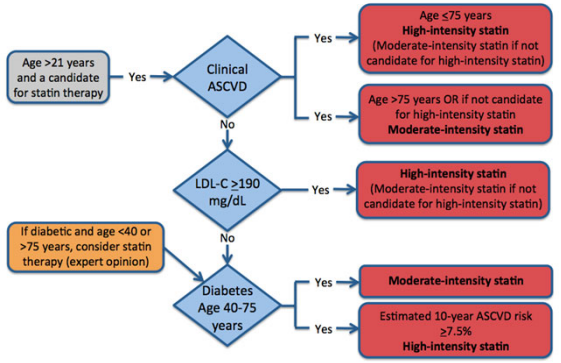
N = 15,152 patients and 14,820 controls in 52 countries.
Yusuf S et al. *Lancet* 2004;364:937-952

It's All About Reducing the Area Under the Curve



Nordestgaard BG et al. *Eur Heart J* 2013;34:3478-3490

2013 ACC/AHA Blood Cholesterol Guidelines



Stone NJ et al. *J Am Coll Cardiol* 2014;63:2889-2934

Lifestyle Interventions to Lower LDL-Cholesterol

Dietary Modification	Recommendation	~LDL-C Reduction
Saturated fat	<7% calories	8%-10%
Dietary cholesterol	<200 mg/d	3%-5%
Plant stanols/sterols	Up to 2 g/d	6%-10%
Viscous dietary fiber	5-10 g/d	3%-5%
Soy protein	20-30 g/d	5%-7%
Almonds	>10 g/d	1%/10 g
Weight reduction	Lose 10 lb (4.5 kg)	5%-8%
Total		30%-45%

Ripsin CM et al. *JAMA* 1992;267:3317-3325,
Rambjor GS et al. *Lipids* 1996;31:S45-S49
Jones PJH. *Curr Atheroscler Rep* 1999;1:230-235
Lichtenstein AH. *Curr Atheroscler Rep* 1999;1:210-214
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Circulation* 2002;106:3143-3421
Jenkins DJ et al. *JAMA* 2003;290:502-510

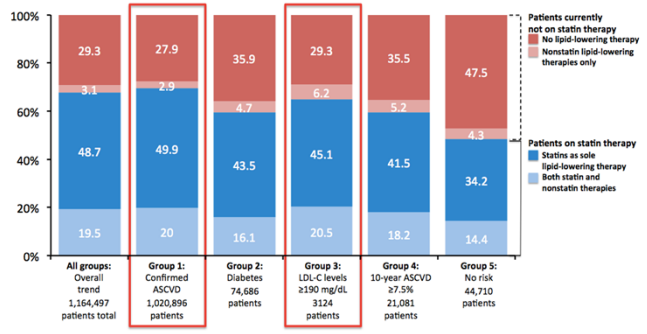
Intensities of Statin Therapy

High Intensity	Moderate Intensity	Low Intensity
Lowers LDL-C on average by ≥50%	Lowers LDL-C on average by 30% to ≤50%	Lowers LDL-C on average by <30%
Atorvastatin 40*-80mg	Atorvastatin 10 (20) mg	Simvastatin 10 mg
Rosuvastatin 20 (40) mg	Rosuvastatin (5) 10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg†	Lovastatin 20 mg
	Pravastatin 40 (80) mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitavastatin 2-4 mg	

Stone NJ et al. *J Am Coll Cardiol* 2014;63:2889-2934

How are We Doing in Those at Highest Risk?

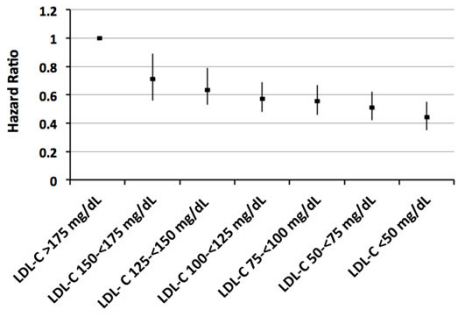
1,174,545 patients from the NCDR PINNACLE registry from 2008-2012



Maddox TM et al. *J Am Coll Cardiol* 2014;64:2183-92

Should We be Pushing LDL-Cholesterol Levels Lower?

Meta-analysis of 38,153 patients from 8 randomized statin trials

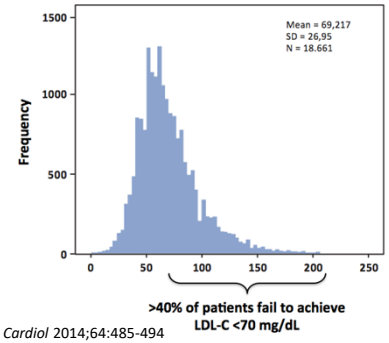


Boekholdt SM et al. *J Am Coll Cardiol* 2014;64:485-494

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Is It Even Possible to Get There?

Subgroup analysis of 18,677 patients assigned to high-intensity statin

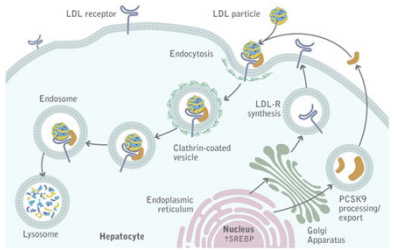


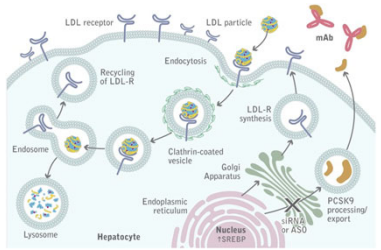
Boekholdt SM et al. *J Am Coll Cardiol* 2014;64:485-494

Mechanism of Action of PCSK9 Inhibitors

PCSK9 promotes the degradation of the LDL receptor and prevents it from recycling to the cell membrane

PCSK9 inhibitors are monoclonal antibodies that bind to PCSK9 and prevent association between the LDL receptor and PCSK9

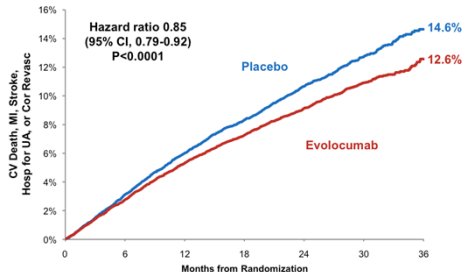




Lambert G et al. *J Lipid Res* 2012;53:2515-2524

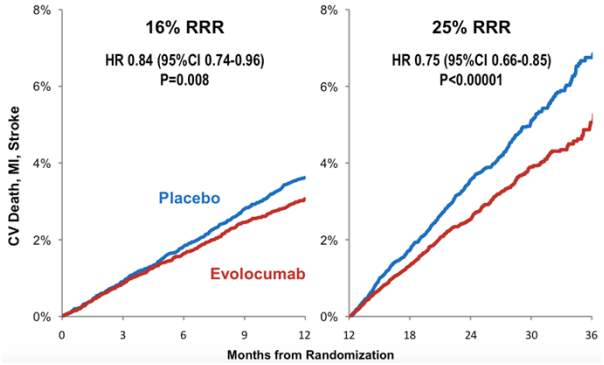
FOURIER Trial

27,564 high risk patients with stable ASCVD and a LDL-cholesterol ≥70 mg/dL on background statin therapy randomized to evolocumab (140 mg every 2 weeks or 420 every month) or placebo for a median of 26 months



Sabatine MS et al. *N Engl J Med* 2017;376:1713-1722

FOURIER Trial—Landmark Analysis



Sabatine MS et al. *N Engl J Med* 2017;376:1713-1722

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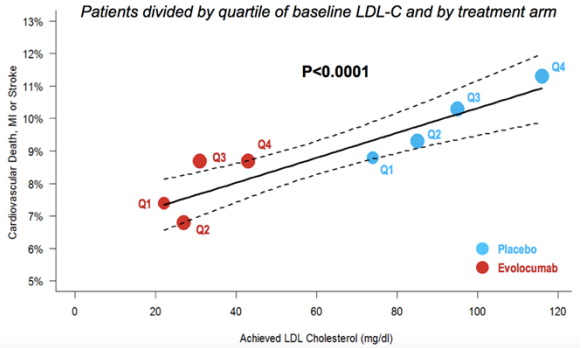
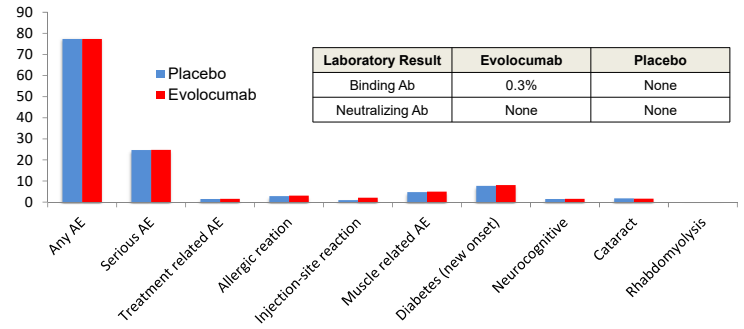
FOURIER Trial—Relationship Between LDL-C and Event Rate



Sabatine MS et al. *N Engl J Med* 2017;376:1713-1722

FOURIER Trial—Safety End Points

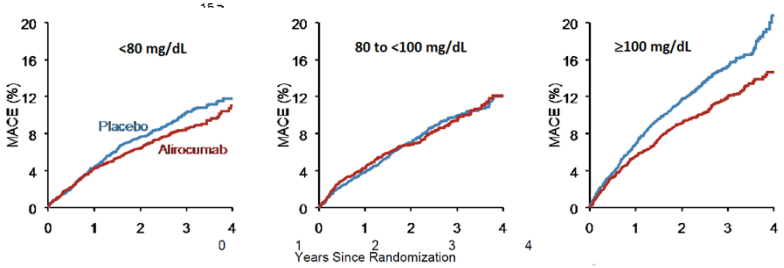


Laboratory Result	Evolocumab	Placebo
Binding Ab	0.3%	None
Neutralizing Ab	None	None

Ab, antibody; AE, adverse event
Sabatine MS et al. *N Engl J Med* 2017;376:1713-1722

ODYSSEY Outcomes Trial

18,924 patients 1-12 months post ACS on high-intensity statin therapy with a LDL-cholesterol ≥70 mg/dL on background statin therapy randomized to alirocumab (75 mg or 150 mg every 2 weeks) or placebo for a median of 2.8 years



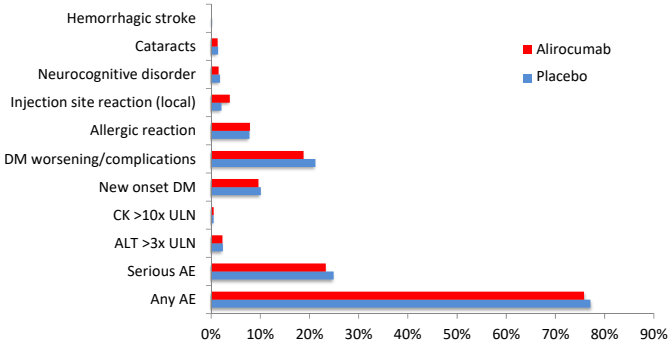
Steg PG et al. Presented at the 2018 American College of Cardiology Scientific Sessions

ODYSSEY Outcomes Trial—Key Efficacy End Points

Endpoint	Alirocumab	Placebo	HR (95% CI)	P-value
MACE	903 (9.5%)	1052 (11.1%)	0.85 (0.78-0.93)	0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76-1.11)	0.38
Non-fatal MI	626 (6.6%)	722 (7.6%)	0.86 (0.77-0.96)	0.006
Ischemic stroke	111 (1.2%)	152 (1.6%)	0.73 (0.57-0.93)	0.01
Unstable angina	37 (0.4%)	60 (0.6%)	0.61 (0.41-0.92)	0.02
Death, MI, ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86 (0.79-0.93)	0.0003
Coronary heart disease death	205 (2.2%)	222 (2.3%)	0.92 (0.76-1.11)	0.38
Cardiovascular death	240 (2.5%)	271 (2.9%)	0.88 (0.71-1.05)	0.15
All-cause death	334 (3.5%)	392 (4.1%)	0.85 (0.73-0.98)	0.026*

*Nominal p-value
Steg PG et al. Presented at the 2018 American College of Cardiology Scientific Sessions

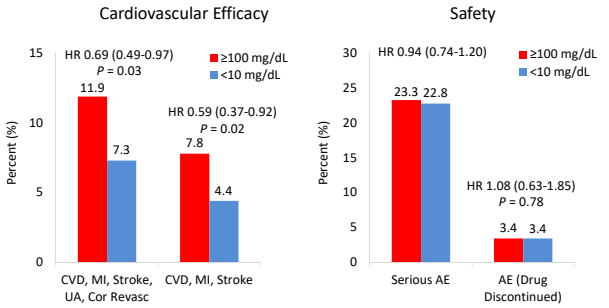
ODYSSEY Outcomes Trial—Key Safety End Points



Steg PG et al. Presented at the 2018 American College of Cardiology Scientific Sessions

Is There Such a Thing as Going Too Low?

Efficacy and safety of patients achieving a LDL-C <10 mg/dL



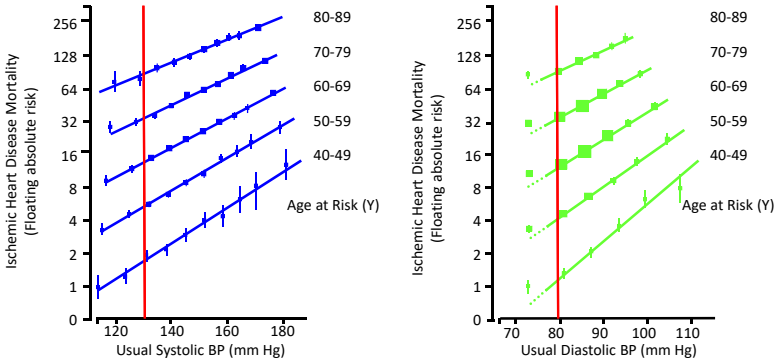
Giugliano RP et al. *Lancet* 2017;390:1962-1971

Important Takeaways

- Statins are the most effective traditional LDL-cholesterol lowering medication and should be used at the maximally tolerated intensity in those at highest risk (ASCVD or FH)
- Currently approved PCSK9 inhibitors (alirocumab and evolocumab) achieve significant reductions in LDL-cholesterol when used alone or in combination
- Both alirocumab and evolocumab significantly and safely reduce the rate of adverse events in patients with ASCVD when added to statin therapy
- Results from the FOURIER and ODYSSEY Outcomes trials provide support for lowering of LDL-cholesterol levels well below current targets for those at highest risk

How Should My Approach to High Blood Pressure Change?

Higher BP is Associated with Increased CV Risk at Every Age



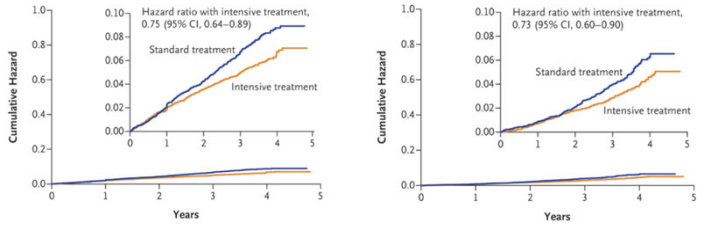
Prospective Studies Collaboration. *Lancet* 2002;360;1903-1913

SPRINT Trial

9,361 patients with a SBP ≥130 mm Hg and increased cardiovascular risk (but without diabetes mellitus) randomized to a SBP <120 mm Hg (intensive treatment) vs. a target SBP <140 mm Hg (standard treatment) for 3.3 years*

MI, ACS, Stroke, HF, or CV Death

All Cause Death



*The trial was stopped prematurely

SPRINT Research Group. *N Engl J Med* 2015;373:2103-2116

SPRINT Trial—Key Safety End Points

Endpoint	Intensive Treatment	Standard Treatment	HR	P-value
Serious adverse event	38.3%	37.1%	1.04	0.25
Hypotension	2.4%	1.4%	1.67	0.001
Syncope	2.3%	1.7%	1.33	0.05
Bradycardia	1.9%	1.6%	1.19	0.28
Electrolyte abnormality	3.1%	2.3%	1.35	0.02
Injurious fall	2.2%	2.3%	0.95	0.71
Acute kidney injury	4.4%	2.6%	1.66	<0.001
Orthostatic hypotension	16.6%	18.3%	0.88	0.01
Orthostatic hypotension w/ sx's	1.3%	1.5%	0.85	0.35

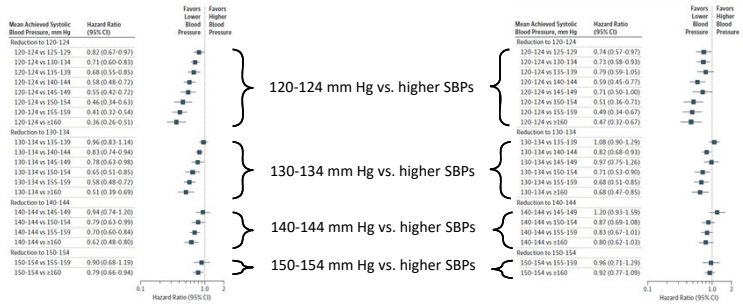
SPRINT Research Group. *N Engl J Med* 2015;373:2103-2116

Cardiovascular Effects and Mortality Benefits of BP Lowering

Network meta-analysis of 42 trials including 144,220 patients

Major Adverse CV Events

All-cause Mortality



Bundy JD et al. *JAMA Cardiol* 2017;2:775-781

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

2017 ACC/AHA High Blood Pressure Guidelines

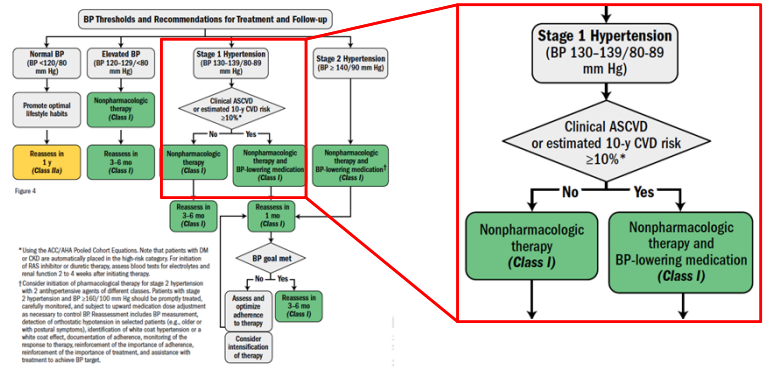
Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	*or*	80–89 mm Hg
Stage 2	≥140 mm Hg	*or*	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category

Whelton PK et al. *J Am Coll Cardiol* 2017;Epub ahead of print

2017 ACC/AHA High Blood Pressure Guidelines



Whelton PK et al. *J Am Coll Cardiol* 2017;Epub ahead of print

Acts of Commission—What to Withhold

Agent	Strategy	Agent	Strategy
Alcohol	• ≤1 drink daily for women • ≤2 drinks daily for men	Immunosuppressives (e.g., cyclosporine)	• Consider converting to tacrolimus, which may be associated with less BP effects
Amphetamines	• Discontinue or decrease dose • Consider behavioral therapies for ADHD	Oral contraceptives	• Use low-dose agents or a progestin-only form of contraception, or alternative forms of birth control
Antidepressants (e.g., MAOIs, SNRIs, TCAs)	• Consider alternative agents (e.g., SSRIs) depending on the indication • Avoid tyramine-containing foods with MAOIs	NSAIDs	• Avoid systemic NSAIDs where possible • Consider alternative analgesics
Atypical antipsychotics	• Discontinue or limit when possible. • Consider behavior therapy where appropriate • Consider alternative agents	Recreational drugs (e.g., cocaine, methamphetamine)	• Avoid use
Caffeine	• Generally limit to <300 mg/day	Systemic corticosteroids	• Avoid or limit use when possible • Consider alternative modes of administration
Decongestants	• Use for shortest duration possible and avoid in severe/uncontrolled hypertension • Consider alternative therapies as appropriate	Angiogenesis and tyrosine kinase inhibitors	• Initiate or intensify antihypertensive therapy
Herbal supplements	• Avoid use		

Whelton PK et al. *J Am Coll Cardiol* 2017;Epub ahead of print

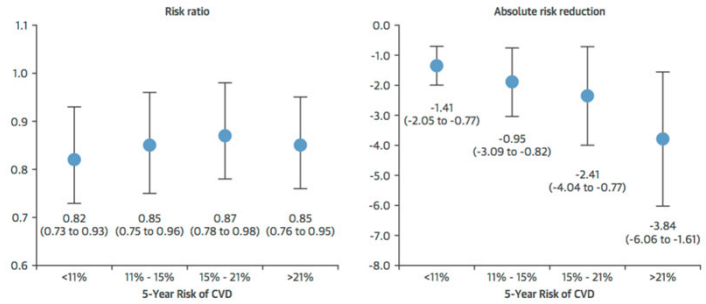
Acts of Ommission—What to Implement

Goal	Nonpharm. intervention	Dose	SBP Impact in Hypertension	SBP Impact in Normotension
Weight loss	Weight/ body fat	• Best goal is ideal body weight • Expect about 1 mm Hg for every 1-kg reduction in body weight	-5 mm Hg	-2/3 mm Hg
Healthy diet	DASH dietary pattern	• Consume a diet rich in fruits, vegetables, whole grains and low-fat dairy products with reduced content of saturated and total fat	-11 mm Hg	-3 mm Hg
Reduced intake of dietary sodium	Dietary sodium	• Optimal goal is <1500 mg/day • Aim for at least a 1000 mg/day reduction in most adults	-5/6 mm Hg	-2/3 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	• Aim for 3500-5000 mg/day, preferably by consumption of a diet rich in potassium	-4/5 mm Hg	-2 mm Hg
Physical activity	Aerobic	• 90-150 min/week • 65%-75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg
Physical activity	Dynamic resistance	• 90-150 min/week; 50%-80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg
Physical activity	Isometric resistance	• 4 x 2 min (hand grip), 1 min rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/week; 8-10 weeks	-5 mm Hg	-4 mm Hg
Moderation of alcohol intake	Alcohol consumption	• ≤1 drink daily for women • ≤2 drinks daily for men	-4 mm Hg	-3 mm Hg

Whelton PK et al. *J Am Coll Cardiol* 2017;Epub ahead of print

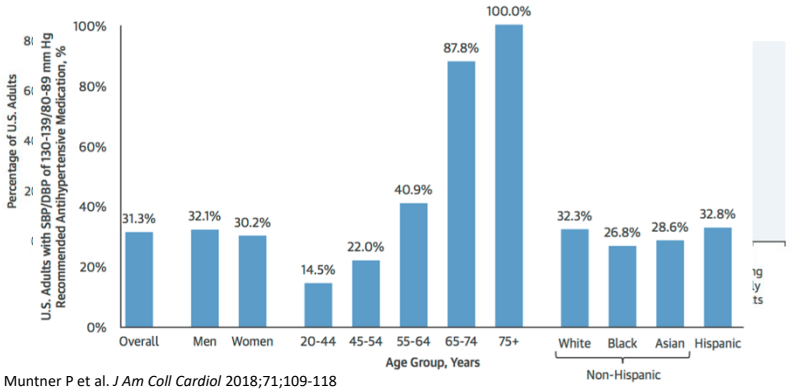
Moving Away From a 'One Size Fits All' Approach

Pooled analysis of 11 randomized controlled trials (n=51,917) of antihypertensive treatment versus placebo



Muntner P et al. *J Am Coll Cardiol* 2017;69;2446-2456

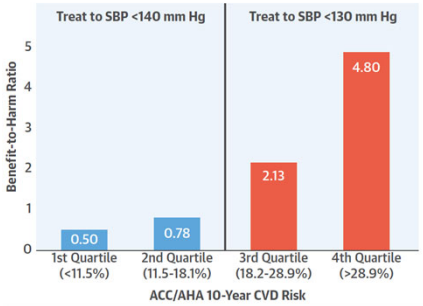
Implications of the 2017 ACC/AHA High BP Guidelines



Muntner P et al. *J Am Coll Cardiol* 2018;71;109-118

Even Further From a 'One Size Fits All' Approach

Post-hoc analysis of the SPRINT trial to evaluate the effect of baseline 10-year ASCVD risk on primary outcome events and all-cause significant adverse events

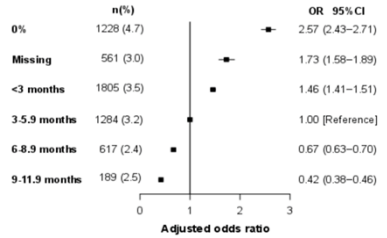


Phillips RA et al. *J Am Coll Cardiol* 2018;Epub ahead of print

BP TITRE Trial

Population record-linkage cohort study of patients (n=169,082) with newly identified high blood pressure in Caliber, England followed for a median of 5 years evaluating the impact of time in target to incident cardiovascular events

Any CV event or death



Pujades-Rodriguez M. Presented at the 2017 American Heart Association Scientific Sessions

Blood Pressure Reduction in Black Barbershops

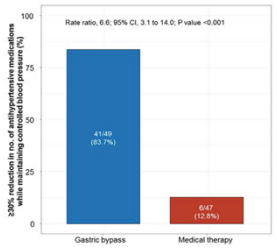
319 patrons (aged 35-74 years) getting ≥1 haircut every 6 weeks with a SBP ≥140 mm Hg for 2 separate days randomized to intervention (pharmacist evaluation and treatment at the barbershop) vs. usual care for 6 months

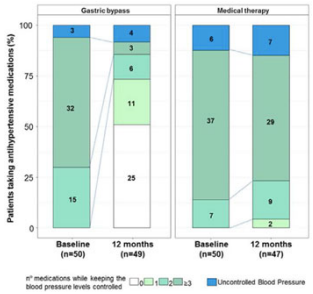
End point	Intervention (mmHg)	Control (mm Hg)	Effect	P-value
Baseline SBP	152.8	154.6		
6-month SBP	125.8	145.4		
Difference SBP	-27.0	-9.3	-21.6 mm Hg	<0.001
BP <130/80	63.6%	11.7%	5.7-fold increase	<0.001
BP drug classes*	2.6	1.4		<0.001

*Step 1: Amlodipine plus irbesartan; Step 2: Add indapamide; Step 3: Add spironolactone
Victor RG. Presented at 2018 American College of Cardiology Scientific Sessions

GATEWAY Trial

100 hypertensive, obese (BMI of 30-39.9 kg/m^2, mean of 39.6 kg/m^2) patients on ≥2 medications at maximum doses or >2 at moderate doses randomized to Roux-en-Y gastric bypass plus medical therapy vs. medical therapy alone





Schiavon CA et al. *Circulation* 2017;Epub ahead of print

Important Takeaways

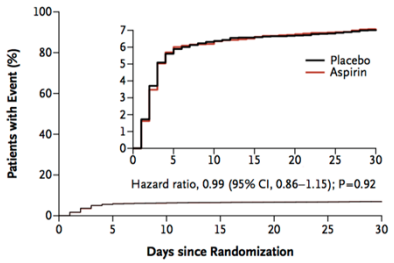
- Observational and randomized clinical trial data provide strong support for more intensive BP goals
- The 2017 ACC/AHA guidelines now define high BP as a systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥80 mmHg
- Intensive BP control provides greater benefit in those at higher baseline CV risk
- Lifestyle interventions represent important, but underutilized means to achieve BP control
- Bariatric surgery and community-based interventions (targeting patients in barber shops) represent innovative strategies to achieve significant BP control

How Should My Management Change in the Perioperative Setting to Minimize Cardiovascular Risk?

POISE-2 Trial

10,010 patients at risk for vascular complications undergoing non-cardiac surgery randomized in a 2 x 2 factorial trial design to aspirin or clonidine vs. placebo

30-day Death or Nonfatal Myocardial Infarction



Life-threatening of Major Bleeding

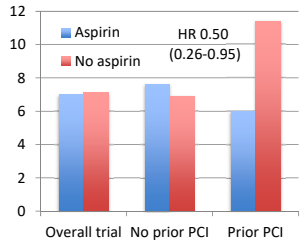
Day	Aspirin	Placebo	P-value
Surgery	6.3%	5.1%	0.01
POD #1	4.0%	2.7%	<0.001
POD #2	2.9%	1.9%	0.002
POD #3	2.2%	1.2%	<0.001
POD #4	1.6%	0.7%	<0.001
POD #5	1.3%	0.6%	<0.001
POD #6	0.9%	0.5%	0.03
POD #7	0.8%	0.5%	0.03
POD #8	0.8%	0.5%	0.29
POD #9	0.6%	0.5%	0.82
POD #10	0.5%	0.5%	0.67

Devereaux PJ et al. *N Engl J Med* 2014;370:1494-1503

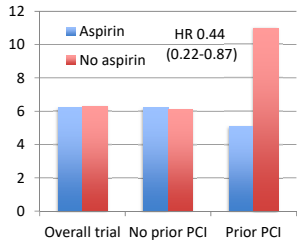
POISE-2 PCI Trial

470 patients from the POISE-2 trial with prior PCI (median of 64 months previously) undergoing noncardiac surgery randomized to aspirin vs. placebo

30-day Death or Nonfatal Myocardial Infarction



30-day Myocardial Infarction



Graham MM. Presented at the 2017 American Heart Association Scientific Sessions

Managing Anticoagulation Periprocedurally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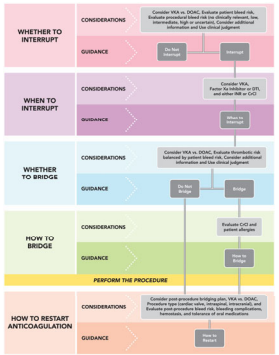
EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

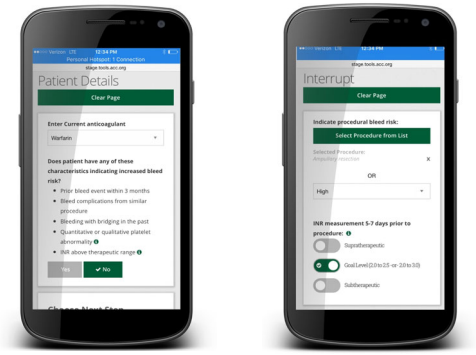


Doherty JU et al. *J Am Coll Cardiol* 2017;69:871-898

BridgeAnticoag App

BridgeAnticoag App

- Search "BridgeAnticoag" on the web
- Available on iTunes and Google Play for free

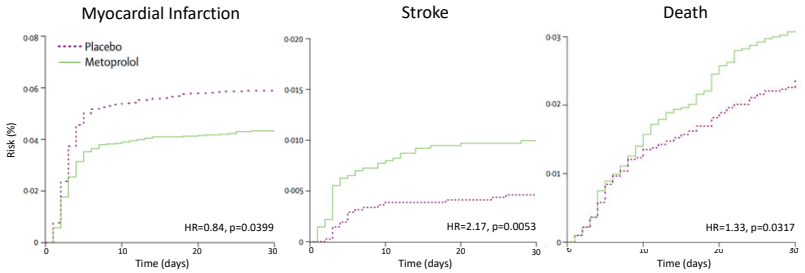


https://www.acc.org/tools-and-practice-support/mobile-resources/features/bridgeanticoag-app

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

POISE Trial

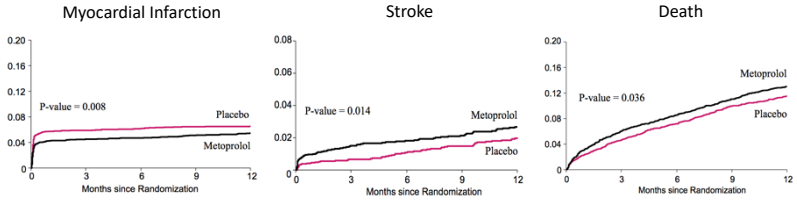
8,351 patients with or at risk for ASCVD undergoing non-cardiac surgery randomized to metoprolol succinate (100 mg preoperatively and 200 mg thereafter) or placebo starting 2-4 hours prior surgery and continuing for 30 days



POISE Study Group. *Lancet* 2008;371:1839-1847

POISE Trial

1-year follow up of patients enrolled in the POISE trial with ability to obtain mortality data and other outcomes in ≥84% and ≥88% of enrolled individuals, respectively



Devereaux PJ . Presented at the 2018 American College of Cardiology Scientific Sessions

Important Takeaways

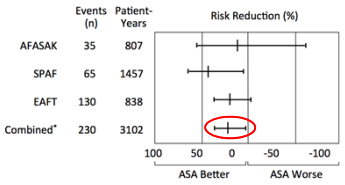
- Use of low-dose aspirin in most patients undergoing non-cardiac surgery is associated with no cardiovascular benefit and a higher rate of major/life-threatening bleeding
- However, among patients with prior PCI, use of low dose aspirin is associated with a significantly lower rate of death or non-fatal myocardial infarction
- The BridgeAnticoag app represents a useful resource to guide periprocedural management of anticoagulation
- Use of extended-release metoprolol in patients undergoing non-cardiac surgery is associated with lower rates of myocardial infarction, but higher rates of stroke and death

How Should My Approach to Antithrombotic Therapy Change in Those With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention?

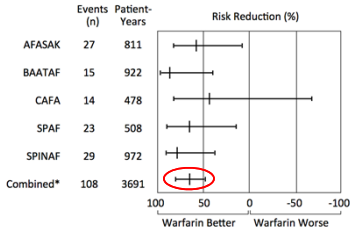
Aspirin or Warfarin in Nonvalvular Atrial Fibrillation

Pooled analyses comparing the impact of aspirin to placebo and warfarin to placebo on rates of ischemic stroke

Aspirin vs. Placebo



Warfarin vs. Placebo

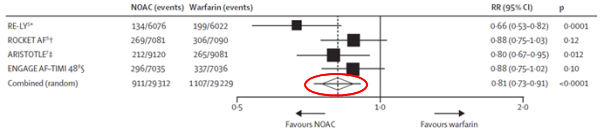


Atrial Fibrillation Investigators. *Arch Intern Med* 1994;154:1449-1457

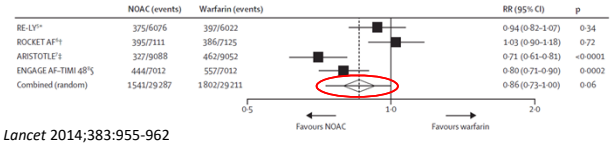
DOACs or Warfarin in Nonvalvular Atrial Fibrillation

Meta-analysis comparing the impact of the direct oral anticoagulants (DOACs) to warfarin on rates of stroke or system embolism and major bleeding

Stroke or system embolism



Major bleeding

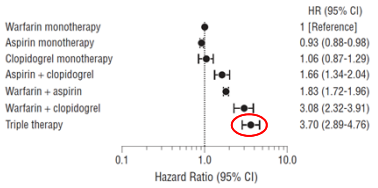


Ruff CT et al. *Lancet* 2014;383:955-962

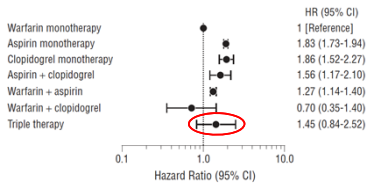
Bleeding and Ischemic Risks with Atrial Fibrillation

Cohort study of 82,854 patients from Denmark discharged after a hospitalization for atrial fibrillation on warfarin, aspirin, or clopidogrel either alone or in combination

Nonfatal and fatal bleeding

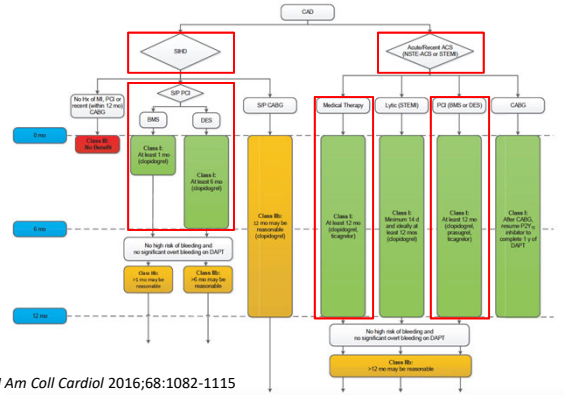


Nonfatal and fatal ischemic stroke



Hansen ML et al. *Arch Intern Med* 2010;170:1433-1441

2016 ACC/AHA Dual Antiplatelet Therapy Guidelines



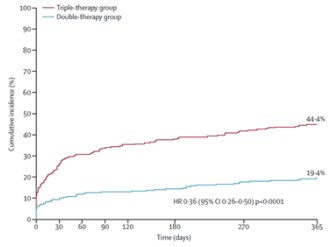
Levine GN et al. *J Am Coll Cardiol* 2016;68:1082-1115

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

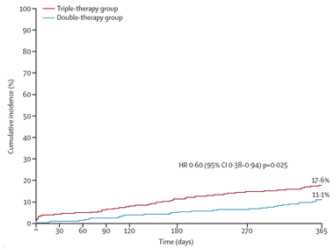
WOEST Trial—Double vs. Triple Antithrombotic Therapy

Open label trial of 573 patients taking oral anticoagulants undergoing PCI randomized to treatment with clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy) for a mean follow up of nearly 1 year

Any Bleeding



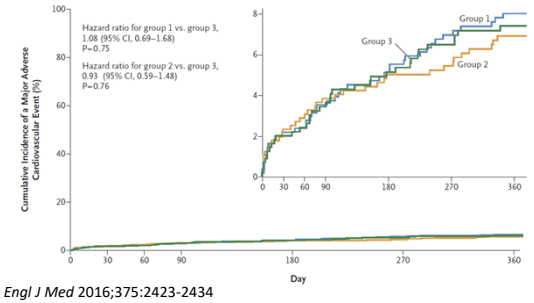
Death, MI, Stroke, TVR, and Stent Thrombosis



Dewilde WJM et al. *Lancet* 2013;381:1107-1115

PIONEER AF-PCI Trial—Double vs. Triple Antithrombotic Therapy

2,124 patients with NVAF who underwent PCI randomized to treatment with rivaroxaban (15 mg QD) + a $P2Y_{12}$ inhibitor (Group 1), rivaroxaban (2.5 mg BID) + DAPT (Group 2), or a VKA + DAPT (Group 3) for 12 months

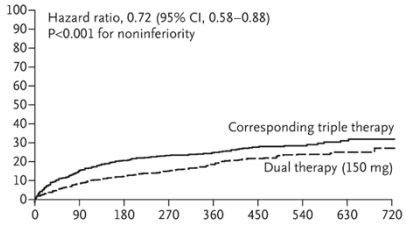


Gibson CM et al. *N Engl J Med* 2016;375:2423-2434

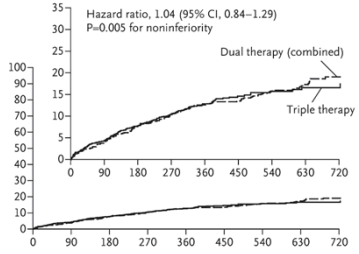
RE-DUAL PCI Trial—Double vs. Triple Antithrombotic Therapy

2,725 patients with NVAF who underwent PCI randomized to treatment with dabigatran (110 mg or 150 mg BID) + a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) or warfarin + a $P2Y_{12}$ inhibitor + aspirin (1-3 months) for a mean of 14 months

Major/Clinically Relevant Non-Major Bleeding



Death, Thromboembolism or Unplanned Revasc.



Cannon CP et al. *N Engl J Med* 2017;377:1513-1524

Important Takeaways

- The direct oral anticoagulants (DOACs) represent an important advance, both from an efficacy and safety standpoint in atrial fibrillation
- Triple antithrombotic therapy carries significantly increased risk of major bleeding without clear ischemic benefit
- The WOEST, PIONEER AF-PCI and RE-DUAL PCI trials provide support for dual antithrombotic therapy (anticoagulant and $P2Y_{12}$ inhibitor) in those with atrial fibrillation undergoing PCI