The Evidence for Current Cardiovascular Disease Prevention Guidelines:

Antiplatelet and Anticoagulation Therapy Evidence and Guidelines

Classification of Recommendations and Levels of Evidence

SIZE OF TREATMENT EFFECT →

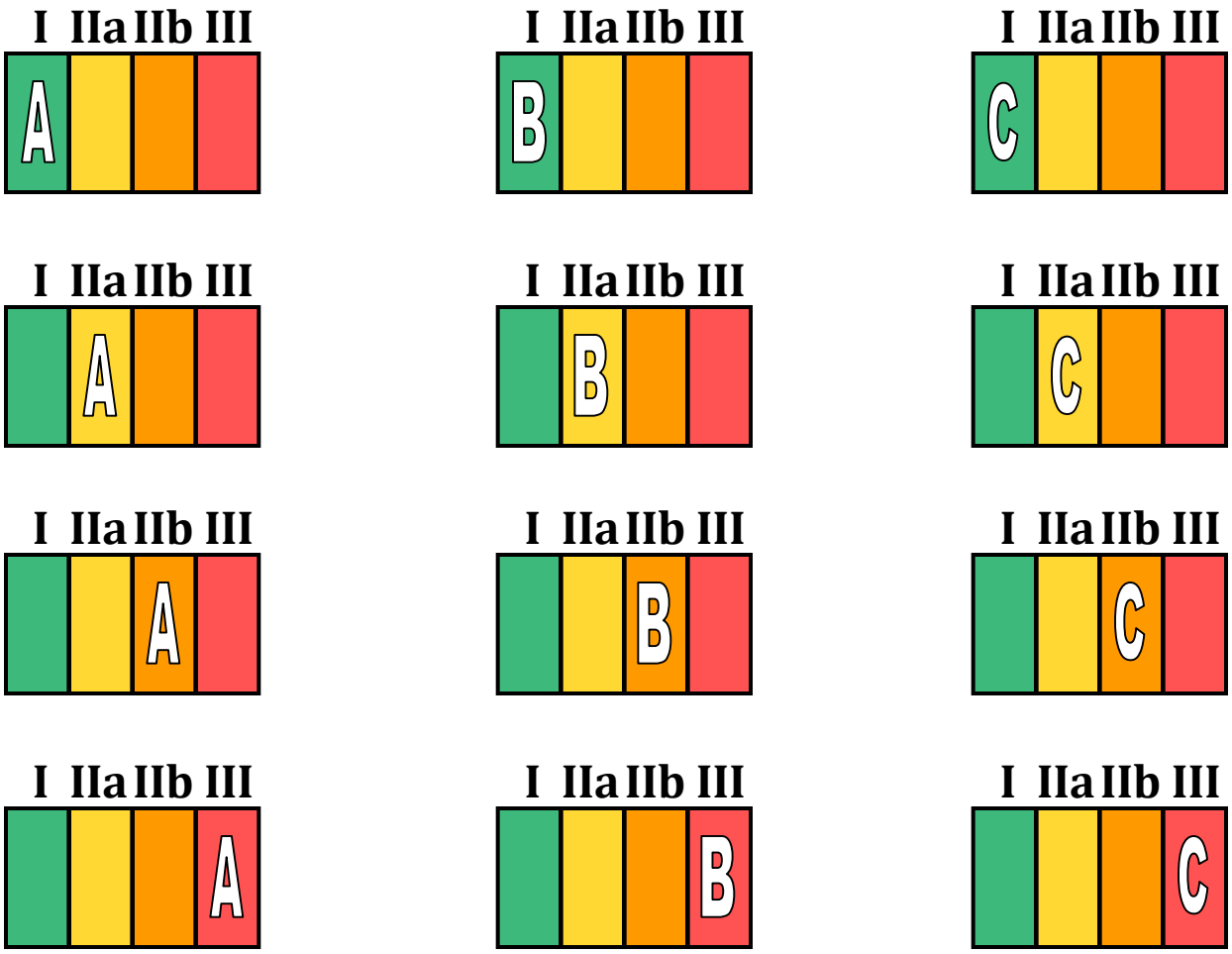
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

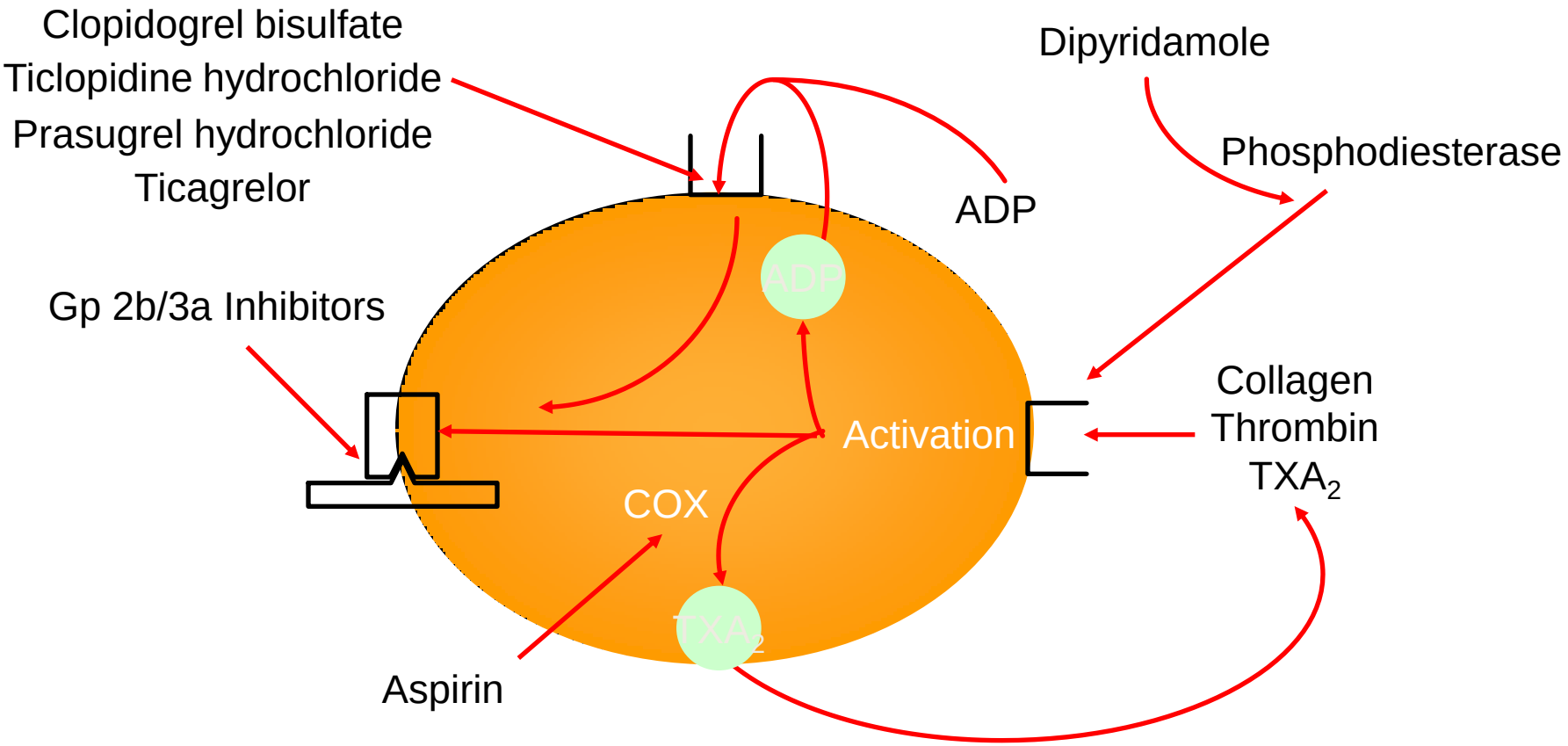
Icons Representing the Classification and Evidence Levels for Recommendations



Evidence for Current Cardiovascular Disease Prevention Guidelines

Antiplatelet Therapy Evidence and Guidelines

Antiplatelet Therapy: Targets



ADP=Adenosine diphosphate, COX=Cyclooxygenase, TXA_2=Thromboxane A_2

Source: Schafer AI. Antiplatelet Therapy. *Am J Med* 1996;101:199–209

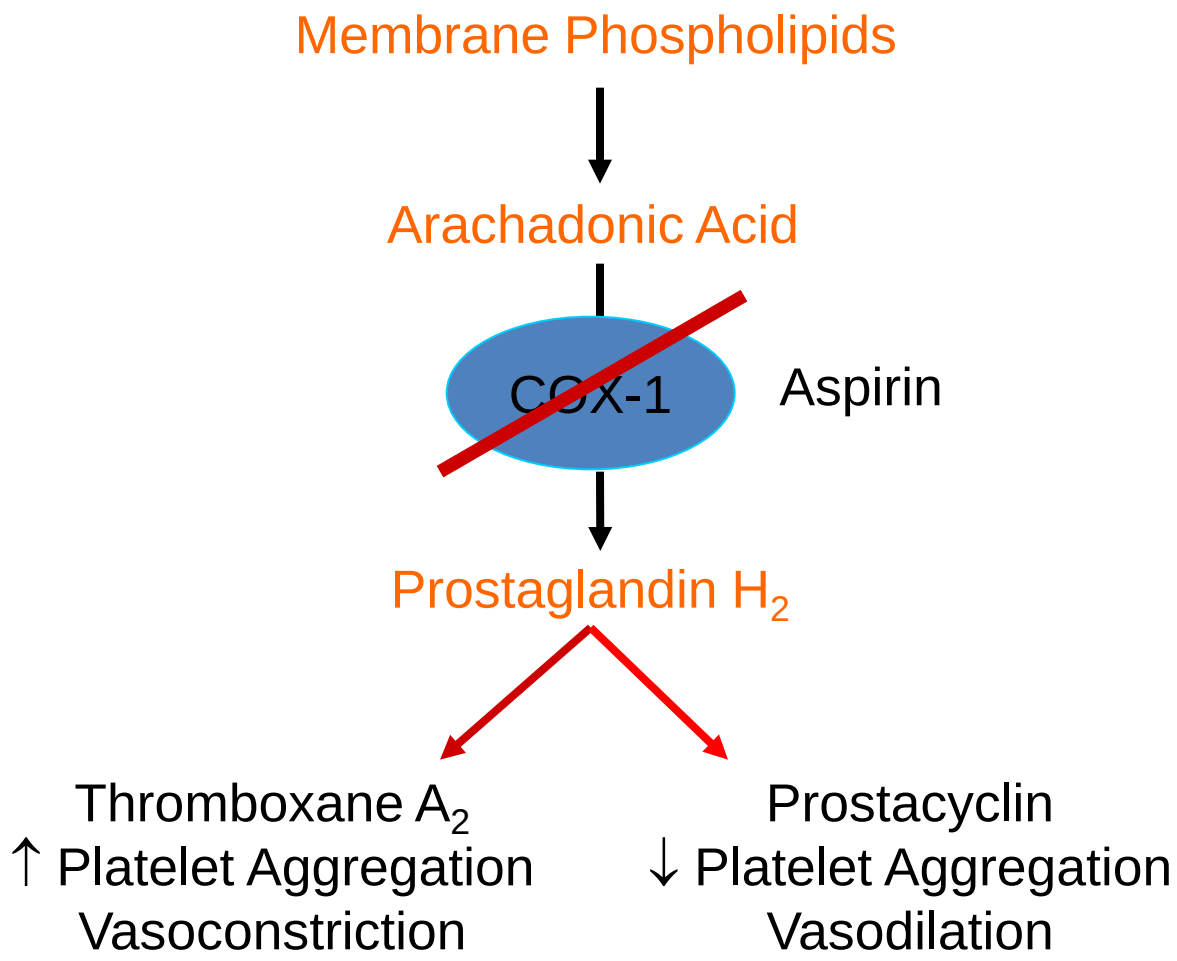
Antiplatelet Therapy: Common Oral Agents

	Acetylsalicylic acid (ASA)	Ticlopidine hydrochloride	Clopidogrel bisulfate	Prasugrel hydrochloride	Ticagrelor
Class	Salicylate	P_2Y_{12} Receptor Antagonist	P_2Y_{12} Receptor Antagonist	P_2Y_{12} Receptor Antagonist	P_2Y_{12} Receptor Antagonist
Formulation	Active Drug	Active Drug	Pro-Drug	Pro-Drug	Active Drug
Maintenance Dose	75-325 mg daily*	250 mg BID	75 mg daily	10 mg daily	90 mg BID
Reversible	No	No	No	No	Yes

*81 mg is the low dose aspirin option in the United States

Sources:
[1]Pearson TA, et al. *Circulation*, 2002;106:388-391
[2]Mosca L, et al. *Circulation*, 2007;115:1481-1501
[3] Smith SC Jr. et al. *JACC* 2011;58:2432-2446
[4]http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/19-979S018_Ticlid_prntlbl.pdf
[5]http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf
[6]http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s001lbl.pdf
[7]http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383.pdf

Aspirin:
Mechanism of Action



Aspirin Evidence: Primary Prevention

Physician's Health Study (PHS)

22,071 male participants randomized to aspirin (325 mg every other day) followed for an average of 5 years

End point	Relative Risk (95% CI)	P value
CV Mortality	0.96 (0.60-1.54)	0.87
Myocardial infarction		
Fatal	0.34 (0.15-0.75)	0.007
Nonfatal	0.59 (0.47-0.74)	<0.00001
Total	0.56 (0.45-0.70)	<0.00001
Stroke		
Fatal	1.51 (0.54-4.28)	0.43
Nonfatal	1.20 (0.91-1.59)	0.20
Total	1.22 (0.93-1.60)	0.15

Aspirin reduces the risk of myocardial Infarction among men

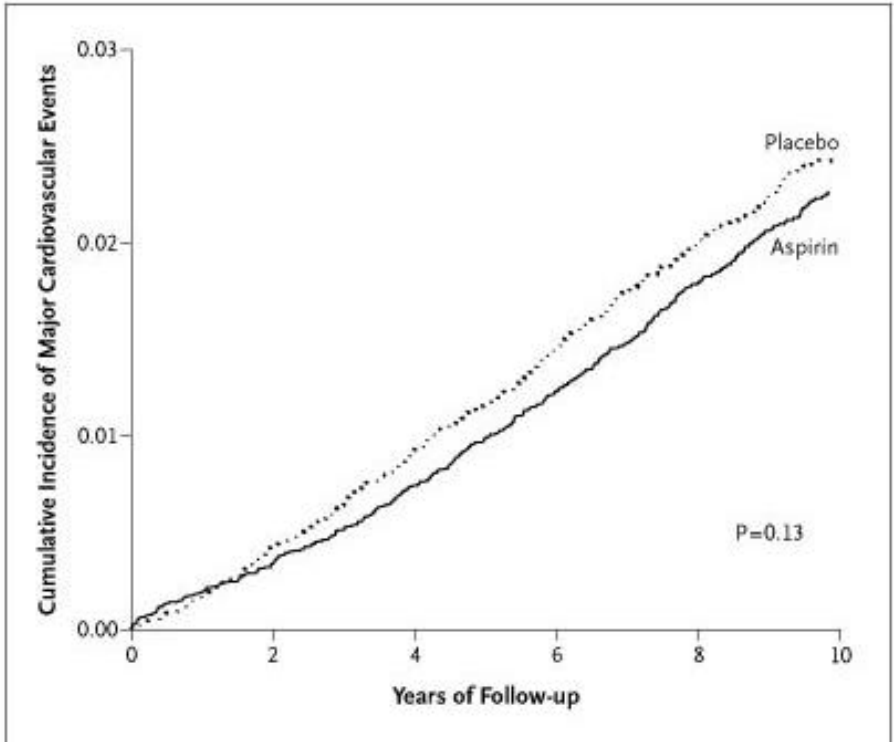
CI=Confidence interval, CV=Cardiovascular

Source: Steering Committee of the Physicians' Health Study Research Group. *NEJM* 1989;321:129-135

Aspirin Evidence: Primary Prevention

Womens' Health Study (WHS)

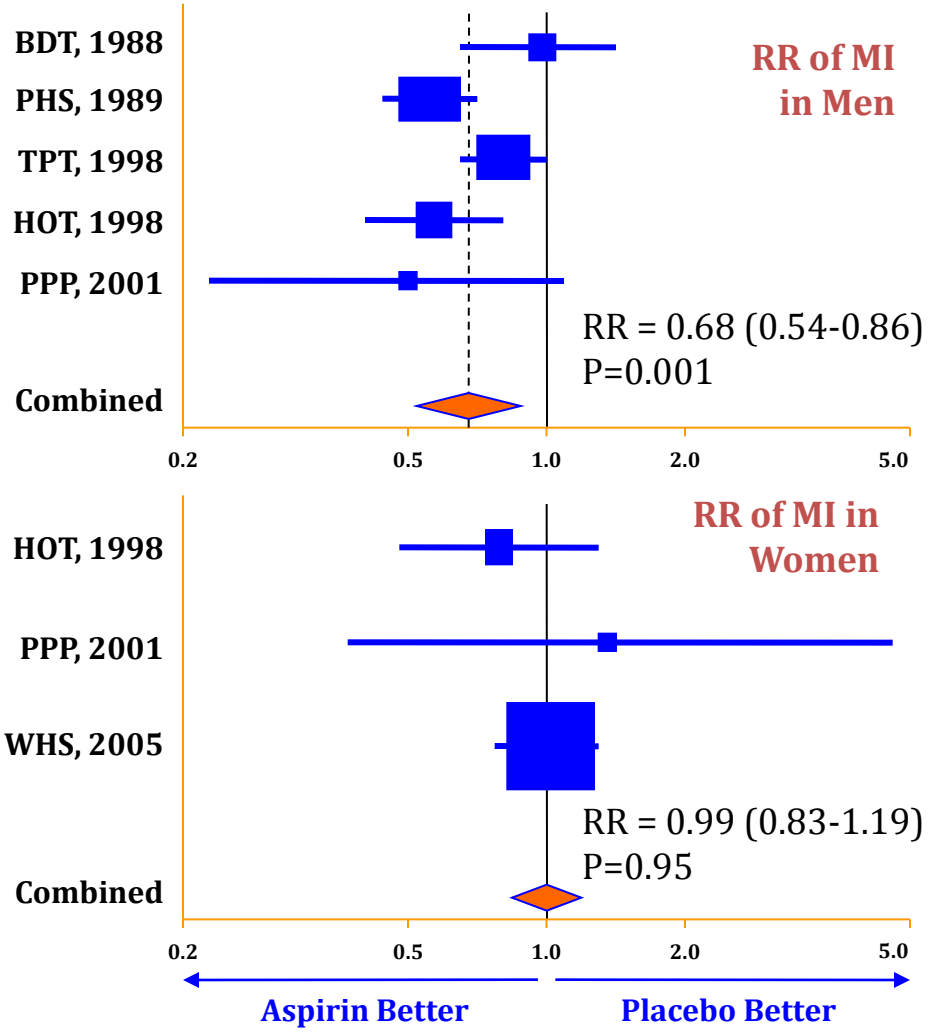
39,876 women randomized to aspirin (100 mg every other day) or placebo for an average of 10 years

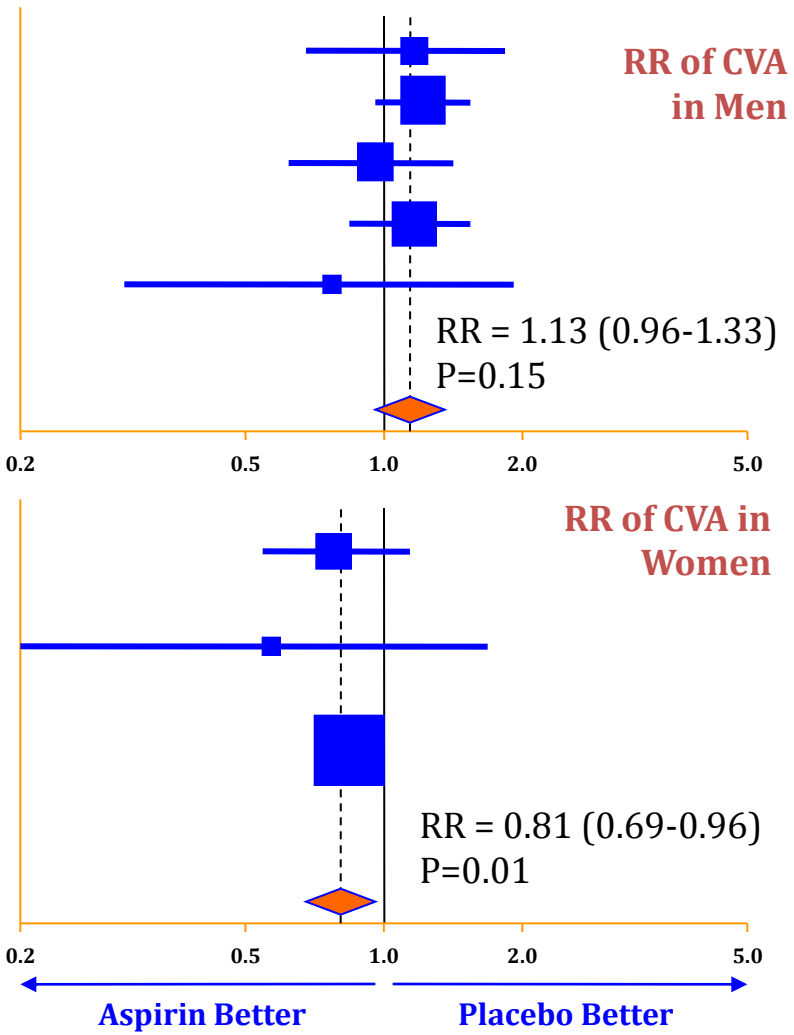


Aspirin does not reduce cardiovascular events among women

Source: Ridker P et al. *NEJM* 2005;352:1293-1304

Aspirin Evidence: Primary Prevention



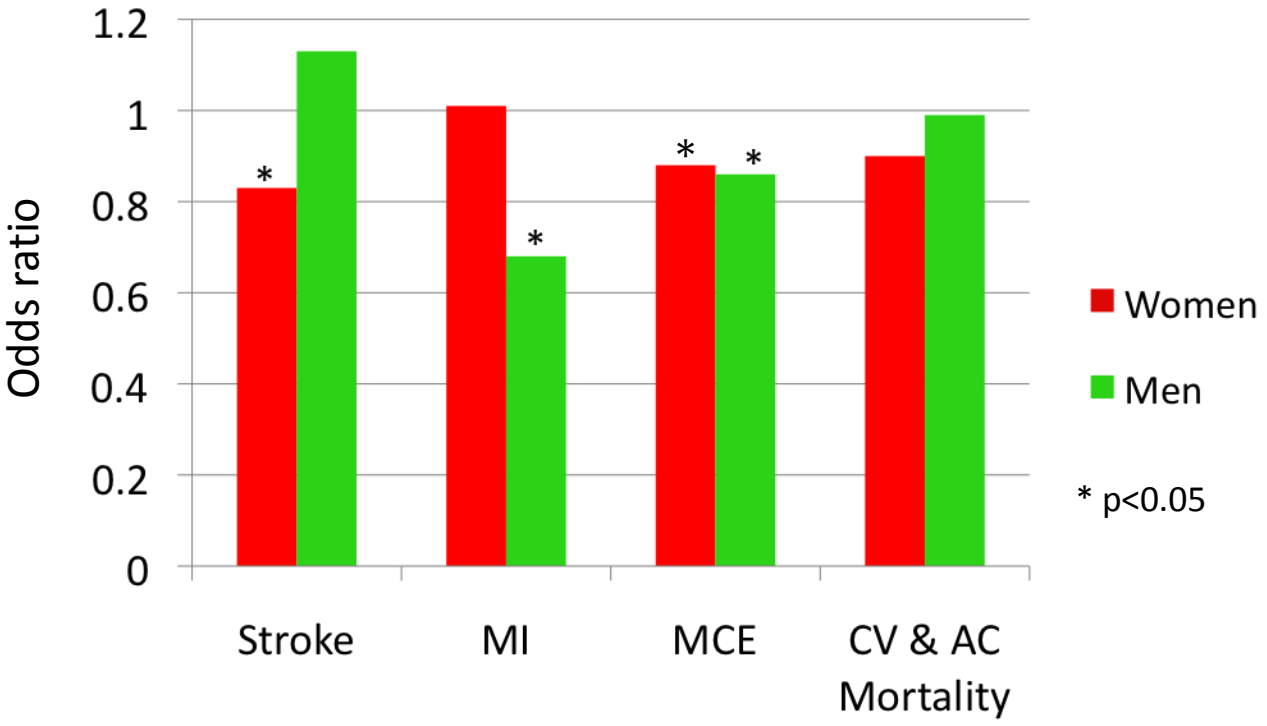


CVA=Cerebrovascular accident, MI=Myocardial infarction, RR=Relative risk

Source: Ridker P et al. *NEJM* 2005;352:1293-1304

Aspirin Evidence: Primary Prevention

Sex-specific meta-analysis of 51,342 women and 44,114 men randomized to aspirin (doses ranging between 100 mg every other day to 500 mg daily) vs. placebo for 3.7-10 years



Aspirin reduces the risk of stroke in women and MI in men

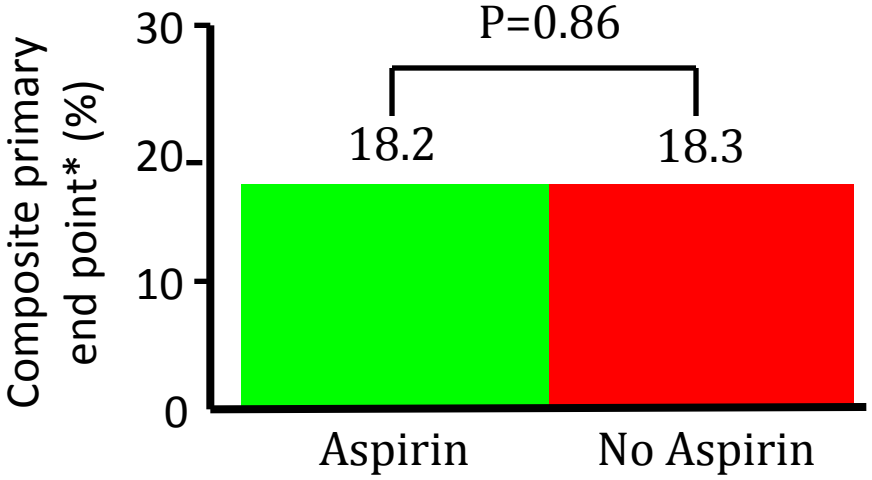
AC=All cause, CV=Cardiovascular, MCE=Major cardiovascular events, MI=Myocardial infarction

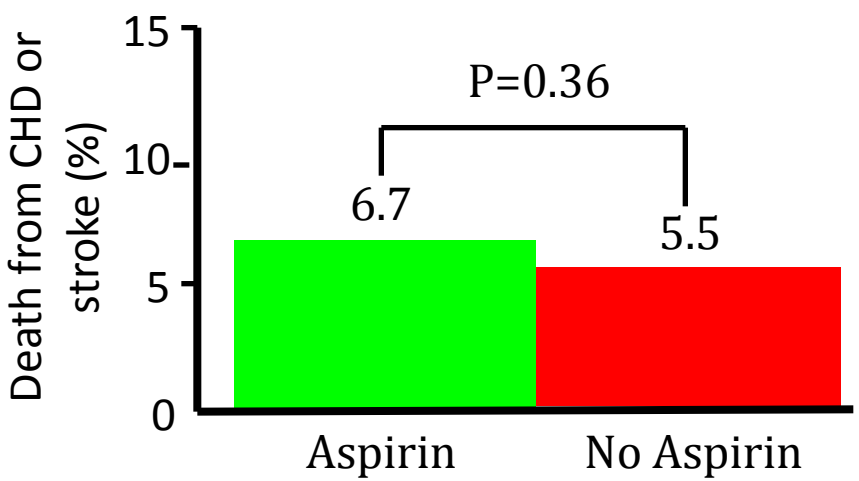
Source: Berger JS et al. *JAMA.* 2006;295:306-313

Aspirin Evidence: Primary Prevention

Prevention of Progression of Arterial Disease and Diabetes (POPADAD) Study

1,276 asymptomatic patients with DM and an ABI <0.99 randomized in a 2 x 2 design to aspirin (100 mg), antioxidants, aspirin plus antioxidants, or placebo





Aspirin does not reduce the risk of adverse CV events in diabetics

*Includes fatal CHD or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia

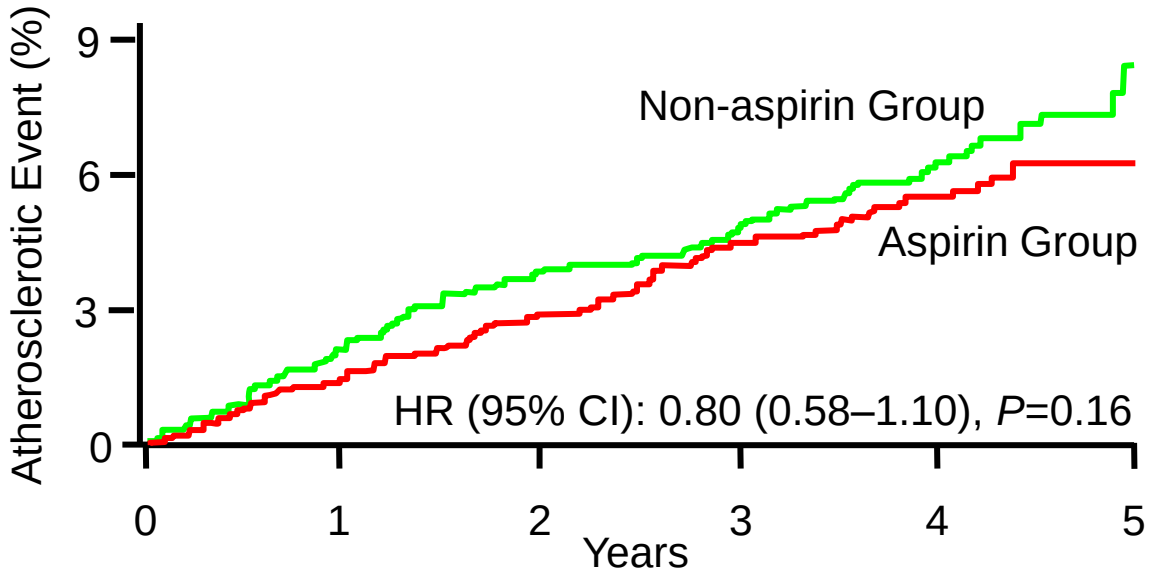
ABI=Ankle brachial index, CHD=Coronary heart disease, CV=Cardiovascular, DM=Diabetes mellitus, MI=Myocardial infarction

Source: Belch J et al. *BMJ*. 2008;337:a1840

Aspirin Evidence: Primary Prevention

Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) Study

2,539 diabetic patients without known coronary artery disease randomized to aspirin (81-100 mg) or placebo for a median of 4.7 years



Aspirin does not reduce the risk of adverse CV events in diabetics

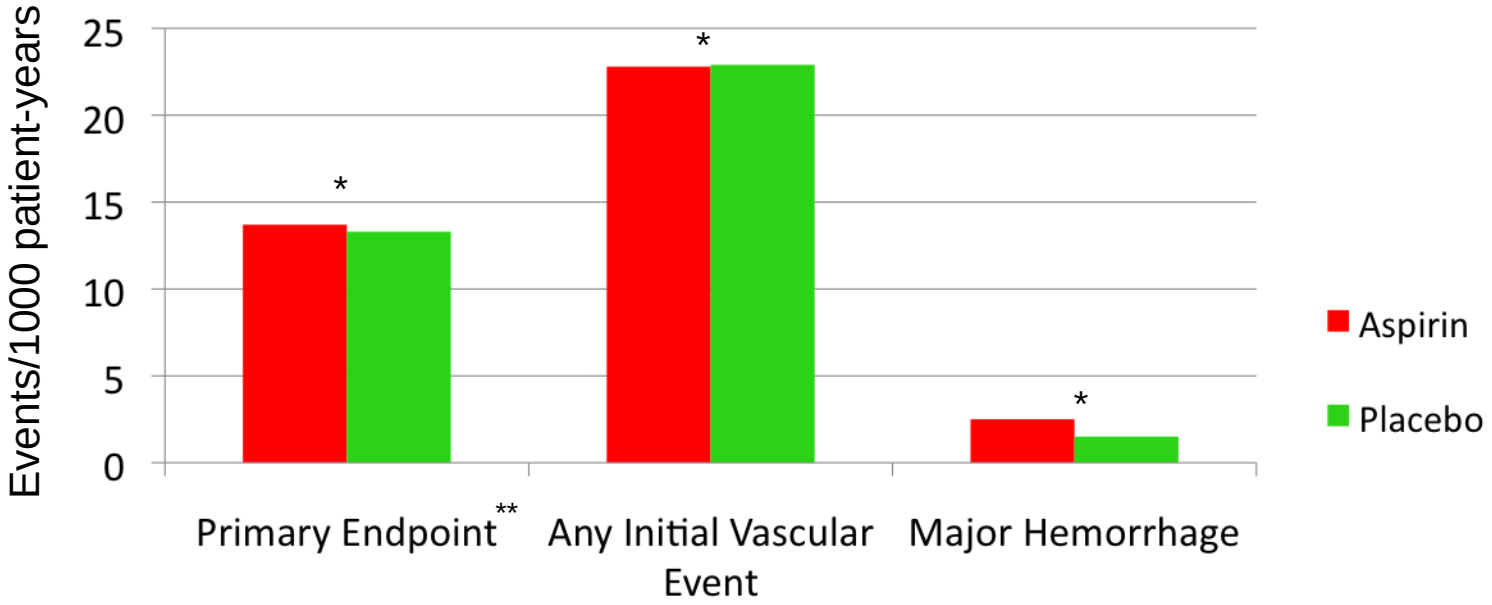
CI=Confidence interval, CV=Cardiovascular, HR=Hazard ratio

Source: Ogawa H et al. *JAMA* 2008;300:2134-2141

Aspirin Evidence: Primary Prevention

Aspirin for Asymptomatic Atherosclerosis Trial

3,350 patients with an ABI <0.95 but no known cardiovascular disease randomized to aspirin (100 mg) or placebo for 8.2 years



Aspirin does not reduce the risk of CV events in those with an ABI <0.95

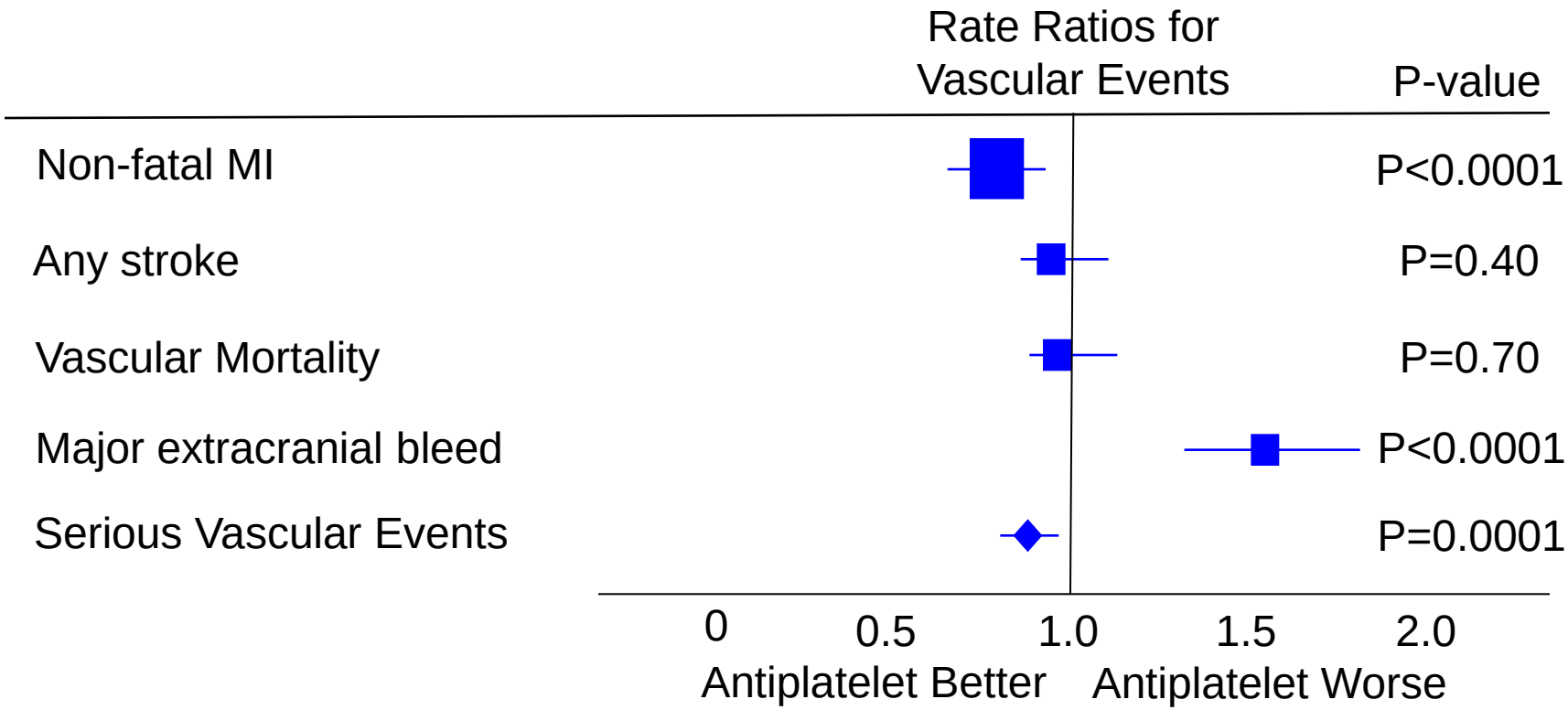
*Not statistically significant
**Composite of initial fatal or nonfatal coronary event or stroke or revascularization

ABI=Ankle brachial index, CV=Cardiovascular

Source: Fowkes FGR et al. *JAMA* 2010;303:841-848

Aspirin Evidence: Primary Prevention

Antithrombotic Trialists' (ATT) Collaboration



Aspirin reduces the risk of MI and vascular events at the expense of bleeding

Source: Antithrombotic Trialists' Collaboration. *Lancet* 2009;373:1849-1860

Aspirin Evidence: Primary Prevention

Antithrombotic Trialists' (ATT) Collaboration

Meta-analysis of 95,456 low risk patients randomized to aspirin (100 mg every other day to 500 mg daily) vs. placebo for 3.7-10 years

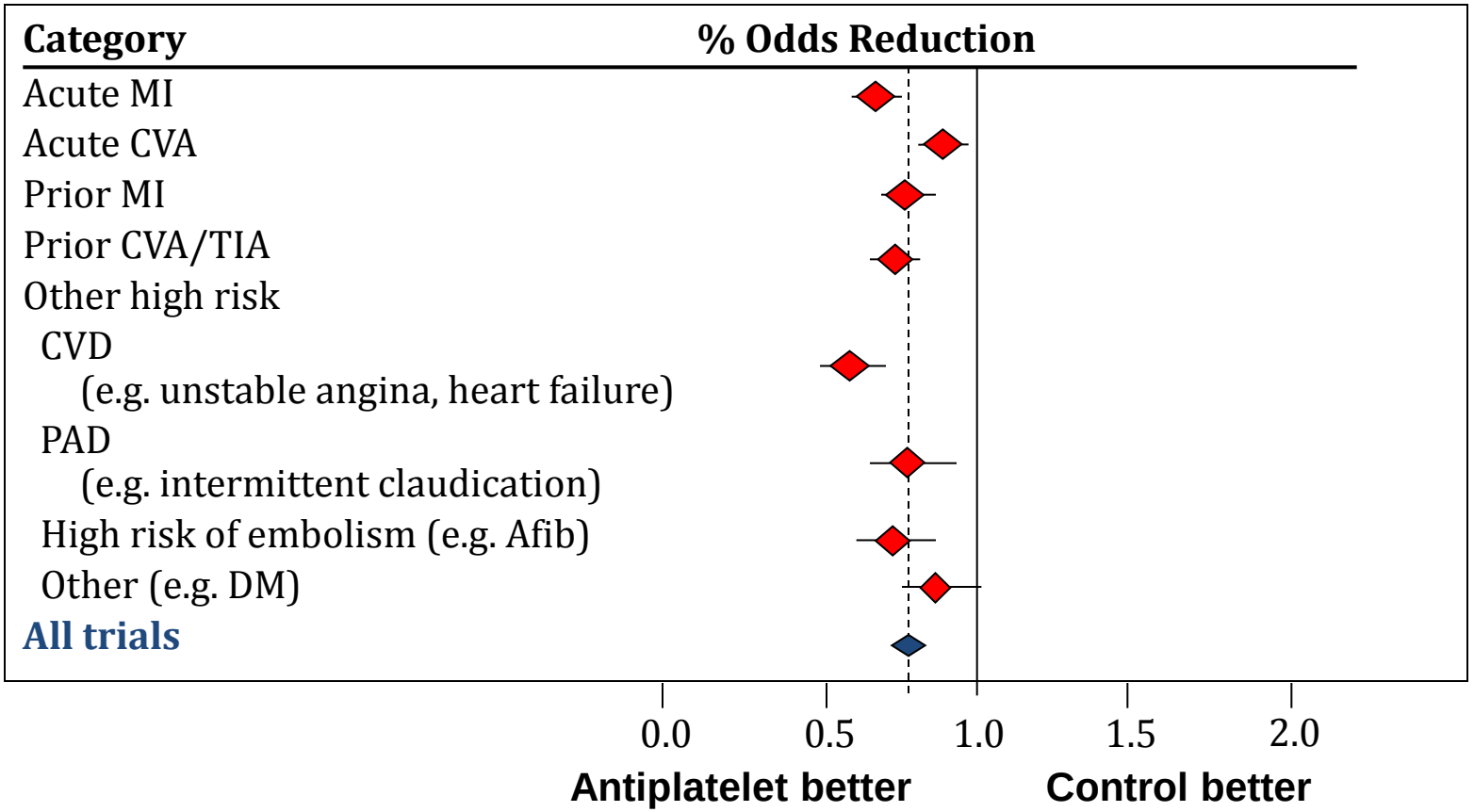
	Number of Events (Aspirin vs. Control)	Rate ratio (95% CI) (Aspirin vs. Control)
Major coronary event	934 vs. 1115	0.82 (0.75-0.90)
Non-fatal MI	596 vs. 756	0.77 (0.69-0.86)
CHD mortality	372 vs. 393	0.95 (0.82-1.10)
Stroke	655 vs 682	0.95 (0.85-1.06)
Hemorrhagic	116 vs. 89	1.32 (1.00-1.75)
Ischemic	317 vs. 367	0.86 (0.74-1.00)
Unknown cause	222 vs. 226	0.97 (0.80-1.18)
Vascular death	619 vs. 637	0.97 (0.87-1.09)
Any serious vascular event	1671 vs. 1883	0.88 (0.82-0.94)
Major extracranial bleed	335 vs. 219	1.54 (1.30-1.82)

Aspirin reduces the risk of ischemic events, but with a higher rate of bleeding

Source: Antithrombotic Trialists' Collaboration. *Lancet* 2009;373:1849-1860

Aspirin Evidence: Secondary Prevention

Effect of antiplatelet treatment* on vascular events**



Aspirin reduces the risk of adverse cardiovascular events

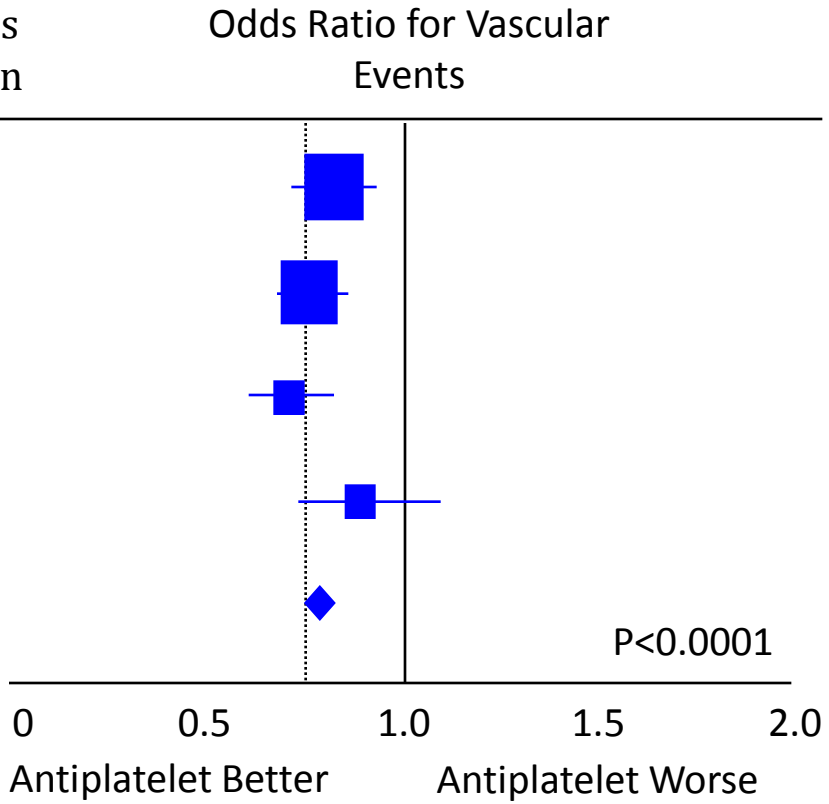
*Aspirin was the predominant antiplatelet agent studied
**Include MI, stroke, or death

Source: Antithrombotic Trialists' Collaboration. *BMJ* 2002;324:71–86

Aspirin Evidence: Dose and Efficacy

Effect of aspirin doses on vascular events in high-risk patients (excluding those with acute stroke)

Aspirin Dose	No. of Trials	% Odds Reduction
500-1500 mg	34	19
160-325 mg	19	26
75-150 mg	12	32
<75 mg	3	13
Any aspirin	65	23



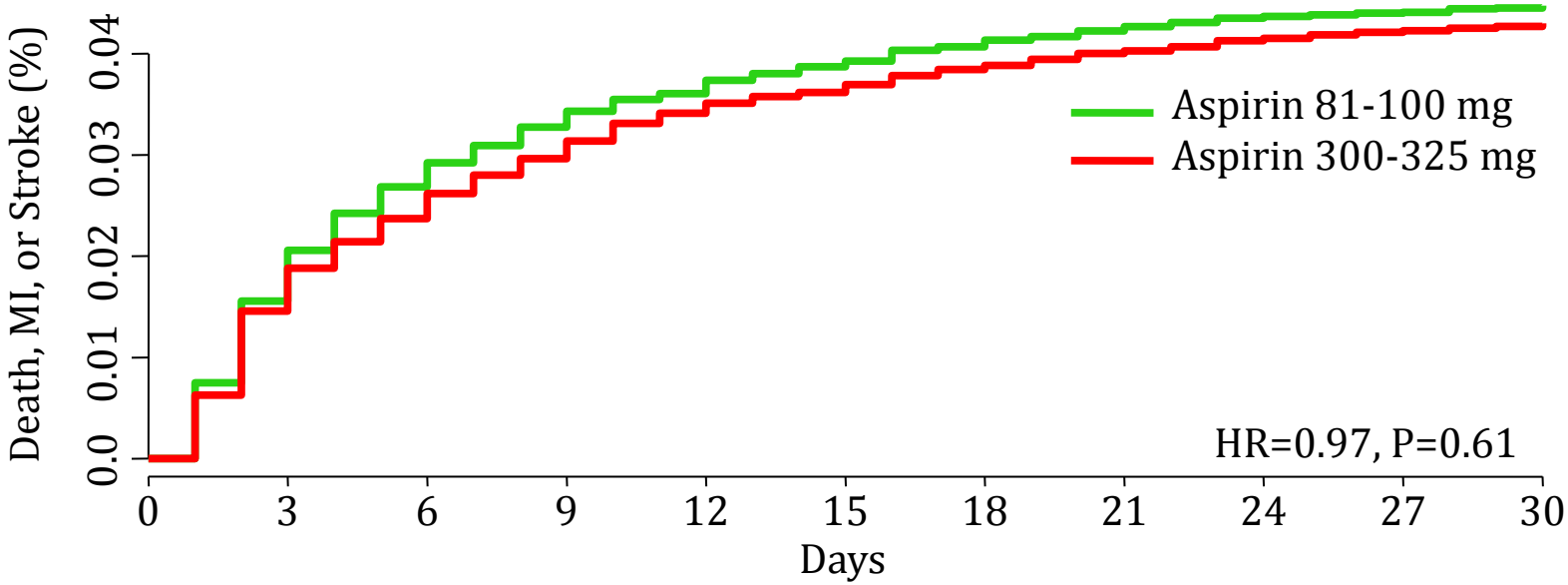
High dose aspirin does not provide improved efficacy

Source: Antithrombotic Trialists' Collaboration. *BMJ* 2002;324:71-86

Aspirin Evidence: Dose and Efficacy

Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events (CURRENT)-OASIS 7 Trial

25,087 patients with an ACS randomized in a 2 x 2 factorial trial to double dose clopidogrel (600 mg LD, 150 mg x 7 days, then 75 mg MD) vs. standard dose clopidogrel (300 mg LD and 75 mg MD) and high dose aspirin (300-325 mg) vs. low dose aspirin (75-100 mg)



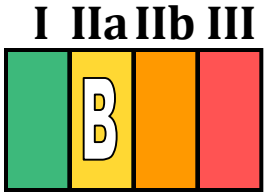
Higher dose aspirin does not provide benefit in ACS

ACS=Acute coronary syndrome, MI=Myocardial infarction, LD=Loading dose, MD=Maintenance dose

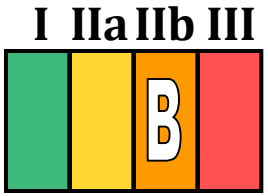
Source: CURRENT-OASIS 7 Investigators. *NEJM* 2010;363:930-942

Aspirin Recommendations

Primary Prevention



Aspirin (81 mg daily or 100 mg every other day) in at risk women ≥65 years of age



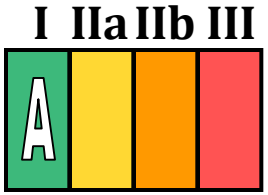
Aspirin in at risk women <65 years of age for ischemic stroke prevention

Aspirin in optimal risk women <65 years of age

Source: Mosca L et al. *Circulation* 2007;115:1481-1501

Aspirin Recommendations (Continued)

Primary Prevention



Aspirin (75-162 mg daily) in [men]* at intermediate risk (10-year risk of CHD ≥10%)

*Specific guideline recommendations for men do not exist, but these guidelines are based on previous general (not gender specific) primary prevention guidelines

CHD=Coronary heart disease

Source: Pearson TA et al. *Circulation* 2002;106:388-391

ADA/AHA/ACCF Primary Prevention of CV Disease Antiplatelet Agent Recommendations

Primary Prevention

Low-dose aspirin therapy (75-162 mg/day) is reasonable for adults with DM and no previous history of vascular disease who are at increased CVD risk (10-year risk >10%) and who are not at increased risk for bleeding (based on a history of previous GI bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk such as NSAIDs or warfarin). Those adults with DM at increased CVD risk include most men >50 years of age or women >60 years of age who have at least one additional major risk factor.*†

*ADA Level C

†Includes those with family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria

ACCF=American College of Cardiology Foundation, ADA=American Diabetes Association, AHA=American Heart Association, CV=Cardiovascular, CVD=Cardiovascular disease, DM=Diabetes mellitus, GI=Gastrointestinal, NSAIDs=Non-steroidal anti-inflammatory drugs

Source: Pignone M et al. *Circulation* 2010;121:2694-2701

ADA/AHA/ACCF Primary Prevention of CV Disease Antiplatelet Agent Recommendations (Continued)

Primary Prevention

Aspirin should not be recommended for CV prevention for adults with DM at low CVD risk (men <50 years of age and women <60 years of age with no major additional CVD risk factors* [10-year risk <5%], as the potential adverse effects from bleeding offset the potential benefits.†

Low-dose aspirin (75-162 mg/day) may be considered for those with DM at intermediate CVD risk (younger patients with ≥1 risk factors* or older patients with no risk factors*, or patients with a 10-year risk of 5-10% until further research is available.‡

*Includes those with family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria
†ADA Level C, ‡ADA Level E

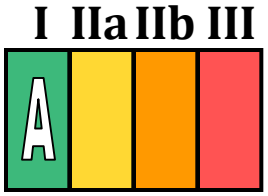
ACCF=American College of Cardiology Foundation, ADA=American Diabetes Association, AHA=American Heart Association, CV=Cardiovascular, CVD=Cardiovascular disease, DM=Diabetes mellitus

Source: Pignone M et al. *Circulation* 2010;121:2694-2701

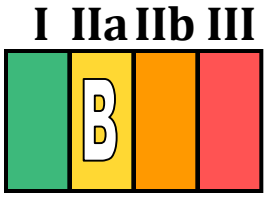
Aspirin Recommendations (Continued)

Secondary Prevention

Aspirin (75-162 mg daily) if known CAD† or NSTE-ACS‡



Aspirin (81-325 mg daily) following PCI or fibrinolytic therapy for a STEMI*



Aspirin (preferentially at 81 mg daily) following PCI for a NSTE-ACS# or a STEMI* or fibrinolytic therapy for a STEMI*

ASVD=Atherosclerotic vascular disease, CAD=Coronary artery disease, NSTE-ACS=Non-ST segment elevation acute coronary syndrome, PCI=Percutaneous coronary intervention, STEMI=ST-segment elevation myocardial infarction

Sources:

†\Smith SC Jr. et al. *JACC* 2011;58:2432-2446

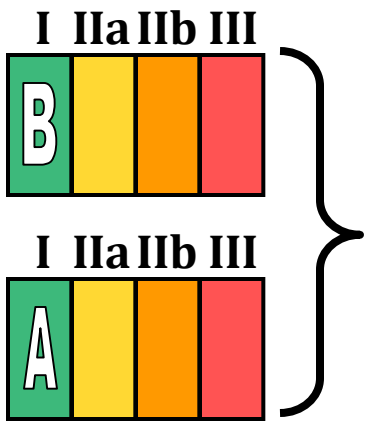
‡Wright RS et al. JACC 2011;57:e215-367

*O'Gara PT et al. *JACC* 2013;61:e78-e140

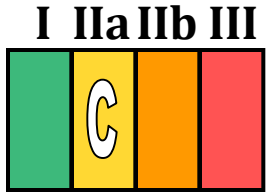
#Jneid H et al. *JACC* 2012;60:645-681

Aspirin Recommendations (Continued)

Secondary Prevention



Aspirin (162-325 mg daily) for at least 1 month after bare metal stent implantation (Class I, Level B), at least 3 months after sirolimus-eluting stent implantation (Class I, Level B), and at least 6 months after paclitaxel-eluting stent implantation (Class I, Level B) after which aspirin (75-162 mg daily) should be continued indefinitely (Class I, Level A for a bare metal stent and Class I, Level B for a drug eluting stent)



Aspirin (75-162 mg daily) as the initial dose after stent implantation in those at higher bleeding risk

Source: King SB 3rd et al. *JACC* 2008;51:172-209

Aspirin Recommendations (Continued)

Secondary Prevention

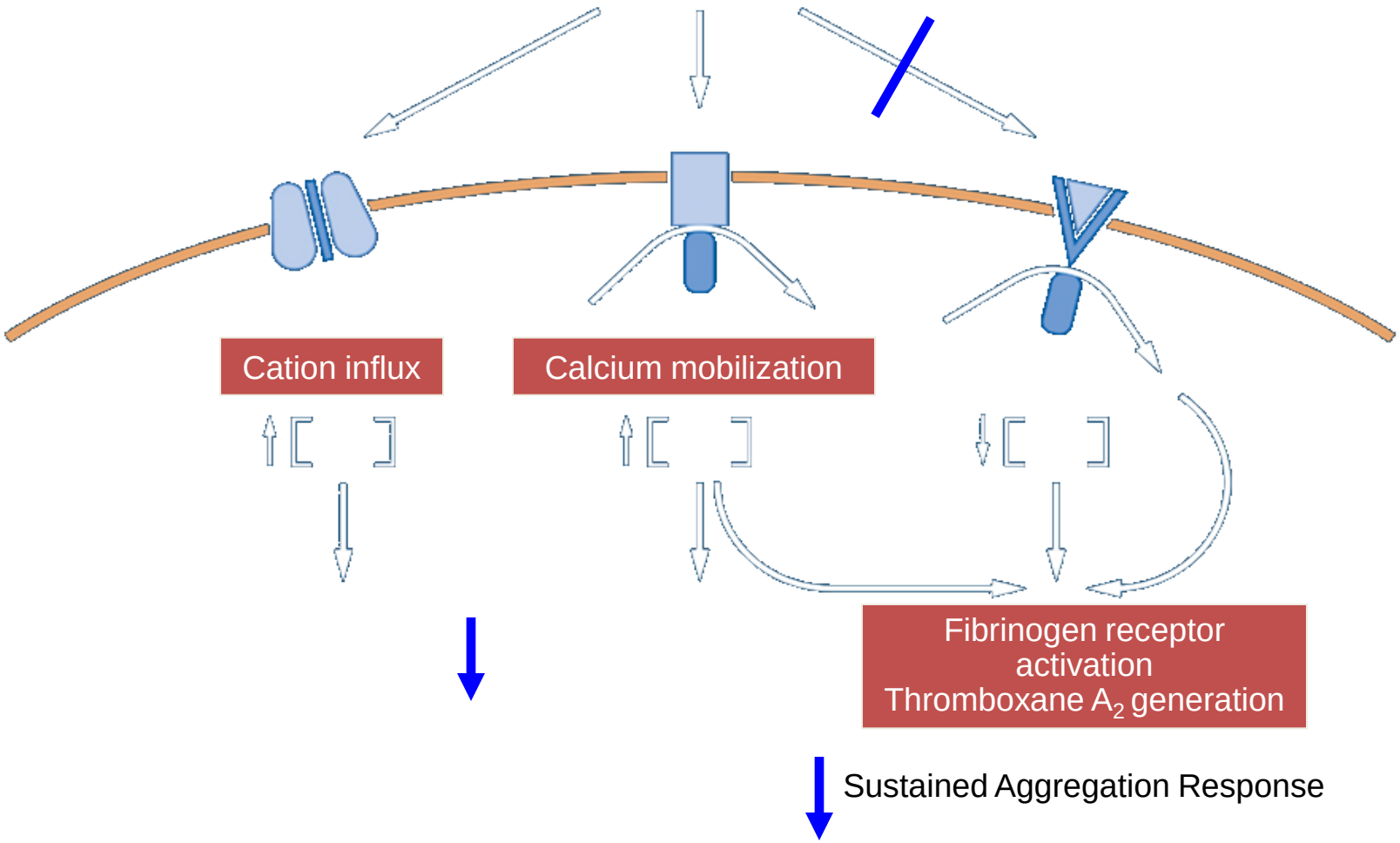
Aspirin (100-325 mg daily) following CABG surgery*

*To be initiated within 6 hours of surgery

CABG=Coronary artery bypass graft

Source: Hillis LD et al. *JACC* 2011;58:e123-210

$P2Y_{12}$ Receptor Antagonist: Mechanism of Action

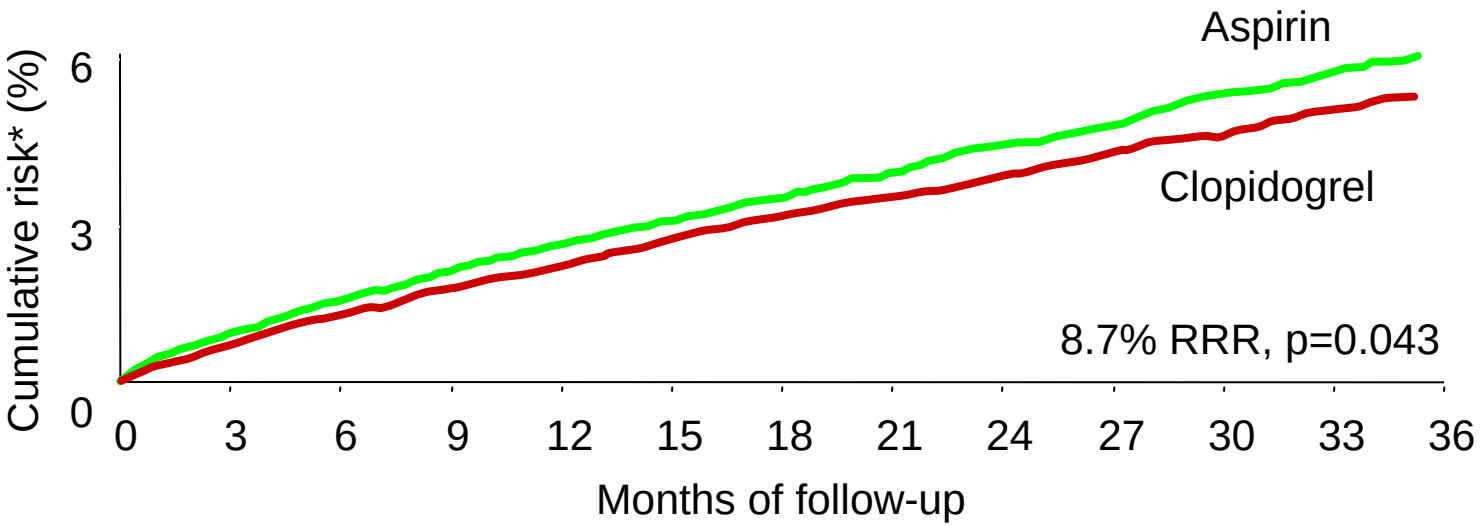


Sources:
Savi P *et al. Biochem Biophys Res Commun* 2001; 283:379–383
Ferguson JJ. *The Physiology of Normal Platelet Function*. In: Ferguson JJ, Chronos N, Harrington RA (Eds). *Antiplatelet Therapy in Clinical Practice*. London: Martin Dunitz; 2000: pp.15–35

Clopidogrel Evidence: Secondary Prevention

Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) Trial

19,185 patients with ischemic CVA, MI, or PAD randomized to daily aspirin (325 mg) or clopidogrel (75 mg) for 2 years



Clopidogrel provides slightly greater risk reduction than aspirin

*Composite of myocardial infarction, ischemic stroke, or vascular death

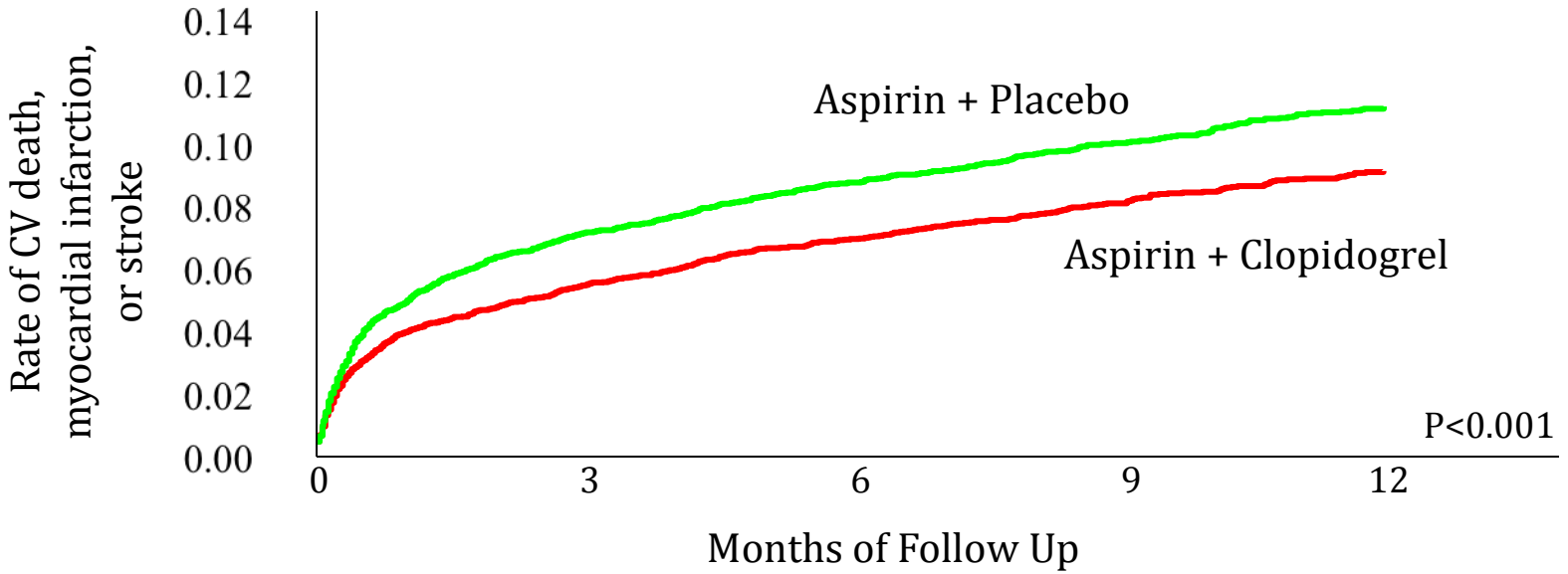
CVA=Cerebrovascular accident, MI=Myocardial infarction, PAD=Peripheral arterial disease

Source: CAPRIE Steering Committee. *Lancet* 1996;348:1329-1339

Clopidogrel Evidence: Secondary Prevention

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial

12,562 patients with a NSTE-ACS randomized to daily aspirin (75-325 mg) or clopidogrel (300 mg load, 75 mg thereafter) plus aspirin (75-325 mg) for 9 months



Dual antiplatelet therapy is more efficacious in a NSTE-ACS

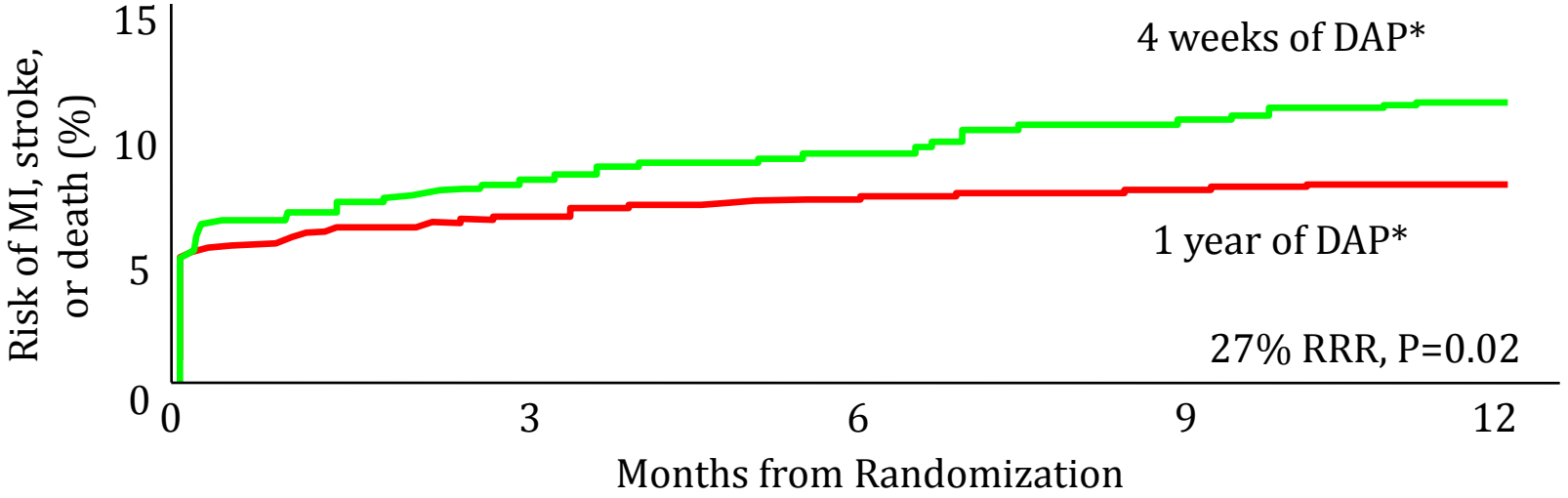
NSTE-ACS=Non ST-segment elevation acute coronary syndrome

Source: Adapted from Figure 1 *in* The CURE Trial Investigators. *NEJM* 2001;345:494-502

Clopidogrel Evidence: Secondary Prevention

Clopidogrel for the Reduction of Events during Observation (CREDO) Trial

2,116 patients undergoing PCI randomized to 4 weeks of DAP* followed by aspirin (75-325 mg) monotherapy vs. persistent DAP* for 1 year



DAP therapy produces greater benefit when used for 1 year

*Dual antiplatelet therapy=Aspirin (75-325 mg daily) plus clopidogrel (300 mg load followed by 75 mg daily)

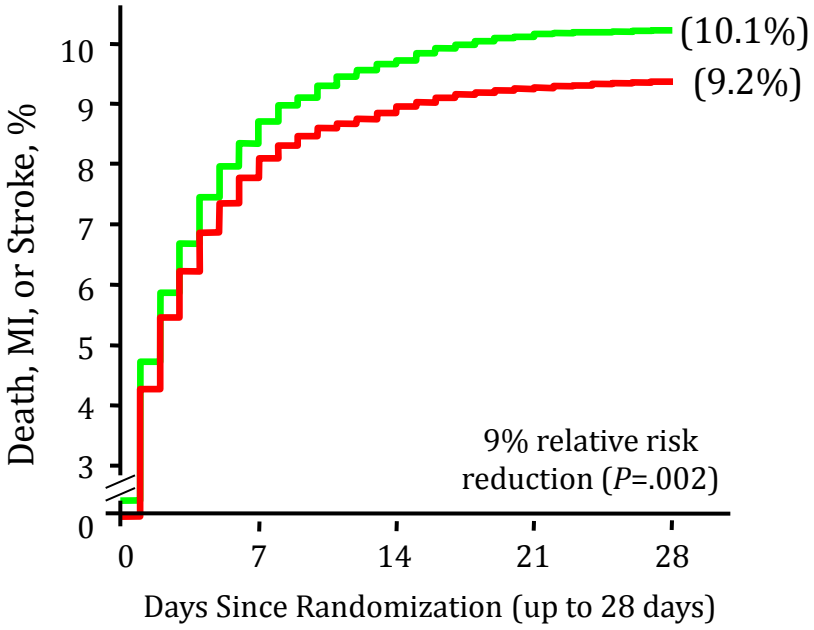
DAP=Dual antiplatelet, PCI=Percutaneous coronary intervention, RRR=Relative risk reduction

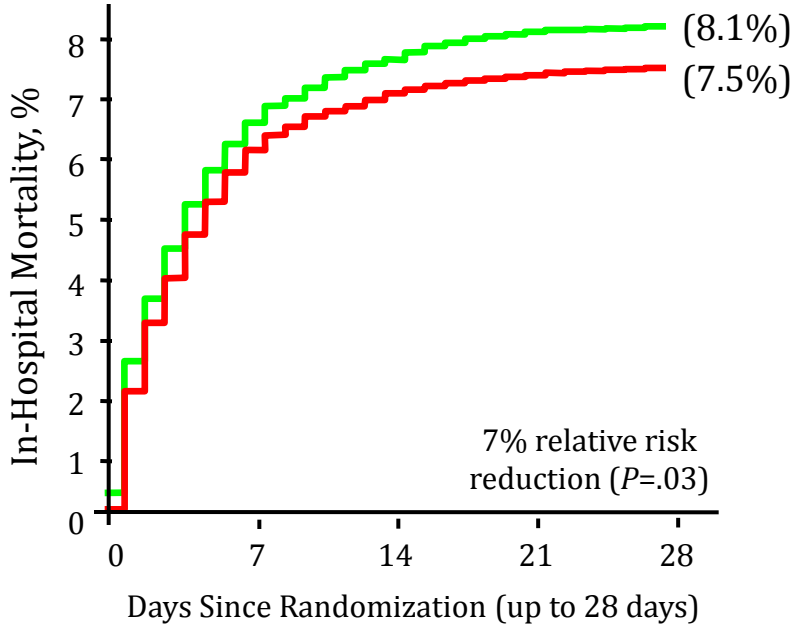
Source: Steinhubl S et al. *JAMA* 2002;288:2411-2420

Clopidogrel Evidence: Secondary Prevention

Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)

45,852 patients presenting within 24 hours of a STEMI treated medically and randomized to clopidogrel (75 mg daily) vs. placebo





DAP therapy produces greater benefit in medically managed STEMI patients

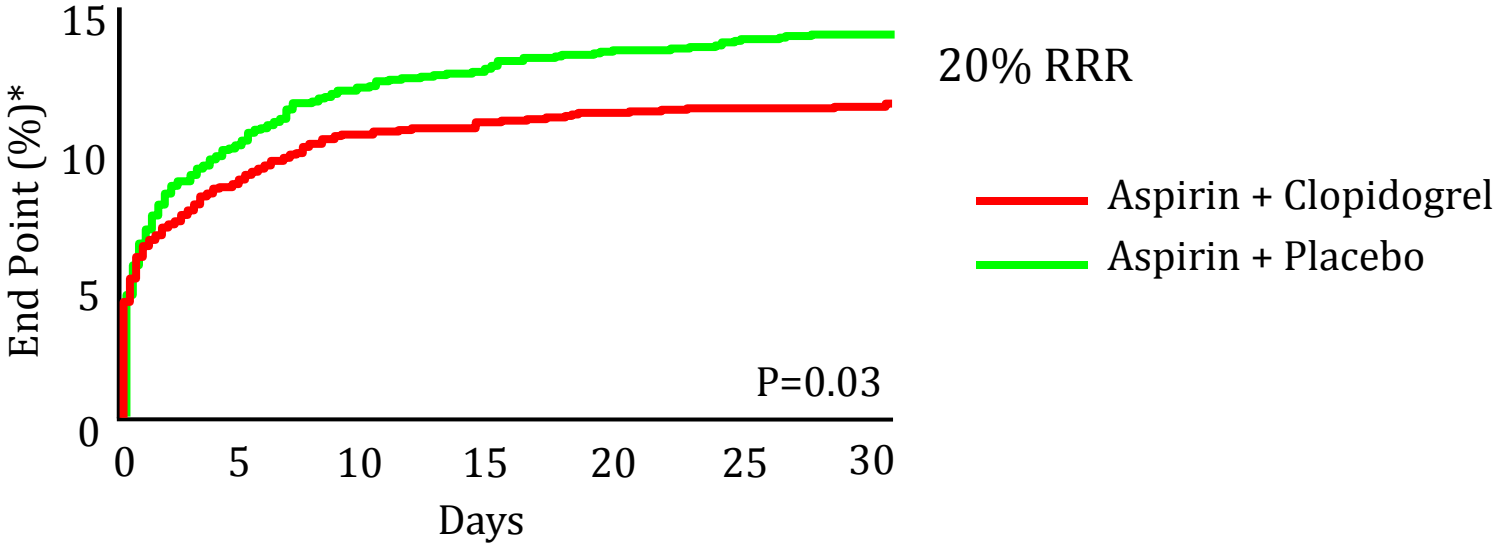
DAP=Dual antiplatelet, MI=Myocardial infarction, STEMI=ST-segment elevation myocardial infarction

Source: COMMIT Collaborative Group. *Lancet* 2005;366:1607-1621

Clopidogrel Evidence: Secondary Prevention

Clopidogrel as Adjunctive Reperfusion Therapy in Thrombolysis in Myocardial Infarction (CLARITY) Trial

3,491 patients (<75 years of age) presenting within 12 hours of a STEMI treated with fibrinolytic, aspirin, and heparin and randomized to clopidogrel (300 mg load followed by 75 mg daily) vs. placebo



DAP therapy benefits STEMI patients treated with fibrinolytic therapy

*Composite of cardiovascular death, myocardial infarction, and need for urgent revascularization

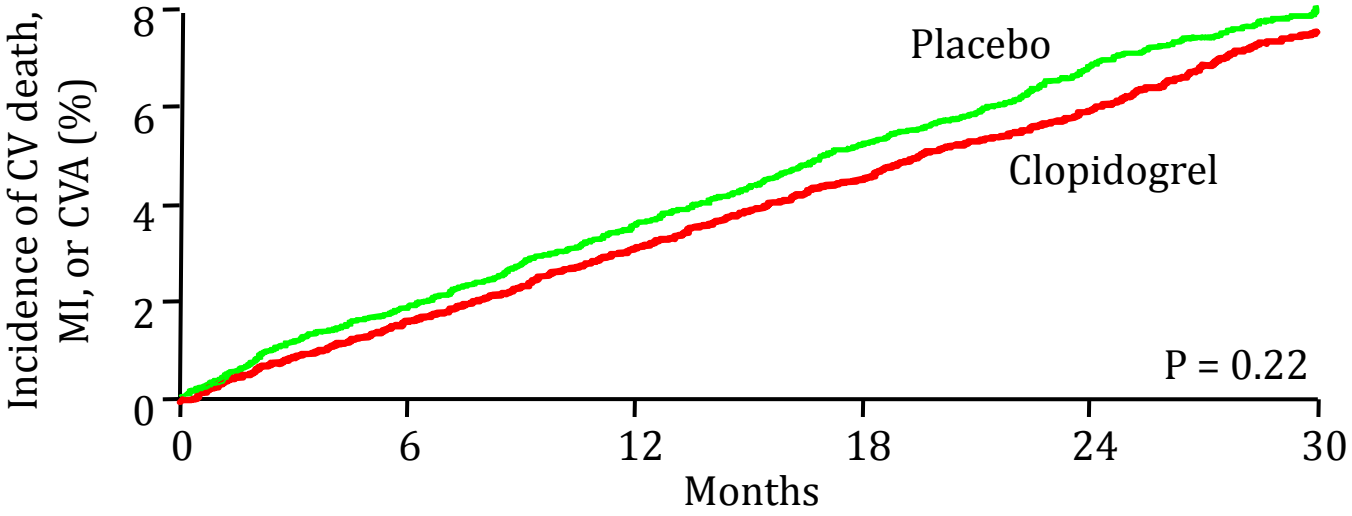
STEMI=ST-segment elevation myocardial infarction

Source: Sabatine MS et al. *NEJM* 2005; 352:1179-1189

Clopidogrel Evidence: Secondary Prevention

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial

15,603 patients with multiple CV risk factors or known CVD randomized to aspirin (75-162 mg) or aspirin (75-162 mg) & clopidogrel (75 mg) for a mean of 30 months



Routine DAP therapy offers little long-term benefit

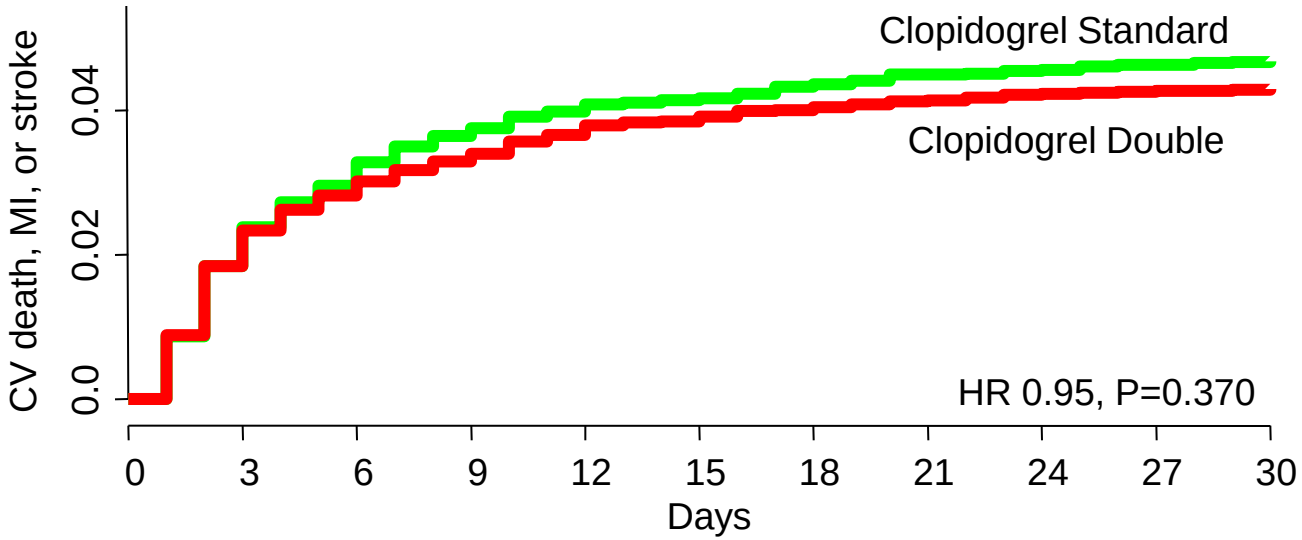
CV=Cardiovascular, CVA=Cerebrovascular accident, CVD=Cardiovascular disease, DAP=Dual antiplatelet, MI=Myocardial infarction

Source: Adapted from Figure 4 *in* Bhatt DL et al. *NEJM* 2006;354:1706-1717

Clopidogrel Evidence: Secondary Prevention

Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events (CURRENT)-OASIS 7 Trial

25,087 patients with an ACS randomized in a 2 x 2 factorial trial to double dose clopidogrel (600 mg LD, 150 mg x 7 days, then 75 mg MD) vs. standard dose clopidogrel (300 mg LD and 75 mg MD) and high dose aspirin (300-325 mg) vs. low dose aspirin (75-100 mg)



Type of Bleeding	D (%)	S (%)
TIMI Major	1.7	1.3
CURRENT Major*	2.5	2.0
Fatal	0.13	0.11
ICH	0.03	0.05
CABG-related	1.0	0.9

High dose clopidogrel does not provide benefit in ACS

*p=0.01

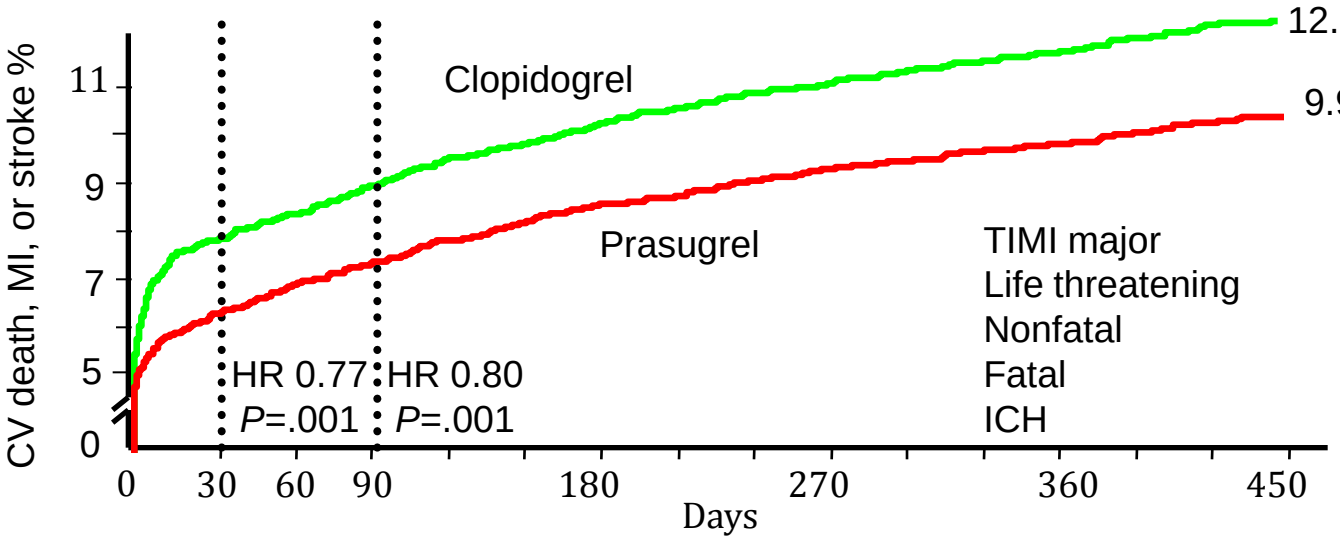
ACS=Acute coronary syndrome, CABG=Coronary artery bypass graft, ICH=Intracranial hemorrhage, LD=Loading dose, MD=Maintenance dose

Source: CURRENT-OASIS 7 Investigators. *NEJM* 2010;363:930-942

Prasugrel Evidence: Secondary Prevention

Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38)

13,608 patients with high-risk ACS scheduled for PCI randomized to clopidogrel (300 mg LD and 75 mg MD) or prasugrel (60 mg LD and 10 mg MD) for a median of 12 months



HR 0.81, *P*=0.0004

Bleeding Events	C (%)	P (%)	*P-value*
TIMI major	1.8	2.4	.03
Life threatening	0.9	1.4	.01
Nonfatal	0.9	1.1	.23
Fatal	0.1	0.4	.002
ICH	0.3	0.3	.74

Prasugrel reduces ischemic events with a higher rate of bleeding

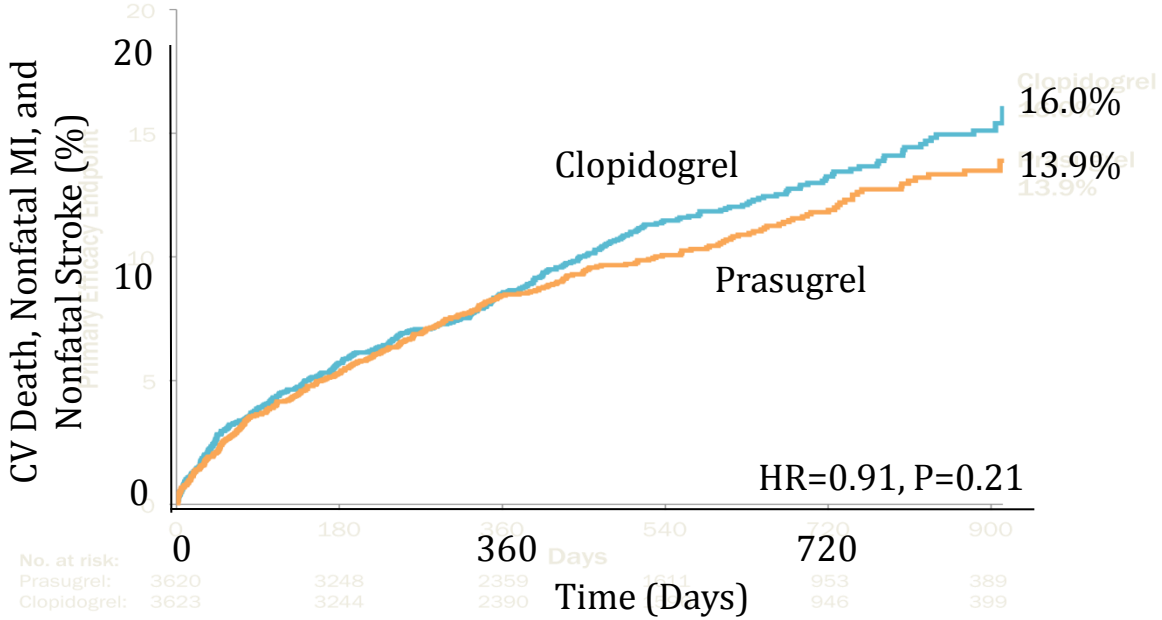
ACS=Acute coronary syndrome, ICH=Intracranial hemorrhage, LD=Loading dose, MD=Maintenance dose

Source: Wiviott SD et al. *NEJM* 2007;357:2001-2015

Prasugrel Evidence: Secondary Prevention

Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS)

7243 patients with a medically managed NSTE-ACS randomized to prasugrel (10 mg) or clopidogrel for up to 30 months



Prasugrel does not provide benefit in medically managed NSTE-ACS

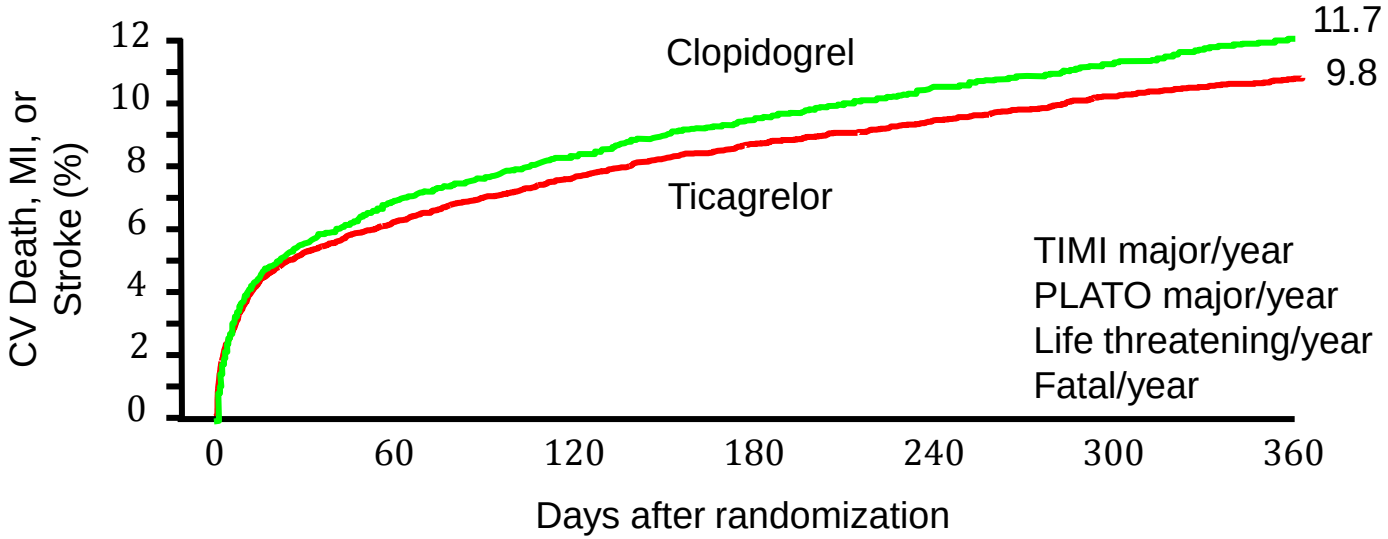
CV=Cardiovascular, MI=Myocardial infarction, NSTE-ACS=Non-ST-segment elevation acute coronary syndrome

Source: Roe, MT et al. *NEJM* 2012;367:1297-1309

Ticagrelor Evidence: Secondary Prevention

Platelet Inhibition and Patient Outcomes (PLATO) Study

18,624 patients with a moderate to high risk ACS randomized to clopidogrel (300-600 mg LD and 75 mg MD) or ticagrelor (180 mg LD and 90 mg twice daily MD) for 12 months



HR 0.84, p=0.001

	Bleeding Events* C (%)	T (%)
TIMI major/year	7.9	7.7
PLATO major/year	11.6	11.2
Life threatening/year	5.8	5.8
Fatal/year	0.3	0.3

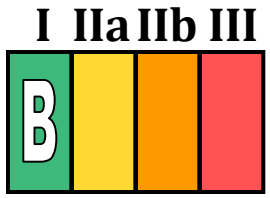
Ticagrelor reduces ischemic events with no higher rate of bleeding overall

*No statistically significant differences were observed in bleeding rates overall

ACS=Acute coronary syndrome, CV=Cardiovascular, LD=Loading dose, MD=Maintenance dose

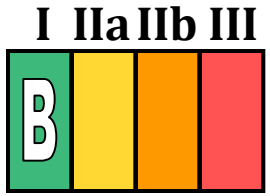
Source: Wallentin L et al. *NEJM* 2009;361:1045-1057

$P2Y_{12}$ Receptor Antagonist Recommendations



Secondary Prevention

Clopidogrel (75 mg daily; Class I, Level B), prasugrel* (10 mg daily; Class I, Level C), or ticagrelor (90 mg twice daily; Class I, Level C) if aspirin intolerance or a true aspirin allergy following a NSTE-ACS



Clopidogrel (75 mg daily) or ticagrelor (90 mg twice daily) in addition to aspirin for up to 1 year following a NSTE-ACS managed conservatively

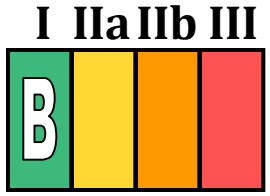
*In PCI treated patients

NSTE-ACS=Non ST-segment elevation acute coronary syndrome; PCI=Percutaneous coronary intervention, STEMI=ST-segment elevation myocardial infarction

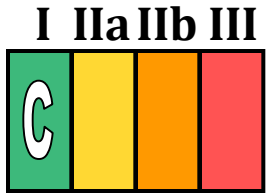
Source: Jneid H et al. *JACC* 2012;60:645-681

$P2Y_{12}$ Receptor Antagonist Recommendations

Secondary Prevention



Clopidogrel (75 mg daily), prasugrel (10 mg daily), or ticagrelor (90 mg twice daily) in addition to aspirin for 1 year following PCI for a NSTE-ACS† or a STEMI‡



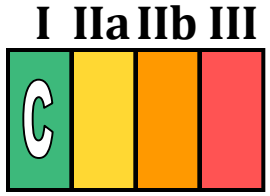
Clopidogrel (75 mg daily) in addition to aspirin for a minimum of 14 days (Class I, Level A) and up to 1 year (Class I, Level C) following fibrinolytic therapy for a STEMI‡

NSTE-ACS=Non ST-segment elevation acute coronary syndrome; PCI=Percutaneous coronary intervention, STEMI=ST-segment elevation myocardial infarction

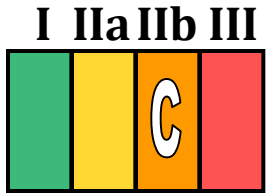
Sources:
†Jneid H et al. *JACC* 2012;60:645-681
‡O'Gara PT et al. *JACC* 2013;61:e78-e140

$P2Y_{12}$ Receptor Antagonist Recommendations (Continued)

Secondary Prevention



If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by a $P2Y_{12}$ receptor antagonist, earlier discontinuation should be considered



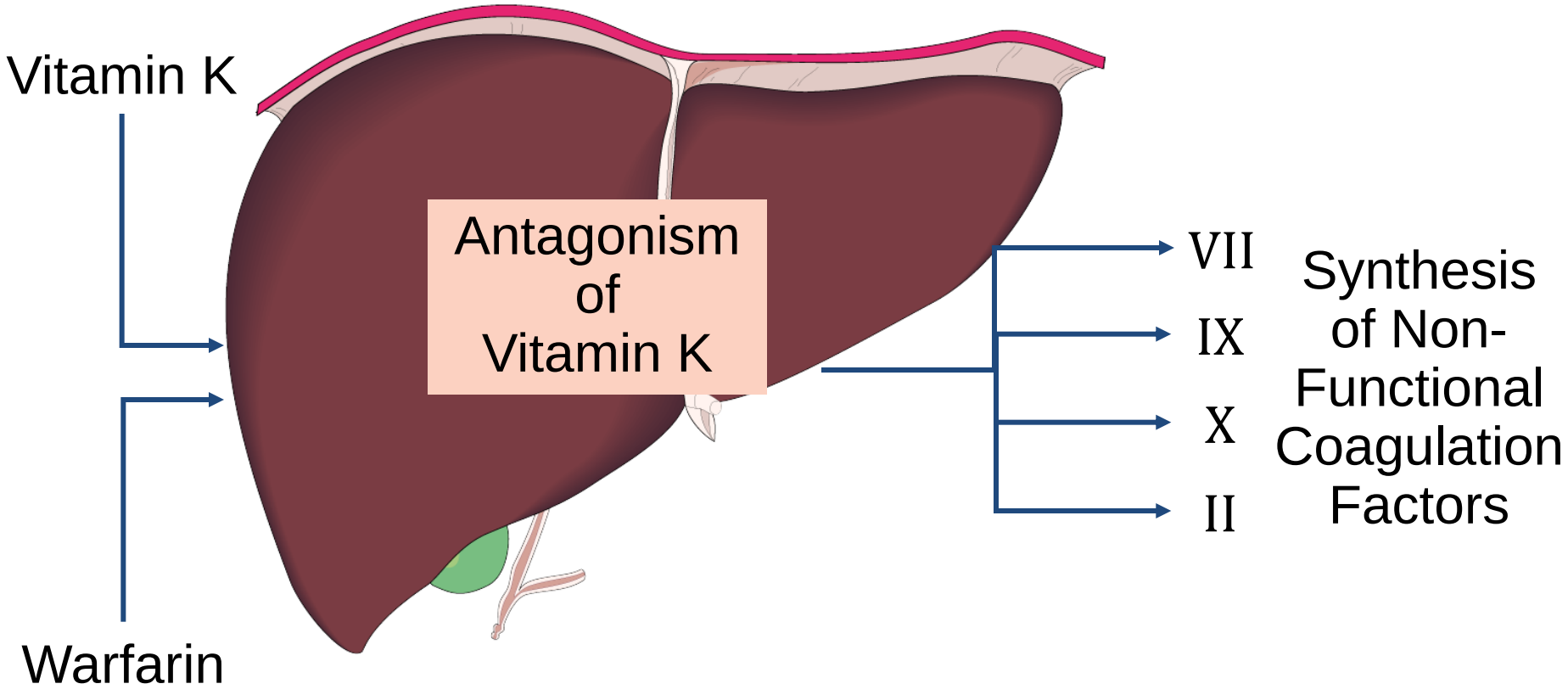
Continuation of a $P2Y_{12}$ receptor antagonist beyond 1 year may be considered in patients undergoing drug eluting stent placement

Sources:
Kushner F et al. *JACC* 2009;54:2205-2241
Jneid H et al. *JACC* 2012;60:645-681
O'Gara PT et al. *JACC* 2013;61:e78-e140

Evidence for Current Cardiovascular Disease Prevention Guidelines

Anticoagulant Therapy Evidence and Guidelines

Warfarin: Mechanism of Action



Source: Ansell J et al., Council on Clinical Cardiology. *American Heart Association*, Management of Oral Anticoagulant Therapy, www.americanheart.org/downloadable/heart/3491_Mgt.ppt

Warfarin Evidence: Primary Prevention

Thrombosis Prevention Trial (TPT)

5,499 men at high risk for CHD randomized to aspirin (75 mg), warfarin (mean INR=1.5), warfarin and aspirin, or placebo for 6.4 years

	WA N=1277	W N=1268	A N=1268	P N=1272
MI and coronary death (primary end point)	71 (0.87%)	83 (1.03%)	83 (1.02%)	107 (1.33%)
Stroke	29 (0.36%)	22 (0.27%)	18 (0.22%)	26 (0.32%)
All cause mortality	103 (1.24%)	95 (1.14%)	113 (1.36%)	110 (13.1%)
RRR of ischemic heart disease events compared to placebo	34% (p=0.006)	21% (p=0.02)	20% (p=0.04)	N/A

Warfarin provides similar efficacy to aspirin

A=Aspirin, CHD=Coronary heart disease, P=Placebo, W=Warfarin, WA=Warfarin and aspirin

Source: The Medical Research Council's General Practice Research Framework. *Lancet* 1998;351:233-241

Warfarin Evidence: Secondary Prevention

Meta-analysis of 31 trials comparing the effects of oral anticoagulation with and without aspirin on CV outcomes

	Events prevented per 1000 patients treated (95% CI)	Major bleeds per 1000 patients treated (95% CI)
High intensity OA vs. control	98 (73-123)	39 (35-43)
Moderate intensity OA vs. control	24 (22-26)	35 (21-49)
Moderate to high intensity OA and ASA vs. ASA	54 (43-65)	16 (10-22)
Moderate to high intensity OA vs. ASA	13 (11-14)	14 (12-16)
Low intensity OA and ASA vs. ASA	7 (6-8)	5 (4-6)

Warfarin plus aspirin reduces the rate of adverse events with a higher rate of major bleeding

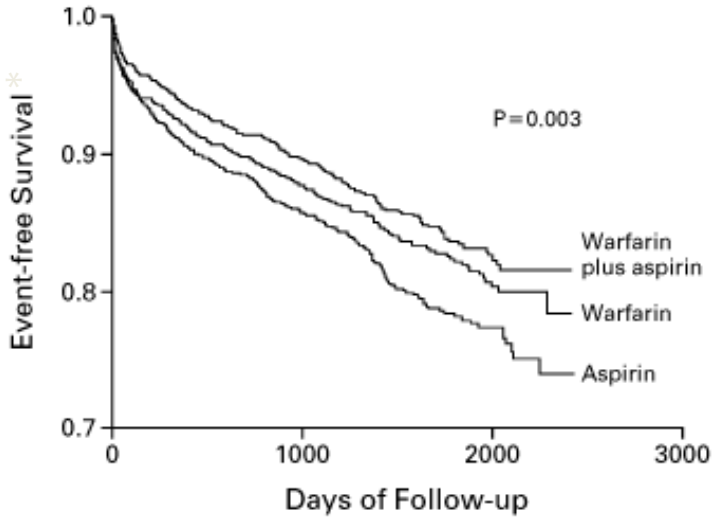
ASA=Aspirin, CI=Confidence interval, CV=Cardiovascular, OA=Oral anticoagulation

Source: Anand SS et al. *JAMA* 1999;282:2058-2067

Warfarin Evidence: Secondary Prevention

Warfarin, Aspirin, or Both After Myocardial Infarction (WARIS II) Trial

3,630 patients following a myocardial infarction randomized to warfarin (INR 2.8-4.2), aspirin (160 mg daily) or warfarin (INR 2.0-2.5) plus aspirin (75 mg daily) for a mean of 4 years



Type of Bleeding	A (n)	W (n)	W + A (n)
Cerebral	1	5	3
GI	6	18	21
Other	1	7	4
Total	8	33	28
Rate**	0.62 %	0.62 %	0.17%

Warfarin plus aspirin reduces the rate of adverse events with a higher rate of major bleeding

*Composite of death, reinfarction, and stroke
**p<0.001

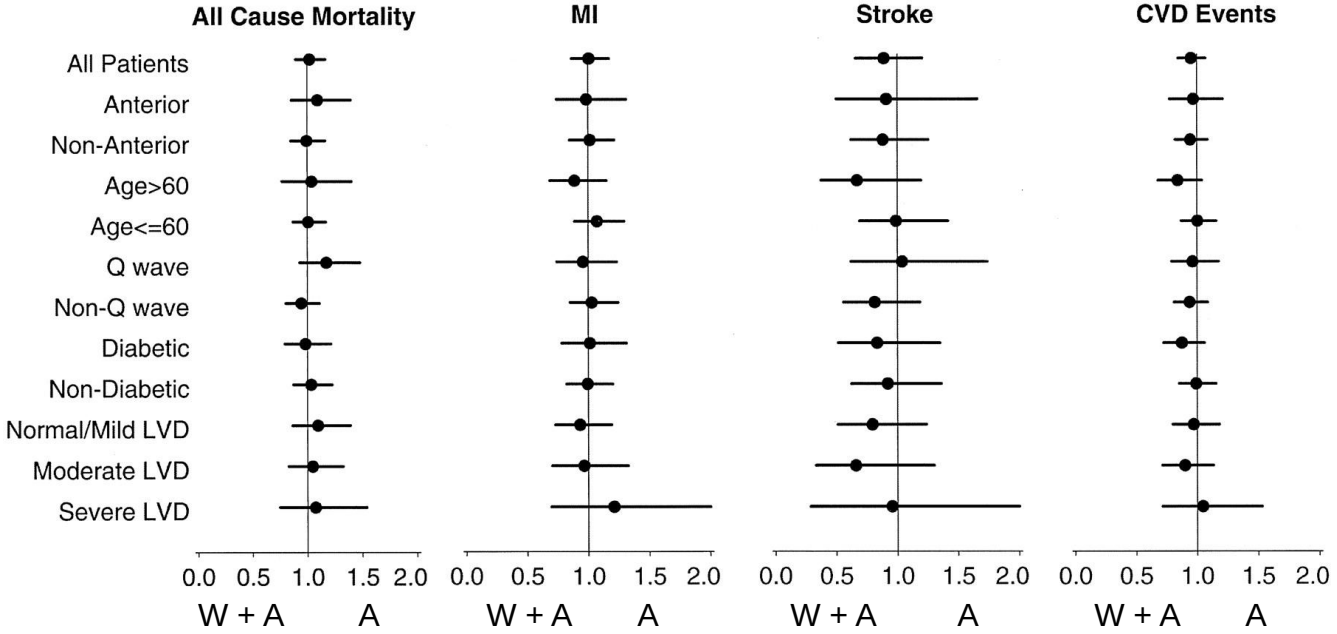
A=Aspirin, W=Warfarin

Source: Hurlen M et al. *NEJM* 2002;347:969-974

Warfarin Evidence: Secondary Prevention

Clinical Trial Comparing Combined Warfarin and Aspirin With Aspirin Alone in Survivors of Acute Myocardial Infarction (CHAMP)

5059 patients within 14 days of a myocardial infarction randomized to aspirin (162 mg daily) or warfarin (INR 1.5-2.5) plus aspirin (81 mg daily) for 2.7 years



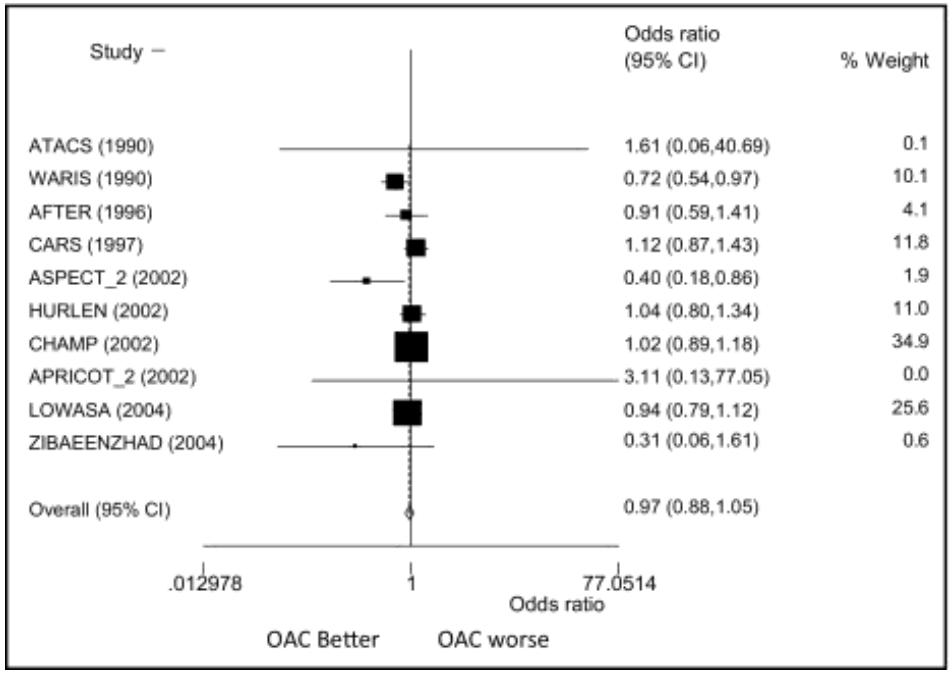
Warfarin plus aspirin provides no greater benefit compared to treatment with aspirin alone

A=Aspirin, CVD=Cardiovascular disease, INR=International normalized ratio, MI=Myocardial infarction, W=Warfarin

Source: Fiore LD et al. *Circulation* 2002;105:557-563

Warfarin Evidence: Secondary Prevention

Meta-analysis of 24,542 patients with recent MI comparing warfarin-containing regimens (OAC) with or without aspirin to non-warfarin-containing regimens with or without aspirin (No OAC)



All-case Mortality

Routine use of warfarin after MI does not reduce all-cause mortality

CI=Confidence interval, MI=Myocardial infarction OAC=Oral anticoagulant

Source: Figure 2 *in* Haq SA et al. *Am J Med*; 2010;123:250-258

Warfarin Evidence: Secondary Prevention

Warfarin and Antiplatelet Therapy in Heart Failure (WATCH) Trial

1,587 patients with HF and LVSD (EF <0.35) randomized to aspirin (162 mg), clopidogrel (75 mg), or warfarin (mean INR=2.6) for 23 months

Outcome	Aspirin (n=523)	Warfarin (n=540)	Clopidogrel (n=524)
Death, MI, or stroke (%)	20.5	19.8	21.8
HF hospitalizations (%)	22.2	16.1	18.3
Major bleeding (number of episodes)	19	30	13*

Clopidogrel and warfarin provide no greater benefit than aspirin in LVSD

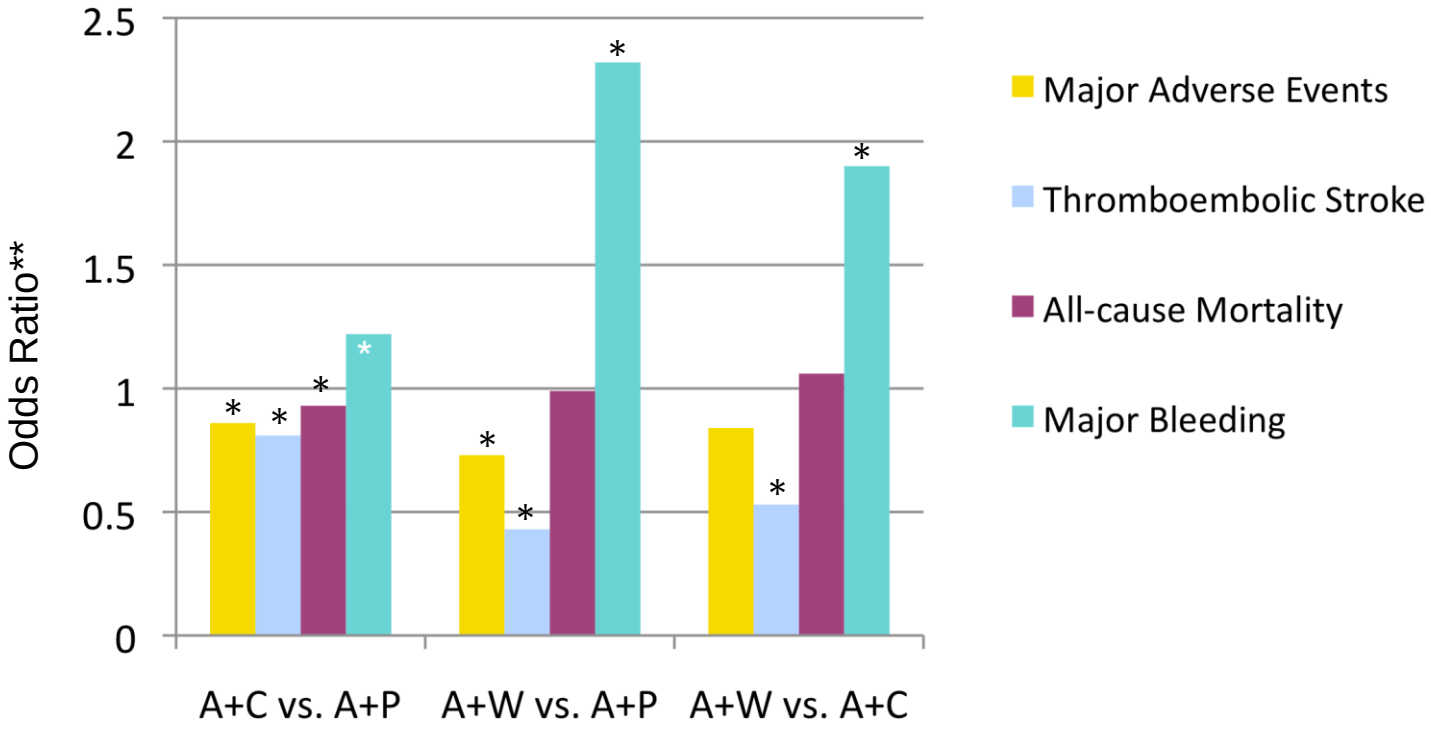
*p=0.012 vs warfarin

EF=Ejection fraction, HF=Heart failure, LVSD=Left ventricular systolic dysfunction, MI=Myocardial infarction

Source: Massie BM, et al. *Circulation* 2009;119:1616-1624

Warfarin Evidence: Secondary Prevention

Meta-analysis of 61,905 patients with CV disease comparing treatment regimens with aspirin plus warfarin, aspirin plus clopidogrel, or aspirin alone



A + W provide comparable benefit to A + C but with greater bleeding

*p<0.05

**Include all-cause mortality, acute MI, thromboembolic stroke, major bleeds, and other types of stroke

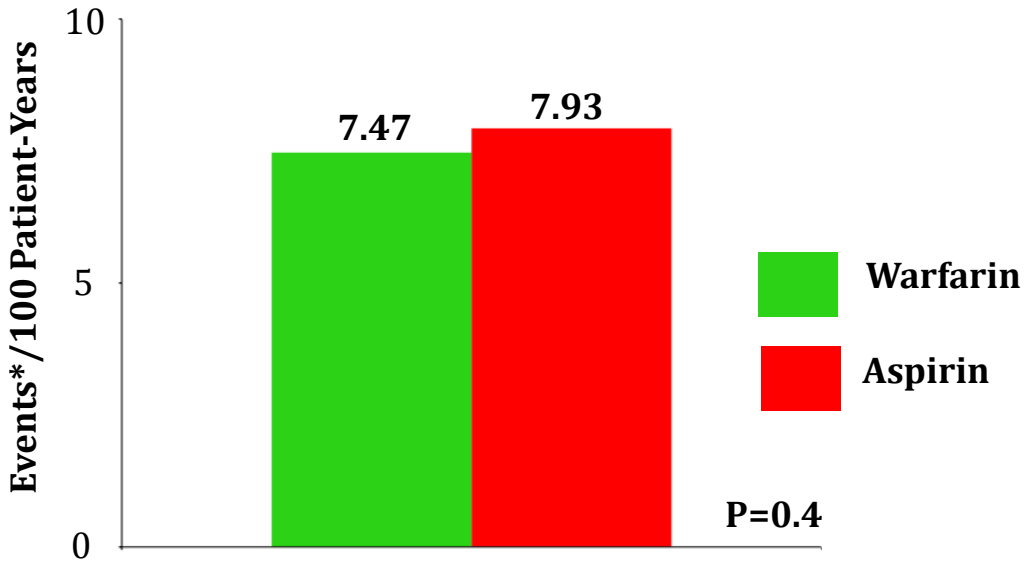
A=Aspirin, C=Clopidogrel, P=Placebo, W=Warfarin

Source: Testa L et al. *Am J Cardiol*. 2007;99(12):1637-1642

Warfarin Evidence: Secondary Prevention

Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial

2305 patients with LV systolic dysfunction (mean LV EF of 25%) and sinus rhythm randomized to warfarin or aspirin



Warfarin provides no greater benefit than aspirin in LVSD

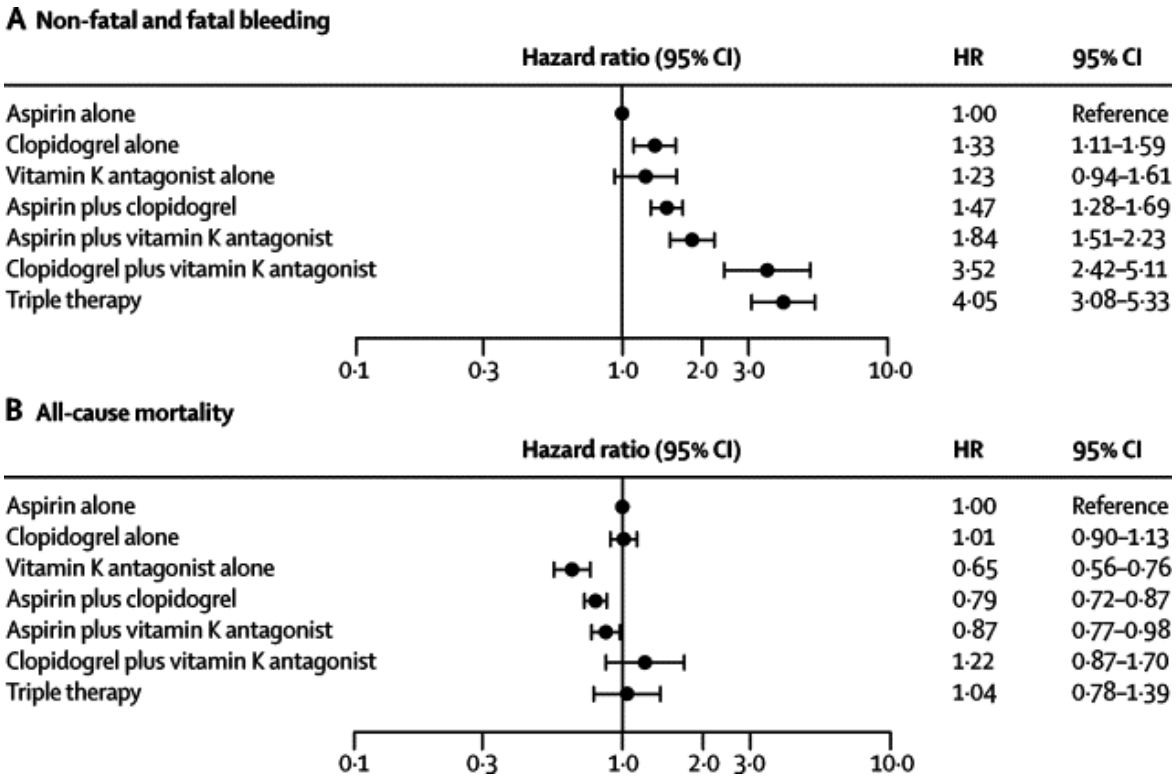
*Composite of death, ischemic stroke, or intracerebral hemorrhage

LVSD=Left ventricular systolic dysfunction

Homma S et al. *NEJM* 2012;366:1859-1869

Triple Antithrombotic Therapy Evidence: Secondary Prevention

Retrospective analysis of 40,812 patients admitted with a first myocardial infarction in a national registry in Denmark



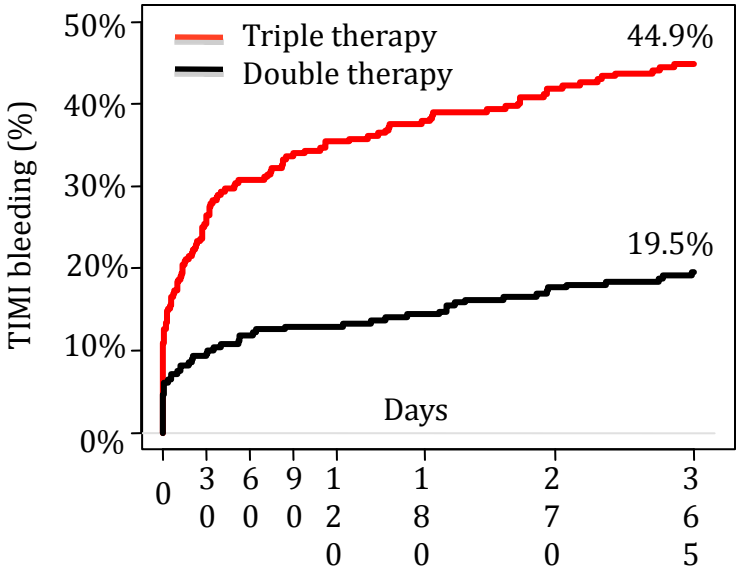
Triple antithrombotic therapy significantly increases the rate of bleeding

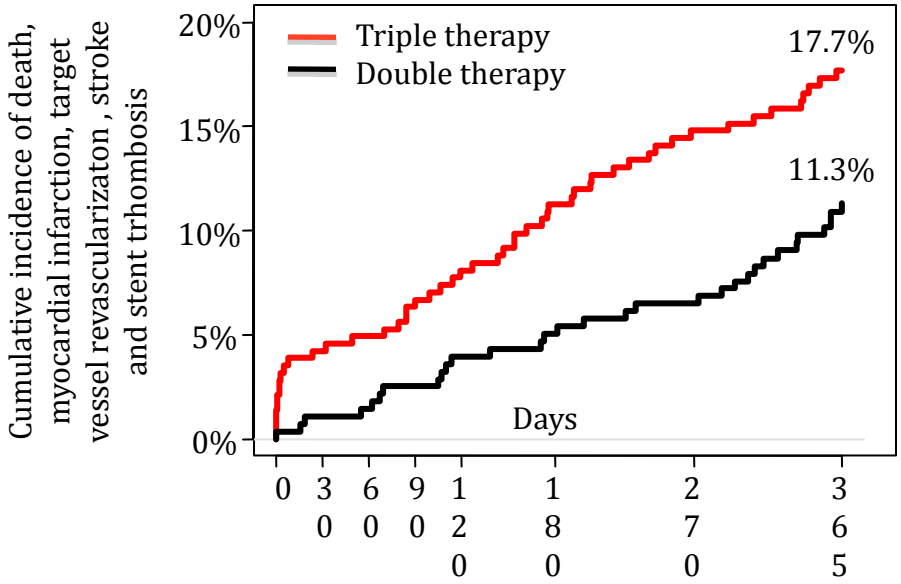
Source: Sorensen R et al. *Lancet* 2009;374:1967-1974

Warfarin Evidence: Secondary Prevention

What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) Trial

573 patients undergoing PCI with an indication for oral anticoagulation randomized to double versus triple antithrombotic therapy*





Dual antithrombotic therapy significantly reduces CV risk and bleeding

*Triple therapy=Aspirin (80 mg/day), clopidogrel, and OAC, Double therapy=Clopidogrel and OAC

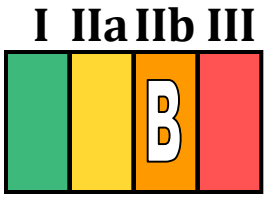
OAC=Oral anticoagulant

Source: Presented at the Eurospean Society of Cardiology Congress, August 2012

Warfarin Recommendations

Secondary Prevention

Use of warfarin in conjunction with aspirin and/or a $P2Y_{12}$ receptor antagonist is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially GI, and seek medical evaluation for evidence of bleeding



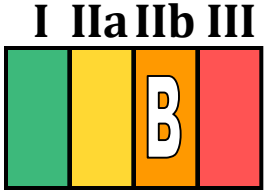
Warfarin either without (INR 2.5-3.5) or with low-dose aspirin (81 mg daily, INR 2.0-2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of a $P2Y_{12}$ receptor antagonist

CAD=Coronary artery disease,
INR=International normalized ratio

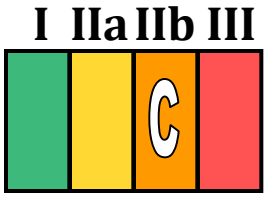
Source: Jneid H et al. *JACC* 2012;60:645-681

Warfarin Recommendations (Continued)

Secondary Prevention



The addition of warfarin (INR 2.0-3.0) may be reasonable for patients with a NSTE-ACS who have an indication for anticoagulation*



Targeting oral anticoagulant therapy to a lower INR (2.0-2.5) might be reasonable in patients with a NSTE-ACS or STEMI managed with aspirin and a $P2Y_{12}$ receptor antagonist

*Indications for anticoagulation include: atrial fibrillation; left ventricular thrombus; or central, venous, or pulmonary emboli

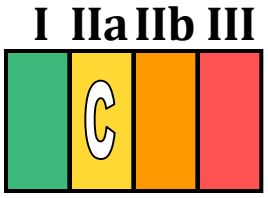
INR=International normalized ratio, NSTE-ACS=Non ST-segment elevation acute coronary syndrome, STEMI=ST-segment elevation myocardial infarction

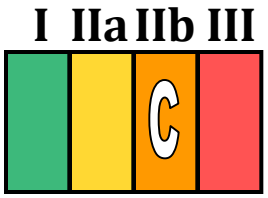
Sources:
Jneid H et al. *JACC* 2012;60:645-681
O'Gara PT et al. *JACC* 2013;61:e78-e140

Warfarin Recommendations (Continued)

Secondary Prevention

Anticoagulation therapy with a Vitamin K antagonist should be provided to patients with STEMI and atrial fibrillation with $CHADS_2$ score $\geq$2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder





Anticoagulant therapy with a Vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi (Class IIa, Level C) and may be considered for patients with STEMI and anterior-apical akinesis or dyskinesis (Class IIb, Level C)

LV=Left ventricular, STEMI=ST-segment elevation myocardial infarction

Source: O'Gara PT et al. *JACC* 2013;61:e78-e140

Warfarin Recommendations (Continued)

Secondary Prevention

The duration of triple antithrombotic therapy with a Vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor antagonist should be minimized to the extent possible to limit the risk of bleeding.

Source: O'Gara PT et al. *JACC* 2013;61:e78-e140