Maine Independent Clinical Information Service

Balanced Data About Medications

Introduction

Antiplatelet drugs are widely-used for the primary and secondary prevention of myocardial infarction, stroke and other cardiovascular events.

Antiplatelet Drugs

- Aspirin
- clopidogrel (Plavix)
- prasugrel (Effient)
- Dipyridamole + aspirin (Aggrenox)

Clopidogrel v. Aspirin

- Evidence supporting aspirin's efficacy in a variety of clinical settings has existed for more than two decades
- Clopidogrel (Plavix) has been increasingly used since the publication of the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial in 1996

Clopidogrel:
Alternative vs. Adjunct to ASA Therapy?

- Interpretation and clinical application of studies can be challenging because dual antiplatelet therapy increases the risk of bleeding, necessitating a careful risk-benefit analysis.

Newer Drugs: Aggrenox and Effient

- Aggrenox (Dipyridamole combined with aspirin)
  - management of patients after stroke
- Effient (Prasugrel)
  - acute coronary syndromes who have undergone coronary stent insertion
    - Works in a similar manner as clopidogrel
    - Highly Effective
    - Associated with Substantial Bleeding Risk

Choosing the Right Antiplatelet Therapy

1. Understanding the benefits and risks of specific regimens
2. Understanding the drugs role in different clinical settings
3. $$$: clopidogrel and combination aspirin and extended-release dipyridamole are much more expensive than aspirin

Clopidogrel: The second best-selling drug in the world in 2008. Sales Total $8.6 Billion

A substantial proportion of this use is in situations where clinical trials have found aspirin to be an equally effective, safer, and substantially less expensive alternative.

Acute Coronary Syndromes

Definition:

1. Unstable angina
2. Non-ST-segment elevation myocardial infarction (N-STEMI)
3. ST-segment elevation MI (STEMI)

ACS: Aspirin

- Trials convincingly show that giving aspirin to **acute MI patients** in hospital and continuing treatment for an average of 1 month reduces the risk of re-infarction, stroke, or cardiovascular death by 30%
- Also reduces the risk of a major vascular event by 46% when given acutely to patients with **unstable angina**

ACS: Clopidogrel

No trials have evaluated clopidogrel as an alternative to aspirin for patients with ACS.

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)

- Enrolled patients with NSTEMI or UA
- Randomized them to clopidogrel or placebo
  - [all patients receiving aspirin]
- Patients received assigned therapy for one year after discharge
  - Mean 9 months

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)

Patients in the dual antiplatelet group had a significantly lower risk of death from cardiovascular causes, non-fatal MI, and non-fatal stroke.

As a result, dual therapy is recommended for all NSTEMI and unstable angina patients.

Recommended Length of Therapy: 12 months

Key trials comparing aspirin plus clopidogrel versus aspirin alone for patients with acute coronary symptoms

Trial Name	Who was enrolled?	What was studied and for how long?	What was the primary outcome?	What were the main results?					
				Prevention of vascular events			Risk of major bleeding		
				Aspirin alone	Clopidogrel plus aspirin	Absolute difference	Aspirin alone	Clopidogrel plus aspirin	Absolute difference
CURE (NEJM 2001)	NSTEMI/UA (n=12,562)	Clopidogrel + aspirin v. aspirin alone (for 3-12 months)	Death from cardiovascular causes, non-fatal MI, non-fatal stroke	11.4%	9.3%	2.1%	2.7%	3.7%	1%
CLARITY-TIMI 28 (NEJM 2005)	STEMI (n=3,491)	Clopidogrel + aspirin v. aspirin alone (until angiography, day 8 or hospital discharge)	Occluded infarct-related artery on angiography, death, or recurrent MI	21%	15%	6%	1.3%	1.1%	Not significant
COMMIT (Lancet 2005)	STEMI (n=45,852)	Clopidogrel + aspirin v. aspirin alone (until discharge or up to 4 weeks in hospital)	Death, re-infarction or stroke	10.1%	9.2%	0.9%	0.58%	0.55%	Not significant

Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events in Patients Undergoing Percutaneous Coronary Intervention (PCI-CURE)

- Sub-study of the CURE trial
- Dual antiplatelet therapy with clopidogrel and aspirin vs. aspirin alone
- ACS patients undergoing PCI
- The group that received clopidogrel and aspirin had a 30% lower relative rate of cardiovascular events than patients given aspirin alone.

Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) *and* Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)

- Evaluated patients hospitalized for STEMI
- Both Trials Show: Clopidogrel-aspirin therapy administered in hospital was superior to aspirin alone in preventing major vascular events
- In CLARITY, the benefit of dual therapy was also observed in the subgroup of patients who underwent PCI

Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) *and* Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)

(continued)

- Trials were extremely short: No Outpatient Data
- As recommended by the current American Heart Association/American College of Cardiology guidelines, like NSTEMI/US patients, STEMI patients will also benefit if therapy is continued for at least **one year.**

ACS: Prasugrel

TRITON-TIMI

- 13,608 patients with acute coronary syndrome (UA, NSTEMI, or STEMI) scheduled for PCI
- Patients received prasugrel or clopidogrel
- All patients also received aspirin
- Study's primary efficacy endpoint was death from cardiovascular causes, nonfatal MI, or nonfatal stroke
  - **Endpoint occurred significantly less frequently in patients receiving prasugrel**
- Main finding was due to the difference in non-fatal MI
- Recommended Length of Therapy with Prasugrel:
  - 15 months

Added benefit of prasugrel is much smaller in several important subgroups

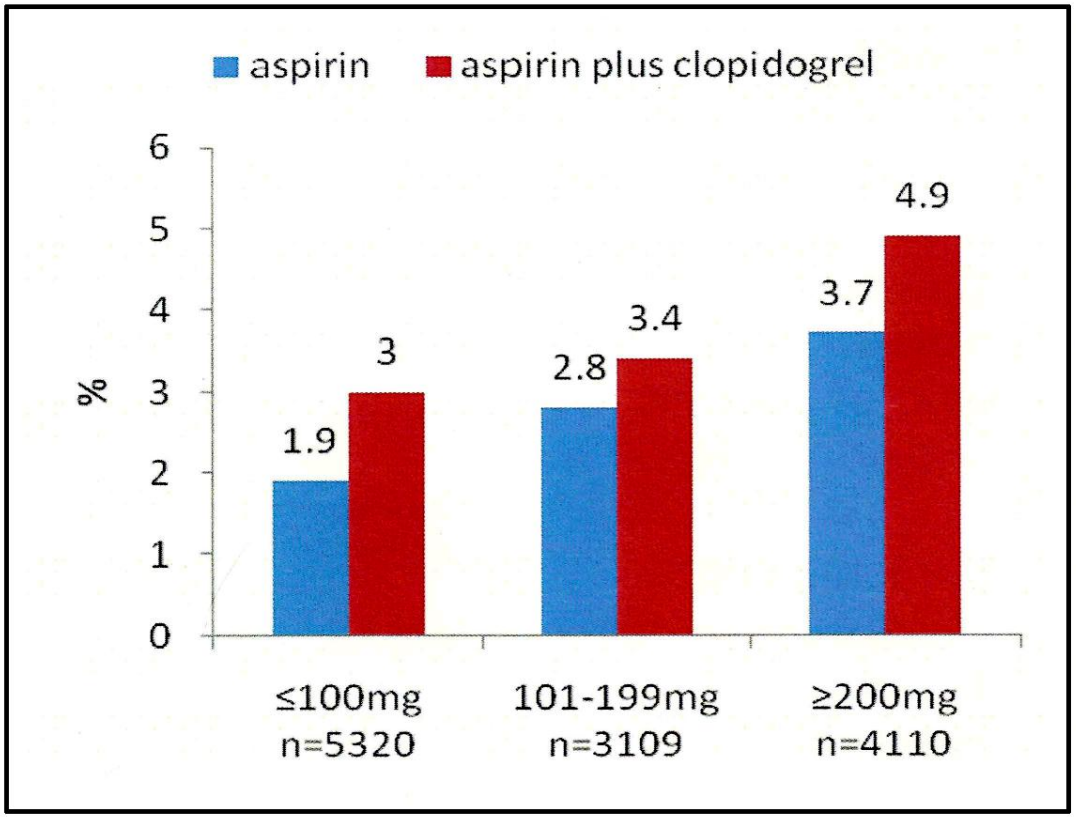
Patients with:

- History of stroke
- Transient ischemic attack
- Age ≥ 75 years
- Weight of less than 60 kg

Risks of Antiplatelet Therapy

Increased risk of gastrointestinal and intracranial bleeding.

Risk increases with higher doses of aspirin



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Bleeding Risks: Combined Aspirin and Clopidogrel

- Short-term: similar to those of patients treated with aspirin alone
  - (COMMIT) (CLARITY)
- Longer-term trials: higher risk of bleeding than antiplatelet monotherapy
  - (CURE) (TRITON TIMI 38)

In CURE, clopidogrel plus aspirin caused:

- Higher incidence of major bleeding than aspirin alone, including bleeding that required transfusion
- No increase in the risk of life-threatening bleeding
- No increase in hemorrhagic stroke

In TRITON-TIMI 38, prasugrel + aspirin caused:

Higher risk of major bleeding than clopidogrel plus aspirin in **three subgroups**

- History of stroke of transient ischemic attack
- Aged ≥75 years
- Weight under 60kg

For these patients, its advantage is not documented. If used, a reduced dose (5mg daily rather than the usual 10mg daily) should be considered

BOTTOM LINE

Dual therapy with **clopidogrel** and **aspirin** for at least one year is the currently recommended treatment for all ACS patients.

For many **ACS** patients who have undergone **PCI**, a recent trial suggests that **prasugrel and aspirin** for 15 months is likely the appropriate choice.

Recent or Remote MI

In patients with prior MI, aspirin reduces the risk of subsequent vascular events by more than 25%.

CAPRIE Trial:

Clopidogrel (75mg daily) vs. Aspirin (325mg daily)

- 19,000 patients
  - Recent MI
  - Recent stroke
  - Peripheral vascular disease
- Clopidogrel was superior **but** the magnitude of this effect was very small
  - 0.5% absolute risk reduction
  - 8.7% relative risk reduction

CAPRIE post-MI subgroup

In post-MI subgroup alone, clopidogrel was equivalent to aspirin

⁂ **routine use of clopidogrel for all post-MI patients is NOT recommended.**

CAPRIE High-Risk Subgroups

Patients with:

- History of bypass surgery
- Prior stroke or MI
- Arterial disease in two or more areas
- Diabetes
- High cholesterol

Showed a particular benefit from **clopidogrel** compared to aspirin. NOTE: These analyses were post-hoc, therefore these associations may be due to statistical chance.

Nevertheless, the use of clopidogrel is reasonable in these subgroups and in patients who are aspirin intolerant.

CHARISMA Trial:

clopidogrel (75mg daily) + aspirin (75-162mg daily) *vs.* aspirin alone (75-162mg daily)

- 15,000 patients
  - –Symptomatic vascular disease
  - –Multiple risk factors for vascular disease

Combination antiplatelet therapy was not better than aspirin alone **and** resulted in a higher rate of bleeding

Risks of Antiplatelet Therapy

The risk of serious bleeding has been reported to be minimally lower with clopidogrel than with aspirin.

In CAPRIE:

- Risk of intracranial hemorrhage:
  - 0.35% in clopidogrel patients
  - 0.49% in aspirin patients

  Not statistically significant

- Risk of gastrointestinal hemorrhage
  - 1.99% in clopidogrel patients
  - 2.66% in aspirin patients

  Statistically significant, however aspirin-treated patients received 325mg of aspirin, a dose higher than is commonly used

  ⁂ **unknown whether clopidogrel is safer than lower doses of aspirin**

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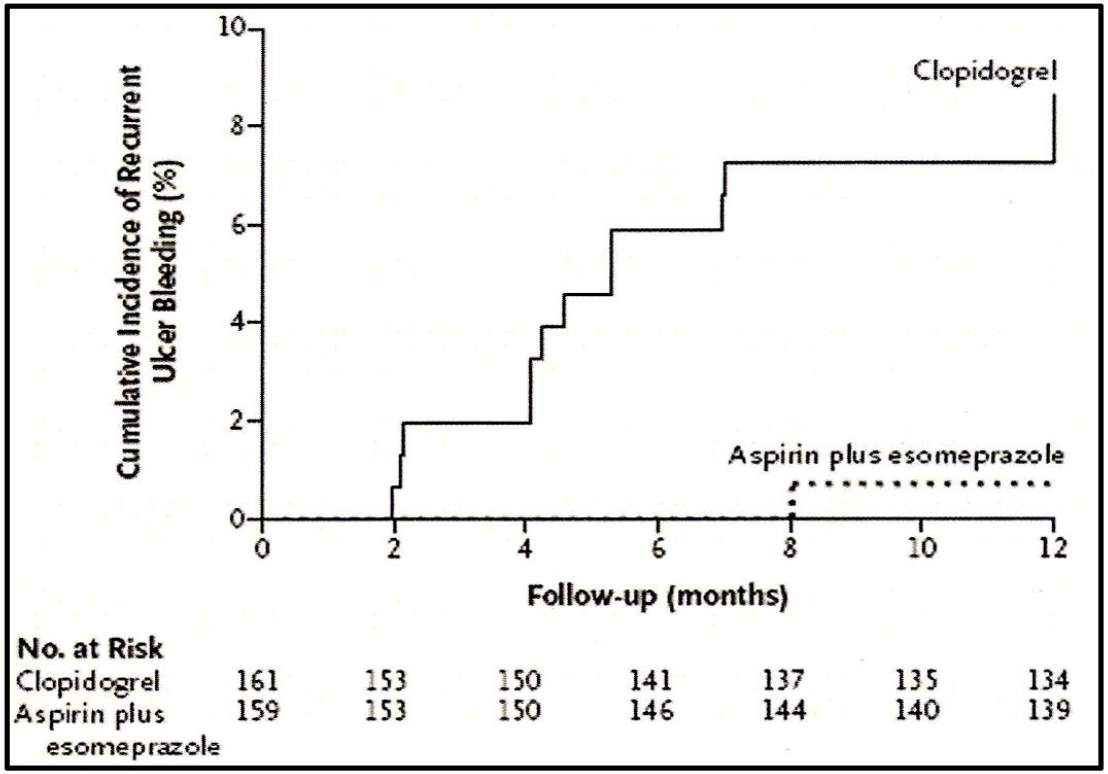
Risks of Antiplatelet Therapy



In a recent trial of patients who developed peptic ulcer bleeding while taking aspirin found that the combination of aspirin **plus a** proton pump inhibitor **was significantly more effective than clopidogrel at reducing the risk of re-bleeding.**

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BOTTOM LINE

- Most patients with a history of MI (but not an acute MI) should be treated with aspirin alone
- Clopidogrel alone should be used in case of aspirin allergy or in high-risk patients
- For GI bleed while on aspirin, adding a proton-pump inhibitor is more effective in preventing another bleed than using clopidogrel instead of aspirin.

Stable Angina

Aspirin clearly benefits patients with stable angina.

- In 7 trials of 2,920 patients, aspirin caused a 33% reduction in the risk of stroke, MI, or vascular death
- There is no evidence on the comparative value of clopidogrel vs. aspirin in patients who have stable angina

Stable Angina (continued)

- CHARISMA trial enrolled a variety of patients including those with stable angina and found no advantage of clopidogrel plus aspirin compared to aspirin alone.
- Clopidogrel monotherapy should be used in patients with a contraindication to aspirin.

BOTTOM LINE

Patients with stable angina should be treated with aspirin unless a contraindication exists, in which case clopidogrel monotherapy is a reasonable option.

Aspirin plus a PPI is better for preventing GI hemorrhage than is clopidogrel.

Elective PCI: Clopidogrel for the Reduction of Events During Observation (CREDO)

- 2,116 patients undergoing elective PCI
  - Randomized patients received clopidogrel for 1 month or 12 months
  - All patients received aspirin
- Patients randomized to receive clopidogrel for 12 months had a 27% relative reduction in the combined risk of death, MI, or stroke
  - Absolute Reduction was 3% p=0.02

BOTTOM LINE

- Patients who have undergone elective PCI should ideally receive clopidogrel plus aspirin for at least one year
- A shorter-duration of treatment should be considered for patients at high risk of bleeding
- Whether or not to continue dual antiplatelet therapy beyond one year for patients at high risk of late-stent thrombosis remains unclear

(Refer to page 10)

Stroke: Monotherapy

The use of aspirin in the acute management of ischemic stroke has been evaluated in trials of over 40,000 patients.

- Aspirin reduces the odds of a subsequent major vascular event by 11%
- Benefit of aspirin for patients with a history of stroke or transient ischemic attack is also well established

Clopidogrel vs. Aspirin: Patients with Recent Ischemic Stroke (CAPRIE)

Clopidogrel was not significantly superior to aspirin, therefore its use is not generally recommended.

An exception may be high-risk subgroups

- History of bypass surgery
- Events involving multiple vascular beds
- History of more than one ischemic event
- Diabetes
- High cholesterol

Major studies compared antiplatelet monotherapy and combined therapy for patients with stroke.

Trial Name	Who was enrolled?	What was studied?	What was the primary efficacy outcome?	What were the main results?					
				Prevention of vascular events			Risk of major bleeding		
				Monotherapy	Dual therapy	Absolute difference	Monotherapy	Dual therapy	Absolute difference
MATCH (Lancet 2004)	Stroke or TIA within previous 3 months who also had ≥1 of prior stroke, prior MI, angina, DM, or symptomatic PVD (n=7,559)	**MONOTHERAPY:** clopidogrel **DUAL THERAPY:** Aspirin + clopidogrel	Ischemic stroke, MI, vascular death, re-hospitalization for acute ischemic event	16.7%	15.7%	Not significant	1%	2%	1%
CHARISMA (NEJM 2006)	Stroke or TIA within the previous 5 years (n=4,478)	**MONOTHERAPY:** aspirin **DUAL THERAPY:** aspirin + clopidogrel	MI, stroke or death	7.3%	6.7%	Not significant	1.3%	1.3%	0.8%
ESPS2 (J Neurol Sci 1996)	Stroke or TIA within previous 3 months (n=3,299)	**MONOTHERAPY:** aspirin **DUAL THERAPY:** aspirin + modified release dipyridamole	Stroke	12.9%	9.9%	3.3%	0.1%	0.1%	Not significant
ESPRIT (Lancet 2006)	Transient ischemic attack or a non-disabling ischemic stroke in the prior 6 months (n=2,739)	**MONOTHERAPY:** aspirin **DUAL THERAPY:** aspirin + dipyridamole	Death from all vascular causes, non-fatal stroke, non-fatal MI	12.6%	10.9%	1.7% (borderline non-significant)	3.9%	2.6%	1.3% (borderline non-significant)
PRoFESS (NEJM 2008)	Ischemic stroke within 90 days or randomization (n=20,332)	**MONOTHERAPY:** clopidogrel **DUAL THERAPY:** aspirin + dipyridamole	Stroke	8.8%	9.0%	Not significant	3.6%	4.1%	0.5%

Stroke: Dual Therapy
MATCH Trial

- Clopidogrel 75 mg daily alone **or**
- In combination with aspirin 75 mg daily

Dual therapy was **not** superior to clopidogrel alone.

Stroke: Dual Therapy
CHARISMA

No benefit of dual antiplatelet therapy compared to aspirin alone.

Stroke: Dual Therapy
ESPRIT

Major bleeding complications occurred **less** frequently in patients treated with dipyridamole **plus** aspirin than aspirin alone, although these differences were not statistically significant.

Stroke: Dual Therapy
PRoFESS

- Twice-daily combination of aspirin 25 mg and extended-release dipyridamole 200 mg **vs.** 75 mg of clopidogrel daily
- Found that the two treatments were **equivalent** in the prevention of recurrent stroke

Stroke: Dual Therapy Risks

- MATCH and CHARISMA
  - Clopidogrel plus aspirin caused higher rates of bleeding than aspirin monotherapy
- ESPS2 and ESPRIT
  - Aspirin plus dipyridamole did not significantly increase the risk of bleeding

BOTTOM LINE

- Clopidogrel or combined aspirin-dipyridamole both appear effective for the prevention of recurrent vascular events in patients with recent stroke
- Clopidogrel should be particularly considered in high-risk stroke patients and in patients with aspirin allergy
- Aspirin monotherapy is recommended for patients with a more remote history of stroke

Peripheral Artery Disease (PAD)

When given to patients with peripheral artery disease (PAD), aspirin reduces the odds of major vascular events by 23%

CAPRIE
Clopidogrel vs. Aspirin

- Patients with
  - Peripheral artery disease
  - Intermittent claudication
  - Undergone surgical revascularization or amputation

clearly benefited from clopidogrel as compared to aspirin

CHARISMA

Dual antiplatelet therapy was found **not** superior to aspirin alone.

PAD: Dual Therapy Risks

The recommendation to use antiplatelet monotherapy for patients with PAD is reinforced by the risks associated with **long-term** dual antiplatelet therapy.

BOTTOM LINE

Antiplatelet monotherapy for PAD with clopidogrel is more effective than aspirin.

Aspirin plus clopidogrel in combination is not superior to aspirin alone, and is associated with more side effects.

Aspirin for the Primary Prevention of Vascular Disease

- Men derive benefit from aspirin from a reduction in **MI** risk
- Women derive benefit from aspirin from a reduction in **ischemic strokes**

Meta-analysis results of randomized trials evaluating aspirin for primary prevention

Outcome	Odds ratio (95% confidence interval) from aspirin v. placebo	
	Men	Women
All cardiovascular events	**0.86 (0.78-0.94)**	**0.88 (0.7-0.99)**
Ischemic strokes	1.00 (0.72-1.41)	**0.83 (0.70-0.97)**
Myocardial infarction	**0.68 (0.54-0.86)**	1.01 (0.84-1.21)
Cardiovascular mortality	0.99 (0.86-1.14)	0.90 (0.64-1.28)

Recent studies of aspirin for primary prevention in patients with diabetes

Trial Name	Who was enrolled?	What was studied and for how long?	What was the primary outcome?	What were the main results?					
				Prevention of vascular events			Risk of major bleeding		
				Aspirin	Placebo	Absolute difference	Aspirin	Placebo	Absolute difference
POPADAD (BMJ 2008)	**DM** and an ankle-brachial index of ≤0.99 but no symptomatic cardiovascular disease (n=1,276)	aspirin 100 mg daily v. placebo (median follow-up 6.7 years)	Fatal or non-fatal MI, fatal or non-fatal stroke or above ankle amputation for limb ischemia	**18.2%**	**18.3%**	**Not significant**	4.4%	4.9%	Not significant
JPAD (BMJ 2008)	**DM** but no symptomatic cardiovascular disease (n=2,539)	aspirin 81 or 100 mg daily v. placebo (median follow-up 4.4 years)	Any atherosclerotic event	**5.4%**	**6.7%**	**Not significant**	0.003	0	Not significant

POPADAD and JPAD

- Evaluated patients with **diabetes**
- In JPAD, deaths from MI or stroke were significantly reduced in the low-dose aspirin group
- Neither trial found reductions in vascular events or mortality

No trials have evaluated clopidogrel monotherapy for the primary prevention of vascular events.

Risks of Antiplatelet Therapy

- In these trials, aspirin increased the risk of bleeding in both women and men
- The harms of aspirin **may** outweigh the benefits for many **low-risk** primary prevention patients
- U.S. Preventive Services Task Force guidelines on aspirin use for primary prevention recommends an explicit **assessment** of a patient's cardiovascular risk **before prescribing aspirin for primary prevention.**

BOTTOM LINE

- Because of the bleeding risk caused by antiplatelet therapy, aspirin should be prescribed for primary prevention only in patients for whom the benefits of therapy outweigh their harms
- Some patients who receive aspirin for primary prevention (e.g., low-risk diabetes) may derive less benefit than traditionally believed.

ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR DISEASE
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Men Age 45-79 Years	Women Age 55-79 Years	Men Age < 45 Years	Women Age < 55 Years	Men & Women Age ≥ 80 Years
Recommendation	Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage	Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage	Do not encourage aspirin use for MI prevention	Do not encourage aspirin use for stroke prevention	No Recommendation
	GRADE: A		GRADE: D		GRADE: I (Insufficient Evidence)

How to Use This Recommendation

Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.

To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.

Risk level at which CVD events prevented (benefit) exceeds GI harms			
Men		Women	
10-year CHD risk		10-year stroke risk	
Age 45 – 59 years	≥ 4%	Age 55 – 59 years	≥ 3%
Age 60 – 69 years	≥ 9%	Age 60 – 69 years	≥ 8%
Age 70 – 79 years	≥ 12%	Age 70 – 79 years	≥ 11%

The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers.
NSAID use and history of GI ulcers raise the risk of serious GI bleeding considerably and should be considered in determining the balance of benefits and harms.
NSAID use combined with aspirin use approximately quadruples the risk of serious GI bleeding compared to the risk with aspirin use alone.
The rate of serious bleeding in aspirin users is approximately 2 – 3 times higher in patients with a history of GI ulcers.

Risk Assessment

For MEN: Risk factors for CHD include age, diabetes, total cholesterol level, HDL level, blood pressure, and smoking.
CHD risk estimation tool: http://healthlink.mcw.edu/article/923521437.html

For WOMEN: Risk factors for ischemic stroke include age, high blood pressure, diabetes, smoking, history of CVD, atrial fibrillation, and left ventricular hypertrophy.
Stroke risk estimation tool: http://www.westernstroke.org/PersonalStrokeRisk1.xls

Relevant Recommendations from the USPSTF

The USPSTF has made recommendations on screening for abdominal aortic aneurysm, carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, and peripheral arterial disease. These recommendations are available at www.preventiveservices.ahrq.gov.

For the full recommendation statement and supporting documents, please go to: www.preventiveservices.ahrq.gov. Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease,

Primary Prevention Resources

- www.ahrq.gov/clinic/cvd/aspprovider.htm
- www.med-decisions.com
- www.westernstroke.org

Assessing CHD Risk in Men

- CHD Risk Calculation Factors
  - Age
  - Gender
  - Total Cholesterol
  - HDL
  - Tobacco Abuse
  - Systolic Blood Pressure
  - Taking Medications for Blood Pressure

Assessing Stroke Risk in Women

- Stroke Risk Calculation Factors
  - Gender
  - Age
  - Systolic Blood Pressure
  - Taking Medication for Blood Pressure
  - Diabetes
  - Tobacco Abuse
  - CVD
  - Atrial Fibrillation
  - Left Ventricular Hypertrophy

Assessing Stroke Risk in Women cont.

- Obesity
  - Obesity increases Stroke risk by approx 50%
  - Obesity is BMI >/= 30

Atrial Fibrillation (AF)

While less effective than warfarin, aspirin does reduce the relative risk of stroke by about 21% in AF patients.

Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W)

- Patients with AF at increased risk of stroke
- Received either:
  - Warfarin
  - Clopidogrel plus aspirin
- Study was stopped early because of clear evidence of superiority of oral anticoagulation therapy
- Rates of major hemorrhage were similar in the two groups
- Patients treated with clopidogrel plus aspirin had significantly more minor bleeding episodes

Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A)

- 7,500 patients with atrial fibrillation at increased risk of stroke in whom warfarin was felt to be **"unsuitable"**
- Clopidogrel plus aspirin vs. aspirin alone
- Rate of major vascular events was substantially reduced with dual antiplatelet therapy **primarily due to a reduction in the rate of stroke**

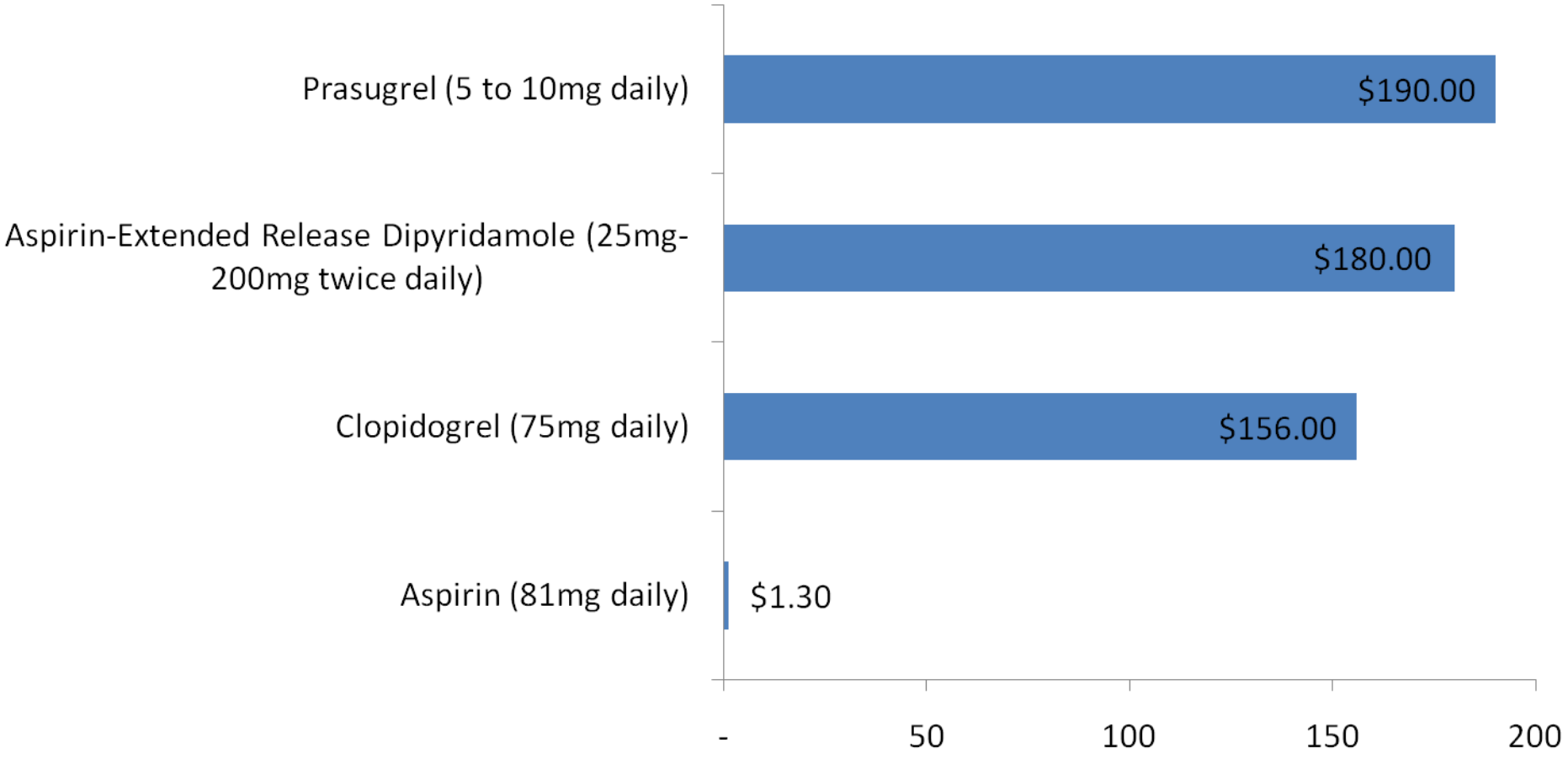
BOTTOM LINE

In the absence of a contraindication, warfarin is the most effective therapy to prevent atrial fibrillation-associated stroke risk by two-thirds.

Dual antiplatelet therapy appears to be more effective than aspirin monotherapy in those patients for whom warfarin is unsuitable, but also **increases the risk of bleeding.**

Costs

Average monthly price for commonly used antiplatelet agents



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Aspirin Dose

Aspirin between 81 and 162 mg daily are generally recommended.

Do NSAIDs interact with aspirin?

Several clinical studies have been performed that suggest that patients taking ibuprofen and aspirin together on a consistent basis may be at **higher risk** of cardiovascular events than patients taking aspirin alone.

The AHA-ACC recommends against the use of ibuprofen in patients taking aspirin.

Aspirin and Clopidogrel resistance

- Platelet-dependent thrombosis can occur despite treatment with aspirin and clopidogrel. “resistance” to the drug
- Variety of causes:
  - Poor adherence
  - Inadequate dosage
  - Coexisting medical conditions
  - Genetic factors

Genetic Factors for Clopidogrel Resistance

- Occurs in an enzyme responsible for the metabolism of the drug
- Clopidogrel is a pro-drug, requiring activation by specific hepatic cytochrome P-450 (CYP) enzymes.
- Carriers of the specific alleles have a diminished response to the effects of clopidogrel

- Use of a proton-pump inhibitor might decrease the platelet inhibitory effect of clopidogrel, because both drugs are metabolized by CYP2C19
- Rates of re-hospitalization for ACS patients treated with clopidogrel and a PPI increased by about 25%
- Those receiving pantoprazole did not have a higher rate of adverse cardiovascular events

A prudent strategy while awaiting more definitive data would be to limit the use of PPIs to those clopidogrel-treated patients at the highest risk of adverse gastrointestinal events.

Putting it all together

Condition	Recommended Treatment	Evidence
Acute coronary syndromes [Unstable angina, non-ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI)]	CLOPIDOGREL + ASPIRIN for at least 1 year. PRASUGREL + ASPIRIN for 15 months may be a superior alternative for some non-elderly ACS patients who have undergone PCI.	CURE, COMMIT, CLARITY, CHARISMA, CAPRIE, TRITON
Past MI	CLOPIDOGREL for high-risk patients*, ASPIRIN for all others	CHARISMA, CAPRIE
Stable angina	ASPIRIN	Antiplatelet Trialists Collaboration, CHARISMA
Elective PCI	CLOPIDOGREL + ASPIRIN for at least a year	CREDO
Stroke	CLOPIDOGREL or ASPIRIN + DIPYRIDAMOLE	MATCH, CHARISMA, ESPS2, ESPRIT, PRoFESS
Peripheral artery disease	CLOPIDOGREL	CHARISMA, CAPRIE
Primary prevention	ASPIRIN only for patients in whom benefits outweigh risks	POPADAD, JPAD, USPSTF

***High risk patients:** history of coronary artery disease, stroke, or TIA, **and** any of the following: bypass surgery, events involving multiple vascular beds, two or more ischemic events, diabetes, or high cholesterol.

Questions?

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