

# Antiplatelet Agents in CV Disease

## What's the Best Option?

Antiplatelet agents are among the mainstays of both acute and chronic therapy for coronary artery disease. But with a variety of agents to choose from, which agent offers the most benefit in a given scenario?

Michelle M. Graham, MD, FRCPC

### Milo's Risk



Milo, 48, is a smoker who presents for his annual checkup.

- Total cholesterol: 5.4 mmol/L
- High-density lipoprotein: 1.15 mmol/L
- Blood pressure: 130/80 mmHg

Does Milo require acetylsalicylic acid (ASA) therapy for primary prevention? For the answer, see page 34.

Because of the important role of thrombosis in the pathogenesis and complications of atherosclerosis, antiplatelet therapy is essential for both acute and chronic coronary artery disease. Acetylsalicylic acid (ASA) and clopidogrel are important components of antiplatelet therapy, and can be used in a variety of clinical settings.

### ASA

ASA is a cyclo-oxygenase inhibitor that prevents the formation of thromboxane A<sub>2</sub>, a platelet aggregant and potent vasoconstrictor. It has been a cornerstone of therapy for over 20 years, and reduces adverse clinical events in a broad group of patients.

A systematic review from the Antithrombotic Trialists' Collaboration demonstrated an odds reduction in vascular events of 46% in patients with acute coronary syndromes, and the landmark second International Study of Infarct Survival showed that ASA alone could reduce mortality in ST-segment elevation MI (STEMI) by 23% (this was even more impressive when used in combination with thrombolytic agents). The benefits of ASA therapy have also been demonstrated in patients with chronic stable angina, with a substantial reduction in the development of first MI.

As a result of these and other studies, all patients with suspected acute coronary syndromes and those with stable coronary artery disease (CAD) should be considered for ASA treatment, unless there is:

- a documented severe reaction,
- recent gastrointestinal bleeding or
- suspected intracranial hemorrhaging.



### About the author...

**Dr. Graham** is an Assistant Professor of Medicine, Division of Cardiology, at the University of Alberta Hospital, Edmonton, Alberta.

The benefits of initial therapy are sustained long-term, therefore this agent should be started as early as possible and continued indefinitely.

Five large trials have examined the use of ASA for primary prevention in men. A meta-analysis of these trials confirmed a significant relative risk reduction of 15% for all cardiovascular events and 30% for MI. There was no effect on the incidence of stroke. The risk of major bleeding events balances the reduction in cardiovascular events in patients who are at lower risk of a cardiac event. Therefore, it is recommended that low-dose ASA be used as a primary prevention agent in those patients who are at least at moderate risk (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10% [Table 1]).

### *Clopidogrel*

Clopidogrel is a thienopyridine that inhibits platelet aggregation. It is generally well-tolerated, with a more favourable safety profile compared to its predecessor, ticlopidine. Evidence for its use in a wide variety of cardiac patients is rapidly accumulating, especially from the Clopidogrel in Unstable angina to prevent Recurrent Events trial, which demonstrated significant reductions in adverse events in acute coronary syndrome patients treated with clopidogrel in addition to ASA. Benefits of this therapy were seen in patients with MI, ST-segment deviation, diabetes, older age and in those with high-risk features. It is, therefore, recommended that all patients with acute coronary syndromes be considered for therapy with this agent for nine to 12 months. Clopidogrel may also be of use in patients with chronic stable angina who are at high risk for the development of acute MI.

Clopidogrel has also been recently assessed in patients with STEMI who are treated with thrombolysis. One such study, the CLOpidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction study 28, showed that the addition of clopidogrel to ASA and a standard fibrinolytic regimen decreased ischemic com-

#### FAQ

##### **How long should clopidogrel be continued after a stent procedure?**

Bare metal stents require a minimum of one month of therapy. Drug-eluting stents require longer therapy—a minimum of two to three months for sirolimus stents and six months for paclitaxel stents.

#### FAQ

##### **What dose of ASA is best for patients who are also taking clopidogrel?**

To minimize the risk of bleeding while on two oral antiplatelet agents, it is recommended that lower-dose ASA (75 mg to 100 mg, daily) be used.

#### FAQ

##### **Should clopidogrel be stopped prior to cardiac surgery?**

Because of the increased risk of bleeding during coronary artery bypass graft surgery, it is recommended that clopidogrel be stopped five days prior to the procedure.

Men		Women				
Risk factor	Risk points					
<b>Age group</b>						
20-34	-9					
35-39	-4					
40-44	0					
45-49	3					
50-54	6					
55-59	8					
60-64	10					
65-69	11					
70-74	12					
75-79	13					
<b>Total cholesterol level, mmol/L</b>						
	<b>Age group</b>					
	20-39	40-49	50-59	60-69	70-79	
< 4.14	0	0	0	0	0	
4.15-5.19	4	3	2	1	0	
5.20-6.19	7	5	3	1	0	
6.20-7.20	9	6	4	2	1	
≥ 7.21	11	8	5	3	1	
<b>Smoker</b>						
No	0	0	0	0	0	
Yes	8	5	3	1	1	
<b>High-density lipoprotein cholesterol level, mmol/L</b>						
≥ 1.55	-1					
1.30-1.54	0					
1.04-1.29	1					
< 1.04	2					
<b>Systolic blood pressure, mmHg</b>						
	<b>Untreated</b>		<b>Treated</b>			
< 120	0		0			
120-129	0		1			
130-139	1		2			
140-159	1		2			
≥ 160	2		3			
<b>Total risk points</b>						
	<b>10-year risk, %</b>					
< 0	< 1					
0-4	1					
5-6	2					
7	3					
8	4					
9	5					
10	6					
11	8					
12	10					
13	12					
14	16					
15	20					
16	25					
≥ 17	≥ 30					
<b>10-year risk: _____%</b>						
<b>Women</b>						
<b>Age group</b>						
20-34	-7					
35-39	-3					
40-44	0					
45-49	3					
50-54	6					
55-59	8					
60-64	10					
65-69	12					
70-74	14					
75-79	16					
<b>Total cholesterol level, mmol/L</b>						
	<b>Age group</b>					
	20-39	40-49	50-59	60-69	70-79	
< 4.14	0	0	0	0	0	
4.15-5.19	4	3	2	1	1	
5.20-6.19	8	6	4	2	1	
6.20-7.20	11	8	5	3	2	
≥ 7.21	13	10	7	4	2	
<b>Smoker</b>						
No	0	0	0	0	0	
Yes	9	7	4	2	1	
<b>High-density lipoprotein cholesterol level, mmol/L</b>						
≥ 1.55	-1					
1.30-1.54	0					
1.04-1.29	1					
< 1.04	2					
<b>Systolic blood pressure, mmHg</b>						
	<b>Untreated</b>		<b>Treated</b>			
< 120	0		0			
120-129	1		3			
130-139	2		4			
140-159	3		5			
≥ 160	4		6			
<b>Total risk points</b>						
	<b>10-year risk, %</b>					
< 9	< 1					
9-12	1					
13-14	2					
15	3					
16	4					
17	5					
18	6					
19	8					
20	11					
21	14					
22	17					
23	22					
24	27					
≥ 25	≥ 30					
<b>10-year risk: _____%</b>						

Table 1. Model for estimating the 10-year risk of coronary artery disease in a patient without diabetes mellitus or clinically evident cardiovascular disease, using data from the Framingham Heart Study.

### What Is Milo's Risk Score?

Based on the calculation method shown in Table 1, Milo's risk is calculated as follows:

• Age: 45-49	3 points
• Total cholesterol: 5.20 mmol/L to 6.19 mmol/L	5 points
• Smoker	5 points
• High-density lipoprotein: 1.04 mmol/L to 1.29 mmol/L	1 point
• Systolic blood pressure: 130 mmHg to 139 mmHg, untreated	1 point
<b>Total</b>	<b>15 points</b>

Milo's 10-year risk is 20%.

ASA is recommended in all high-risk patients (10-year coronary artery disease risk of > 10%), unless there is ASA intolerance or a high risk of gastrointestinal bleeding or hemorrhagic stroke.


Milo was prescribed ASA, 81 mg, daily but, unfortunately, he continued to smoke. Three years later, he developed exertional chest discomfort and subsequently underwent percutaneous coronary intervention of his right coronary artery.

plications and increased the patency rate of the infarct-related artery. There is no published data available as yet for patients over the age of 75, but clopidogrel's scope of use is likely to expand quickly.

### Antiplatelet agents following PCI

The use of percutaneous coronary intervention (PCI) for revascularization has expanded dramatically over the last two decades, reflecting both improvements in technology and refinements of adjunctive pharmacotherapy. Very early studies support the use of ASA in these patients to decrease peri-procedural complications. Given its benefits in all subgroups of patients with CAD, it should be continued indefinitely.

Following the advent of stents, it was found that a thienopyridine derivative in combination with ASA was the optimal therapy to prevent sub-acute stent thrombosis and other peri-procedural complications. ASA and clopidogrel are now the standard of care in these patients. More recent evidence has suggested that pre-treatment with clopidogrel prior to PCI further reduces the risk of ischemic complications.

A significant concern arises when patients who have recently undergone PCI require non-cardiac surgery prior to finishing their prescribed course of clopidogrel. Premature discontinuation of clopidogrel in this situation is associated with a high risk of stent thrombosis, MI and death. It is, therefore, recommended that non-emergent surgery be delayed for six weeks following stent implantation. For patients requiring emergent surgery, there must be a careful weighing of bleeding risk versus cardiac risk prior to considering the discontinuation of clopidogrel. 

#### Resources

1. Harrington RA, Becker RC, Ezekowitz M, et al: Antithrombotic therapy for coronary artery disease: The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126 (3 Suppl):513S.
2. Popma JJ, Berger P, Ohman EM, et al: Antithrombotic therapy during percutaneous coronary intervention: The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126 (3 Suppl):576S.
3. Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *NEJM* 2005; 352(12):1179.
4. Genest J, Frohlich J, Fodor G, et al: Recommendations for the management of dyslipidemia and the prevention of coronary artery disease: Summary of the 2003 update. *CMAJ* 2003; 169(9):921.