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## Appropriate Use of Clopidogrel

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Clopidogrel (Plavix®) is an orally administered pro-drug, whose pharmacology and therapeutic role has been extensively reviewed in recent publications.<sup>1-5</sup> In essence, it results in selective and irreversible antagonism of ADP-induced platelet aggregation. Such aggregation normally results in the surface expression of platelet glycoprotein (GP) IIb/IIIa receptors, which facilitate fibrinogen binding as well as consequential further platelet aggregation – the final common pathway of vascular occlusion. Specific cytochrome P450 enzymes are thought to generate the responsible active metabolite (believed to persist transiently). However, dosage adjustment is not recommended in hepatic impairment (unless severe) and drug-drug interactions and co-administration with meals are believed to be unimportant.

Based on clinical trials of outcome, several orally administered anti-platelet drugs have proven efficacy (mainly for secondary prevention) in the context of coronary events, ischaemic strokes and peripheral vascular disease. These include: (1) aspirin, (2) dipyridamole (Persantin), (3) ticlopidine (Ticlid), and (4) clopidogrel (Plavix) all of which have important adverse effects.<sup>6,7</sup> Dipyridamole gives rise to headaches, postural lightheadness, and gastrointestinal symptoms (mainly diarrhea & nausea). The relatively common adverse effects of ticlopidine (neutropenia, thrombocytopenia, hepatitis and diarrhea) pose a problem. With clopidogrel, adverse effects are comparable to aspirin and certainly less frequent and less severe than with ticlopidine. However, it too has been linked to thrombotic thrombocytopenic purpura (even resulting in death).<sup>8</sup> Moreover, clopidogrel's long term safety has not been established, nor are the risks known among ethnic groups (including the Chinese) that

are believed to be more prone to bleeding.

Only a few of the relevant clinical trials have compared different anti-platelet drug treatment intervention regimes to each other with respect to outcomes. In the multi-centre **CAPRIE (Clopidogrel v Aspirin in Patients at Risk of Ischaemic Events)** double blind randomised controlled trial, clopidogrel or aspirin (both 75 mg/day) were given to 19,185 atherosclerotic patients.<sup>9</sup> The protocol entailed randomisation to three groups viz: Stroke, MI & Peripheral arterial disease (PAD), and follow up for 1-3 years. The ensuing results are outlined below (Table 1).

**Table 1. Primary outcome (myocardial infarction, ischaemic stroke or vascular death)**

	Event ensued	No event	Total
Clopidogrel	939	8614	9553
Placebo	1021	8846	9546

The *relative risk reduction (RRR)* was 8.7% (adjusted) with a 95% CI of 0.3-16.5%;  $P < 0.05$ . The more meaningful *absolute risk reduction (ARR)* amounted to 0.86% over an average of 1.91 years. The corresponding *number needed to treat (NNT)* to prevent one patient experiencing an adverse outcome event over that period was 115 (95% CIs 57-∞), which is equivalent to an **NNT/year** of 220. Unexpectedly the benefit was largely confined to patients with prior peripheral arterial disease and stroke.

That drugs such as clopidogrel, which inhibit ADP induced platelet aggregation may complement the antiplatelet activity of aspirin (a cyclo-oxygenase inhibitor) without unduly compromising safety, has kindled interest in using them in combination. In the multi-centre **CURE (Clopidogrel in Unstable angina to prevent Recurrent Events)** trial,<sup>10,11</sup> 12,562 patients taking aspirin (75-325 mg/day) ± heparin, β-blockers,

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statins or calcium channel blockers – were randomised to treatment with clopidogrel (75 mg/day) or placebo for 3-12 (mean of 9) months. The **RRR** (for cardiovascular death, non-fatal stroke or MI) was 20% (adjusted) with a 95% CIs of 10-28%. The corresponding **NNT** was 47 or 35/year. Evidently, the relative risk (**RR**) of major bleeding was 1.38% (95% CIs 1.13-1.67), there being one such additional episode for every 99 patients treated with clopidogrel and aspirin (as opposed to aspirin alone) over this period of time (or 74/year). However, there was no excess in bleeds causing fatality, strokes or need for surgical intervention. Notably, for many of the patients undergoing revascularisation procedures, study medication was temporarily interrupted or given as open label therapy. In the overall analysis, it was estimated that for every 1000 patients treated for 9 months, 28 major events would be prevented at a cost of 3 patients having life-threatening bleeds and 3 more requiring transfusions.<sup>12</sup>

In 2001, clopidogrel was among the Hong Kong Hospital Authority's top 20 items of expenditure on pharmaceuticals, having increased in popularity dramatically over the last year. Compared to aspirin, currently it is many orders of magnitude more expensive. Thus, substituting clopidogrel for aspirin, treatment of 220 patients for 1 year would be expected to prevent 1 of them from suffering an ischaemic event, but depending on which formulation was replaced - corresponding drug costs could increase by between 46 to 205 fold (Table 2). In mitigation, use of clopidogrel may involve cost-savings in terms of slightly reduced numbers of patients having revascularisation procedures and the associated use of much more expensive drugs (GP IIb/IIIa receptor blockers).

Hitherto the conventional indications for prescribing clopidogrel were mainly confined to: (1)

cover (together with aspirin) for patients undergoing angioplasty and/or stenting procedures, and (2) as a substitute for aspirin for individuals in whom the latter drug was contraindicated or poorly tolerated. If the daily cost of clopidogrel treatment (currently up to 205 fold that of aspirin) is not an issue, it may also be reasonable to use it: (3) instead of aspirin in all ischaemic cardiovascular disease states, and (4) in combination with aspirin for patients with unstable angina. However, the long-term safety of this agent is not known.

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**Table 2. Drug acquisition costs**

Drug	Typical dosage/day	HK\$ (Nov 2001)
Clopidogrel	75 mg	12.30
Ticlopidine	250 mg	7.25
Dipyridamole	25 mg	0.09
	75 mg	0.20
Aspirins		
Aspirin	80 mg	0.06
Dispersable aspirin	300 mg	0.27
Cartia	100 mg	0.23
SR Cardiprin	100 mg	0.18