The Role of Intensive Atherosclerosis Management in CVD: Lessons from Major Clinical Trials

Clinical trial evidence has shown that intensive combined-modality pharmacologic treatment can provide benefits to patients with established CV disease and those deemed to be at risk. These modalities include ACE inhibitors, antiplatelet agents, beta-blockers and statins.

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Introduction

Each year, 79,000 Canadians die from heart disease and stroke, making cardiovascular (CV) events the number-one killer of men and women.[1] The number-one killer among these events is ischemic heart disease, accounting for more than half the deaths attributable to CV causes.[1]

In terms of overall prevalence, it is estimated that approximately 5.7% of the total population (and one out of four Canadians over the age of 70 years) has some type of CV disease.[1] As Canadians age, more and more of the population will be at increased risk for these diseases.

One of the central mechanisms in the development of CV disease is the process of atherosclerosis. This process involves a number of variables, including increased expression of adhesion molecules and the binding of lipoproteins into atheromas (retaining them in the vessel wall). This process continues at various locations throughout the systemic circulation and can lead to disease in any vascular bed. Further processes, such as oxidation and inflammation, can destabilize the atherosclerotic plaques and lead to such atherothrombotic events as myocardial infarction (MI) and stroke.

The lesions develop. The inflammatory process within the vessel wall leads to the formation of macrophage foam cells and growth factors, which are key elements of lesion progression.

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In trying to control this systemic problem and reduce its impact on the population, modern medicine employs a number of pharmacologic and nonpharmacologic interventions in patients with established CV disease and those who are deemed to be at risk.

There are several types of agents that have been proven effective in targeting the atherosclerotic process and reducing risk, including angiotensin-converting enzyme (ACE) inhibitors, antiplatelet agents, beta-blockers and statins. Their beneficial effect in CAD has been proven in studies focusing on each type of drug individually, as the first part of this review documents. Evidence also shows that the benefits are incremental when these different drugs are combined;[2] this evidence is presented herein as well.

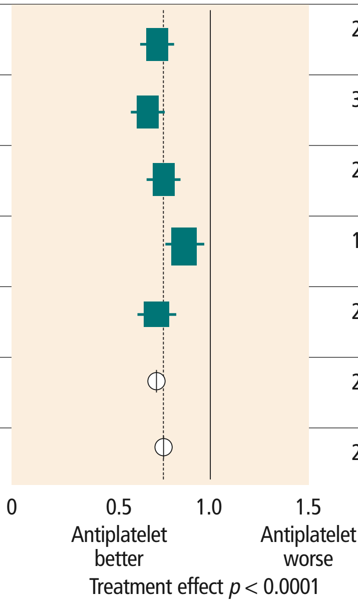
Evidence for Individual Risk-reduction Modalities

Antiplatelet agents, such as acetylsalicylic acid (ASA), clopidogrel and dipyridamole, exert their primary beneficial effect by inhibiting the aggregation of platelets at the site of a plaque rupture. This helps prevent the formation of a thrombus, which could lead to major vascular events.

These agents have a long track record of reducing CV risk, as documented in the 2002 Antithrombotic Trialists Collaboration meta-analysis, which involved 287 studies including more than 200,000 patients.[3] This meta-analysis concluded that antiplatelet therapy reduced the approximate risk of any vascular event by one quarter, regardless of the type of patient group being treated (Table 1). Antiplatelet use also reduced the risk of non-fatal MI by one third, of non-fatal

Table 1 Proportional Effects of Antiplatelet Therapy on Vascular Events by Major Risk Category[3]

Category of trial	No. of trials with data	No. (%) of vascular events: Allocated antiplatelet	No. (%) of vascular events: Adjusted control	Observed-expected	Variance	Odds ratio (CI) Antiplatelet:control	% Odds reduction (SE)
Previous MI	12	1,345/9,984 (13.5)	1,708/10,022 (17.0)	-159.8	567.6		25 (4)
Acute MI	15	1,007/9,658 (10.4)	1,370/9,644 (14.2)	-181.5	519.2		30 (4)
Previous stroke/TIA	21	2,045/11,493 (17.8)	2,464/11,527 (21.4)	-152.1	625.8		22 (4)
Acute stroke	7	1,670/20,418 (8.2)	1,858/20,403 (9.1)	-94.6	795.3		11 (3)
Other high-risk	140	1,638/20,359 (8.0)	2,102/20,543 (10.2)	-222.3	737.0		26 (3)
Subtotal: all except acute stroke	188	6,035/51,494 (11.7)	7,644/51,736 (14.8)	-715.7	2449.6		25 (2)
All trials	195	7,705/71,912 (10.7)	9,502/72,139 (13.2)	-810.3	3244.9		22 (2)



Heterogeneity of odds reductions between:
5 categories of trial: $\chi^2 = 21.4$, df = 4; $p = 0.0003$
Acute stroke vs. other: $\chi^2 = 18.0$, df = 1; $p = 0.00002$

stroke by one quarter and of vascular mortality by one sixth.

There is also evidence showing that certain subgroups of patients can receive even greater benefit from combining two antiplatelet agents with differing mechanisms of action. For example, patients with non-ST-segment-elevation MI have been shown to benefit from combined ASA and clopidogrel, which provides an additional 20% risk reduction for major CV events compared to ASA alone.[4] Likewise, patients who undergo coronary revascularizations have shown a 31% risk reduction with this combination compared to ASA alone.[5]

ACE inhibitors, such as enalapril, quinapril and ramipril, were initially used strictly as antihypertensive agents. They have shown an ability to reduce risk beyond their blood-pressure (BP)-lowering effects in numerous clinical trials in various populations. The large evidence base includes such populations as heart failure,[6,7] post-MI[8-10] and other patients with primary atherosclerotic disease.[11-12] In the post-MI population, for example, a pooled analysis[13] of the SAVE,[8] TRACE[9] and AIRE[10] studies showed that ACE-inhibitor therapy resulted in a 26% reduction in mortality compared to placebo (Figure 1).[13] The HOPE study showed a 22% reduction in the risk of major vascular events in favour of ACE inhibitors in patients with established atherosclerotic disease or in

Figure 1 Mortality Reduction with ACE Inhibitors Post-MI: SAVE, TRACE & AIRE[13]

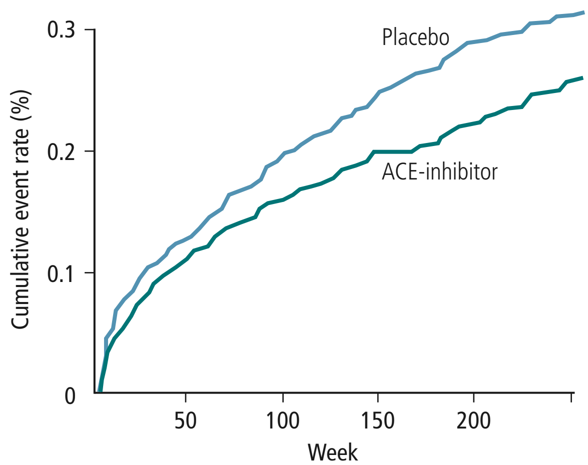
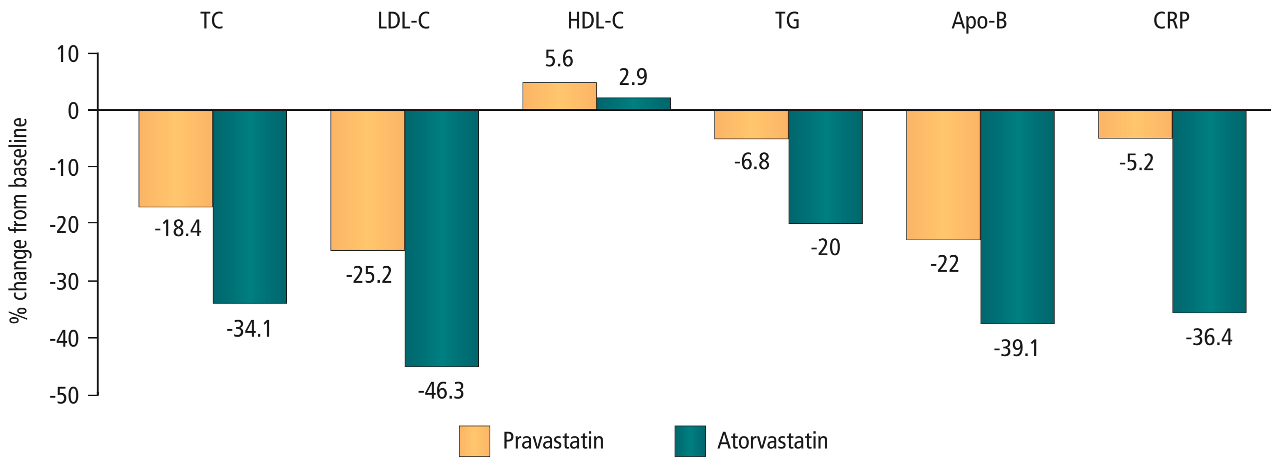


Figure 2 **Percent Change in Lipid Fractions and CRP (REVERSAL)**[34]



Difference in HDL-C was not significant ($p < 0.001$ for all other comparisons).

those with diabetes and one other CV risk factor.

Trials using ACE inhibitors have also shown that the effects of these agents beyond BP lowering include an attenuation of atherosclerotic progression[14,15] and a reduction in markers of inflammation.[16] An ongoing analysis of the EUROPA database is underway, examining the role of ACE-inhibitor therapy on various markers of thrombosis, inflammation, endothelial dysfunction and neurohumoral activation.[17] This should shed further light on the beneficial mechanisms of these agents in atherosclerotic diseases.

Beta-blockers. These agents (*e.g.*, atenolol, metoprolol) have long been known to inhibit the atherosclerotic process.[18] It has been postulated that their beneficial effects are due in part to an ability to alter the structure of lipoproteins, making them less likely to be taken up into atheromatous lesions.[19] Evidence has also shown that they have an anti-inflammatory component.[16]

In the post-MI population, a meta-analysis of beta-blocker trials has shown that these agents are associated with a 23% reduction compared to control in the risk of death in long-term use.[20]

Statins (HMG-CoA reductase inhibitors) have been proven to reduce atherogenic lipoproteins and cardiovascular morbidity and mortality.[21-27]

In fact, statins (*e.g.*, atorvastatin, simvastatin) have already exceeded all other classes of medicines in reducing the incidence of the major adverse outcomes of death, heart attack and stroke in the management of atherosclerotic vascular disease.[28] Statins exert their primary mechanism of benefit by reducing total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides and increasing high-density lipoprotein cholesterol (HDL-C). Other mechanisms include a reduction in inflammatory markers, such as C-reactive protein.[29-31]

In the past 10 years, many large clinical studies have been published documenting the benefits of statins. Such landmark studies as 4S,[21] WOSCOPS,[22] CARE,[23] LIPID,[24] TexCAPS/AFCAPS[25] and ASCOT[27] have proven conclusively that statins reduce CV risk in many populations, in both primary and secondary prevention.

However, the optimal level of LDL-C remains unclear.[32] While current Canadian guidelines recommend reducing LDL-C level to less than 2.5 mmol/L[33] in high-risk patients, there has been a wealth of recent evidence published showing that even lower targets may provide additional benefits.

The REVERSAL study, for example, was a double-blind, randomized, active-control, multicentre study comparing the effects of pravastatin 40 mg/day (moderate reduction group) to atorvastatin 80 mg/day (maximal reduction group) on atherosclerotic progression.[34] A total of 654 patients were randomly assigned to one of these treatment groups and followed for 18 months. Researchers found that intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis more significantly than pravastatin. Compared to baseline values, patients treated with atorvastatin had very little change in atheroma burden (median reduction of 0.4% in atheroma volume), while patients treated with pravastatin showed progression of coronary atherosclerosis (median increase of 2.7%). These differences may be related to the greater reduction in atherogenic lipoproteins and inflammation (as measured by C-reactive protein) in patients treated with atorvastatin (Figure 2).[34]

The authors of the REVERSAL trial concluded that a more rigorous lipid-lowering treatment is required than is currently suggested by national and international guidelines to obtain maximal reduction in the progression of coronary atherosclerosis.[34]

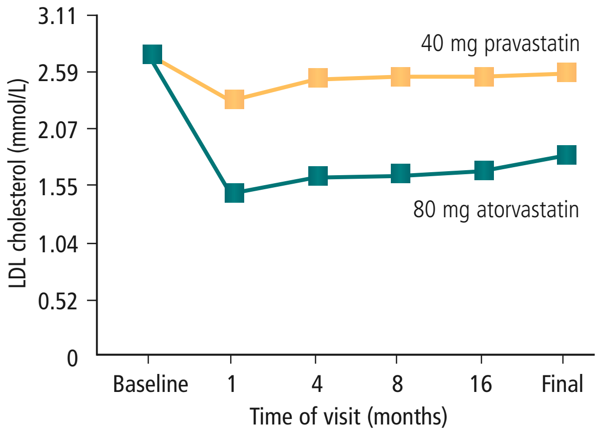
Another recent trial, the PROVE-IT study, compared standard therapy (pravastatin 40 mg/day) to intensive therapy with atorvastatin 80 mg/day in 4,162 patients hospitalized for an acute coronary syndrome (ACS) within the previous 10 days. The primary endpoint was a composite of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization and stroke.

Follow-up lasted an average of 24 months. The median LDL-C level achieved during treatment was 2.46 mmol/L in the standard-dose pravastatin group and 1.60 mmol/L in the high-dose atorvastatin group (Figure 3; $p < 0.001$). The primary endpoint was reached by 26.3% of the pravastatin group at two years compared to 22.4% of the atorvastatin group, reflecting a 16% relative risk reduction in favor of atorvastatin ($p = 0.005$).

The results of the REVERSAL and PROVE-IT studies are supported by findings from other studies examining the effects of more intensive lipid-lowering therapy with statins. The MIRACL study[35] found that treatment with atorvastatin 80 mg was effective in reducing risk in ACS. The AVERT study[36] found that high-dose atorvastatin therapy was superior to percutaneous coronary revascularization for decreasing the incidence of ischemic events (36% relative risk reduction). The ALLIANCE trial[37] found that atorvastatin 80 mg led to a 17% risk reduction in the composite of cardiac death, MI, stroke and hospitalization compared to usual lipid-lowering care. Nonfatal MI was also significantly reduced (47%) in the atorvastatin-treated patients compared to usual care.

Ongoing trials, such as the TNT trial,[38] will provide even further insight into what constitutes optimal lipid-lowering therapy. The large patient numbers in the TNT study (approximately 10,000 patients) and long follow-up (approximately five years) should ensure that there is adequate evidence to definitively determine if reducing LDL-C levels to approximately 1.9 mmol/L can provide clinical benefit superior to the current recommended levels.

Figure 3 **Median LDL-C Levels During the PROVE-IT Study[32]**



*To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586

Evidence for Incremental Benefit

While the evidence for each of the above-mentioned treatment modalities is indeed compelling, real-life practice dictates that we ascertain the effect of the various agents used in combination. There have been several examples in the literature evaluating combinations of risk-reduction agents. Of course, in many of the trials described above, patients were concomitantly taking many other therapies at the same time as the study drug. In the HOPE study, for example, approximately 75% of patients were taking antiplatelets, approximately 40% were taking beta-blockers and approximately 30% were taking lipid-lowering therapy.[11] However, since the goals of these studies were to evaluate the study drug (or drugs), the role of combination therapy did not receive explicit attention.

There have, however, been some attempts to quantify the effect of combined-modality therapy. A 2003 article in the *British Medical Journal* sought to determine the optimal combination of

Table 2 "Appropriateness" Score Based on Use of Evidence-Based Medications[2]

Appropriateness of Evidence-Based Therapy*	Score	Level	RRR vs. Level 0
None of the indicated medications used	0	0	---
1 medication used if 3 or 4 medications indicated	25 or 33.3	I	64%
2 medications used if 3 or 4 medications indicated or 1 medication used if 2 medications indicated	50 or 66.7	II	82%
3 medications used if 4 medications indicated	75	III	83%
All indicated medications used	100	IV	90%

*Evidence-based therapy included antiplatelet agents, beta-blockers, ACE inhibitors, and lipid-lowering therapy

drugs and vitamins that would achieve the largest effect in reducing CAD events, strokes and mortality.[39] The investigators found that the combination best meeting the objectives included a statin, three antihypertensives (*e.g.*, ACE inhibitors, a beta-blocker and a thiazide diuretic), folic acid and aspirin. They estimated that such a combination would reduce CAD events by 88% and stroke by 80% in people older than 55 years and/or with existing CV disease.

Another recent study examined the effects of combined-modality risk-reduction therapy in 1,358 patients with ACS.[40] Statistics on usage of the various combinations were gathered using discharge records. The investigators devised a composite "appropriateness" scale (Table 2) which was calculated by dividing the number of drugs used by the number of drugs potentially indicated.

The primary endpoint of the study was six-month mortality. The relative risk reduction for death was 90% for all indicated medications used (appropriateness level IV) vs. none of the indicated medications used (appropriateness level 0; $p < 0.0001$).

The relative risk reduction vs. appropriateness level 0 was 83%for level III ($p = 0.0018$), 82% for level II nd 64% for level I (Table 2).

The investigators concluded that the use of combination evidence-based medical therapies was independently and strongly associated with reduced six-month mortality in patients with ACS.

Conclusion

Atherosclerosis plays a key role in the development of CV disease and in the occurrence of CV events. A wealth of clinical trial evidence examining antiplatelet agents, ACE inhibitors, beta-blockers and statins has shown that each of these types of agents confers significant protection against CV events. In the case of statins, recent evidence also shows that the amount of risk reduction appears to be dependent on the intensity of the treatment.

While each of these types of therapies has been shown to provide benefit in isolation, studies have also shown that using these agents in combination is the optimal way to aggressively reduce the risk of complications from atherosclerotic CV disease.

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