Vascular Protection: Beyond Risk Reduction

Vascular protection typically involves the effort to reduce major adverse events in patients who are at high risk. In this article, Dr. McDonald and Dr. Gyenes outline some of the more topical cardiovascular protection strategies and the rationale for their use.

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John’s Case

John, 56, presents to clinic for assessment of his cardiovascular status. His medical history reveals:
- percutaneous coronary intervention (PCI), with angioplasty and stenting six months earlier following an episode of unstable angina,
- cardiac risk factors including hypertension and dyslipidemia,
- he is a non-diabetic, non-smoker and
- a review of systems is negative for chest pain or any functional limitation.

John’s medications include:
- 81 mg q.d. of acetylsalicylic acid (ASA),
- 25 mg q.d. of hydrochlorothiazide and
- 10 mg q.d. of atorvastatin.

John’s physical exam reveals that his:
- Heart rate is 76 bpm and his
- BP is 142/85 mmHg when seated.

Arterial and central venous pulsations, precordial evaluation and auscultatory findings all within normal limits.

Further investigations find:
- Fasting glucose: 5.8 mmol/L
- Fasting lipid profile:
  - HDL-cholesterol 0.9 mmol/L
  - LDL-cholesterol 2.4 mmol/L
- Total cholesterol: HDL-cholesterol ratio 4.2
- Serum creatinine: 88 micromol/L
- Potassium: 4.1 mmol/L
- Left ventriculogram: preserved left ventricular systolic function (six months previously)

Is this patient adequately protected from future cardiovascular events?
What further changes can be made to his medication regime?

For more on John, go to page 25

Focusing attention toward strategies for cardiovascular (CV) protection acknowledges the vulnerability of the CV system which is exposed to a complex milieu of risk factors. While much has been written about CV protection, it currently lacks precise definition. Typically, it involves the effort to reduce major adverse events in patients who are at high risk. These events include:
- death
- MI
- recurrent ischemia and
- stroke.

Clinical trials looking at specific therapies have not usually encompassed the broader spectrum of related outcomes, such as:
- heart failure,
- atrial fibrillation,
- deterioration of renal function, or even
- symptomatic peripheral vascular disease.

With this in mind, our review will outline some of the more topical CV protection strategies and the rationale for their use.

FAQ

Should all patients with diabetes mellitus be taking an angiotensin-converting enzyme (ACE) inhibitor for cardiovascular protection?

Diabetes is considered to be an equivalent to coronary artery disease. Benefits regarding CV and renal protection partly through BP lowering in diabetic patients have been well established and those with additional cardiac risk factors should be on an ACE inhibitor.
**Lifestyle modifications**

In patients with diabetes in the post-MI setting and those at high-risk for ischemic events, evidence is well established for the benefits of:

- smoking cessation,
- weight loss and
- tight glycemic control.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines regarding ST elevation MI and stable angina contain a good overview of the available evidence supporting their recommendations for lifestyle interventions.

**Reducing BP and ACE inhibitors**

The concept of CV protection has largely evolved from large-scale angiotensin-converting enzyme (ACE) inhibitor trials. Studies looking at the role of ACE inhibitors in patients with left ventricular dysfunction 15 years to 20 years ago demonstrated unequivocal morbidity and mortality benefits. An unexpected finding from these early studies was the observed reduction in MI and other CV events.

**HOPE study**

The idea that ACE inhibitors could have vascular protective effects was prospectively evaluated in the large-scale Heart Outcomes Prevention Evaluation (HOPE) study. HOPE enrolled patients who were at high-risk for, or who had established vascular disease and found that those taking ramipril experienced fewer CV deaths, MIs or strokes compared to those taking placebo (relative risk 0.78, 95% confidence interval 0.70 to 0.86).

**EUROPA study**

Among patients with documented coronary disease (but at lower overall baseline risk) in the large-scale European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROP A study), perindopril was associated with a 20% reduction in CV death, MI or cardiac arrest compared to placebo.

**PEACE study**

Of interest, the subsequently published Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial did not demonstrate a benefit of the ACE inhibitor trandolapril vs placebo in stable coronary artery disease. The unexpected and contrary findings of this

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**Are ACE inhibitors and angiotensin receptor blockers (ARBs) equivalent and interchangeable?**

Evidence for CV protection with ACE inhibitors is far more robust than for ARBs. ARBs appear safe across a broad spectrum of high-risk patients and ongoing trials will address their potential benefits for vascular protection. At this time, ARBs remain good alternative agents for patients intolerant to ACE inhibitors.

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**About the Authors...**

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trial may be attributed to the lower risk profile of the patients, the majority of whom were concomitantly treated with other protective therapies (Table 1).

**ACE inhibitor benefits**

Much debate has been centered on whether the observed benefits of ACE inhibitors is simply related to their efficacy as antihypertensive agents. Indeed, data from large randomized controlled clinical trials and from meta-analyses have shown that lowering BP with a variety of agents including angiotensin receptor blockers (ARBs), thiazide-type diuretics and calcium channel blockers lowers the risk of major CV events.

However, in patients with established cardiac or vascular disease, many experts feel that ACE inhibitors provide BP independent benefits

### Table 1

**Differences in baseline characteristics of patients enrolled in the HOPE, EUROPA and PEACE trials.**

<table>
<thead>
<tr>
<th>Patient characteristics*</th>
<th>HOPE n = 9297</th>
<th>EUROPA n = 12,218</th>
<th>PEACE n = 8290</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>66</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>Prior MI</td>
<td>53</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Prior CAGB or PCI</td>
<td>40</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>Mean SBP/DBP (mmHg)</td>
<td>139/79</td>
<td>137/82</td>
<td>133/78</td>
</tr>
<tr>
<td>ASA/other antiplatelet</td>
<td>76</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>Lipid lowering therapy</td>
<td>29</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>40</td>
<td>62</td>
<td>60</td>
</tr>
</tbody>
</table>

HOPE: Heart Outcomes Prevention Evaluation
EUROPA: The European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease
PEACE: Prevention of Events with Angiotensin-Converting Enzyme Inhibition
CAGB: coronary artery bypass grafting  LVEF: left ventricular ejection fraction
SBP/DBP: systolic BP / diastolic BP
* Numbers are percentages unless otherwise stated
Vascular Protection

Do I need to be concerned about the adverse effects, such as rhabdomyolysis and liver enzyme elevation, with high dose statins?

FAQ

Statins appear safe, even at higher doses. For example, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT) study evaluating high dose (80 mg) atorvastatin, the incidences of persistent liver enzyme elevation and myalgia/CK elevation were 3.3% each, compared to 1.1% and 2.7% respectively with conventional dose regimes of pravastatin. There were no cases of rhabdomyolysis over five years.

through their effects on vascular remodeling and endothelial function. A recent update from the Blood Pressure Lowering Treatment Trialists’ Collaboration concluded that ACE inhibitors may have a specific protective effect in preventing coronary disease-related events. Evidence for CV protection with ARBs is weaker, and ongoing trials will define the role of renin-angiotensin-aldosterone inhibition with this class of medications in high-risk populations. ARBs have been shown to be safe across a spectrum of patients with respect to MI and they remain effective alternatives to ACE inhibitors.

Lipid Lowering

Lowering LDL-cholesterol (LDL-C) with statin therapy has translated into unequivocal CV morbidity and mortality benefits for a spectrum of high-risk patients. Initial studies demonstrating the efficacy of statins in patients with elevated cholesterol led to their evaluation in a broader group of high-risk patients. The Heart Protection Study (HPS) showed that irrespective of the baseline lipid profile, patients with vascular disease (or vascular disease equivalents) who were treated with 40 mg of simvastatin experienced significantly fewer coronary-related deaths and other major vascular events. There was approximately 20% risk reduction over five years.

Subsequent landmark trials have explored whether incremental benefits could still be achieved with more aggressive lipid-lowering. Results of the The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT) study and Treating to New Targets (TNT) trials have provided compelling evidence that high dose statin regimes yield significant reductions in major CV endpoints over conventional regimes, with the magnitude of benefit reflecting the degree of LDL-C lowering.

A meta-analysis capturing > 90,000 patients from 14 randomized trials of statin therapy has shown that each 1 mmol/L reduction in LDL-C corresponds to an approximate 20% reduction in major vascular events, such as:

- MI,
- coronary death,
- revascularization and
- stroke.

Trials have provided compelling evidence that high dose statin regimes yield significant reductions in major CV endpoints over conventional regimes.
This benefit was noted at all levels of LDL-C, leading authors of this analysis to conclude that goals for statin treatment “should aim chiefly to achieve substantial absolute reductions in LDL-C rather than to achieve particular targets…” Moreover, a more aggressive lipid-lowering approach appears to be well tolerated and is not accomplished at the expense of increased rates of serious adverse effects.

**Antiplatelet protection**

Finally, acetylsalicylic acid (ASA) should be considered standard antithrombotic, vascular protective therapy for anyone with:

- established CV disease,
- diabetes, or at
- moderate-to-high risk of vascular events.

Clopidogrel is an effective alternative therapy for patients intolerant to ASA. The role of clopidogrel in addition to ASA is currently limited to patients who have had high-risk acute coronary syndrome presentations or who have received percutaneous coronary intervention with stenting.

**FAQ Which patients need to be on clopidogrel?**

Clopidogrel is indicated for patients who are ASA intolerant, or who have had a high-risk acute coronary syndrome presentation (with or without revascularization) and for all patients who have received angioplasty with stenting. Patients with stents should remain on clopidogrel as directed by their cardiologist.

**References**