Risk factor management: antiatherogenic therapies
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Despite the advances in interventional techniques, the management of stable atherosclerosis remains the domain of optimal guideline-oriented therapy. Recent studies on the effects of aggressive lipid lowering on atheroma volume changes using intravascular ultrasound indicate that it is possible to achieve atherosclerosis regression by reaching low-density lipoprotein (LDL) levels less than 75 mg/dl. The pleiotropic anti-inflammatory effects of statins contribute to the reduction of cardiovascular (CV) event observed with aggressive lipid lowering. As a second important strategy to prevent disease progression, lifestyle changes with regular physical exercise are capable of halting the atherosclerotic process and reducing angina symptoms and CV events. Optimal medical therapy, a healthy lifestyle with regular physical exercise, and coronary interventions are not mutually exclusive treatment strategies. Over the last few decades, both have proved to be effective in significantly reducing the CV mortality in the Western world. However, risk factor modification contributed to at least half the effect in the reduction of CV mortality. This figure provides an estimate of what could be achieved if we were to take risk factor modification more seriously – especially in the acute care setting. The knowledge is there: today we have a better understanding on how to stop progression and even induce regression of atherosclerosis. Much research still needs to be done and will be done. In the meantime, however, our primary focus should lie in implementing what is already known. In addition, it is essential not just to treat CV risk factors, but also to treat them to achieve the target values as set by the guidelines of the European Society of Cardiology.

What is the therapeutic target in stable coronary artery disease?
For an interventional cardiologist, the question about the therapeutic target in stable coronary artery disease (CAD) is easy to answer: take a significant coronary artery stenosis ( > 50%), a symptomatic patient with exercise-induced angina pectoris and, ideally, a positive stress test documenting exercise-induced myocardial ischemia in the corresponding vascular territory and you have everything in place to identify the target lesion for intervention. The intuitive impetus to ‘cure’ the patient by a coronary intervention with stent placement is indeed hard to resist for the interventional cardiologist; some self-critical colleagues speak of the ‘oculo-stenotic-dilatory reflex’ [1]. However, in recent years, a number of well-designed prospective randomized clinical studies have shattered the widely held belief that symptom-guided interventions in stable CAD actually cure the patient and save lives.

The Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) study was a large US-Canadian multicentre trial which compared a strategy of percutaneous coronary interventions (PCI) plus optimal medical therapy (OMT) with OMT alone in patients with stable angina pectoris with regard to morbidity and mortality [2]. All patients received OMT including aspirin, long-acting metoprolol, amlodipine, simvastatin, and ezetimibe if necessary to reach low-density lipoprotein (LDL) target levels. Medical anti-ischemic therapy included isosorbide mononitrate if needed. Exercise plus niacin/fibrates were used to raise the high-density lipoprotein (HDL) level. After a mean follow-up of 4.6 years, the mortality (5.9 vs. 6.5%) and the rates for nonfatal myocardial infarction (MI) (9.4 vs. 10.4%) were not different between the PCI + OMT group and the...
OMT alone group. The PCI + OMT group had a more rapid relief of symptoms; however, freedom from ischemic symptoms was not different in the OMT group after 4.6 years of follow-up. A major point of criticism of the COURAGE study was the significant crossover from the OMT alone group to PCI of 31.1% during follow-up. This was, however, not included in the predetermined combined primary endpoint (of death or nonfatal MI). Had failure of medical therapy been included in the primary endpoint, the OMT alone group would have fared inferior to the PCI + OMT group [3]. Despite these critical comments, the COURAGE study was regarded as a landmark trial, in the sense that the prognostic role of PCI in the management of stable CAD patients was not confirmed.

In fact, the results of the COURAGE study are well in line with the results of another pivotal trial of a primary conservative strategy in stable CAD – the Atorvastatin Versus Revascularization Therapy study. In this smaller study, a strategy of OMT with high-dose atorvastatin (80 mg/day) led to a 36% reduction in the rate of new ischemic events [cardiovascular (CV) death, nonfatal MI, coronary artery bypass grafting, angioplasty, or hospitalization as a result of worsening angina pectoris] as compared with PCI with conventional medical therapy [4]. Although this study was not powered to analyze differences in mortality, it did provide evidence that the progression of the underlying atherosclerotic disease process was more effectively controlled by OMT.

In the meantime, several meta-analyses of clinical trials comparing PCI versus OMT in patients with stable CAD were published. In the classical meta-analysis by Katritsis [5], no significant difference in cardiac mortality and nonfatal MI was found between patients treated with PCI and medical therapy (with a trend towards higher MI rates in PCI patients). In a recent meta-analysis, Cecil [6] concluded that there was a 12% increase in the relative risk of cardiac death or MI associated with PCIs, as well as a 22% increase in the relative risk of nonfatal MI. In another meta-analysis, Schömig [7] also included trials that enroled patients with recent MI (< 4 weeks) and came to the conclusion that PCI was associated with a significant 26% reduction in the odds ratio for cardiac death and a nonsignificant 10% reduction in the odds ratio of nonfatal MI. This result, with a marginal statistical superiority of PCI, may potentially result from the inclusion of four studies enrolling stable patients after recent MI and four trials with both PCI and coronary artery bypass grafting as revascularization strategies.

Although the book is not yet closed on the comparison of OMT and PCI in stable CAD, it becomes more and more evident that outside the window of revascularization, after MI and leaving aside patients with large areas of myocardium at ischemic risk (i.e., patients with main-stem stenosis, three-vessel disease, or critical ostial lesions), the incremental benefit of the intervention over medical therapy is mainly symptomatic. This view is reflected in the current European Society of Cardiology (ESC) guidelines on the management of stable angina pectoris [8]. The guideline committee gave a clear answer to the question for the treatment target and the therapeutic aims are as follows: (i) to improve prognosis by preventing MI and death. These aims are achieved by lifestyle and pharmacological interventions which (a) reduce plaque progression, (b) stabilize plaque, by reducing inflammation and preserving endothelial function, and finally (c) by preventing thrombosis if endothelial dysfunction or plaque rupture occur [8] (ii) to minimize or abolish symptoms. Depending on the individual risk for CV mortality and on the effectiveness of symptomatic control, lifestyle modifications and medical therapy need to be supplemented by revascularization.

The ESC guideline recommendations pay tribute to the growing evidence that it may be more important to influence the course of the underlying atherosclerotic disease than to treat a single symptomatic coronary stenosis by PCI. This ongoing discussion is not and should not be about the superiority of medical therapy over PCI or vice versa, but about the relative merits of each of the therapeutic strategies in the individual patient.

**The atherogenic process – a one-way street? Evidence that regression is possible**

For decades the atherosclerotic process has been viewed as a one-way street leading from endothelial dysfunction to adhesion of proinflammatory monocytes/macrophages to the vessel wall, their transmigration into the subintima where they were transformed into and trapped as foam cells phagocytosing the lipid and cholesterol deposits in the vascular wall. However, plaque formation is increasingly recognized as a dynamic process where progression and regression are determined by the net balance of cholesterol transport and the degree of local inflammation in the plaque itself.

**Intravascular ultrasound-guided regression studies**

During the last decade, intravascular ultrasound (IVUS) has replaced QCA as the reference method for the assessment of coronary disease progression. The major advantages of IVUS are the direct visualization of the arterial wall and plaque morphology, which permit quantification of plaque volume and the assessment of changes in plaque volume if serial assessments are performed [9–11]. With this novel highly sensitive tool to assess changes in plaque volume, the potentials of aggressive lipid lowering in achieving regression of coronary atherosclerosis were assessed in a series of clinical studies.
The first lipid-lowering study to apply serial IVUS to assess coronary atherosclerosis progression was published in 2004 by Jensen [12]: 40 male patients with CAD were examined by IVUS at baseline, after 3 months of lipid-lowering diet, and after another 12 months of simvastatin 40 mg/day. LDL-cholesterol (LDL-C) was reduced after simvastatin therapy by 43% from 4.0 ± 0.8 to 2.2 ± 0.6 mmol/l. This strong decline in plasma lipids was accompanied by a significant 6.3% reduction in plaque + media volume. For the first time, this small monocenter trial indicated that plaque regression with statin therapy was a possibility.

In the Reversal of Atherosclerosis with Aggressive lipid Lowering (REVERSAL) trial, 654 patients with documented coronary atherosclerosis were randomized to moderate (pravastatin 40 mg/day) or aggressive LDL lowering (atorvastatin 80 mg/day) over a period of 18 months [13]. At baseline and after 18 months, atheroma burden was quantified invasively with IVUS. Patients in the pravastatin showed a 25.2% reduction in LDL levels and a 2.7% median progression in atheroma volume during follow-up. Patients in the aggressive lipid-lowering arm with 80-mg/day atorvastatin had a 46.5% decline in plasma LDL concentrations and a −0.4% median regression of coronary atheroma volume as assessed by IVUS [13]. Analyses from the REVERSAL study indicate that there is a close dose–response relationship between the degree of LDL reduction and the regression of coronary atherosclerosis.

As a sequel to the REVERSAL study with a more potent statin, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID study) assessed the effects of 40-mg/day rosuvastatin treatment on coronary atherosclerosis progression as quantified by atheroma burden by IVUS mechanical pull-back [14]. Patients treated with 40-mg/day rosuvastatin had a dramatic 53.2% reduction in LDL levels and 75% achieved a mean LDL-C concentration below 70 mg/dl and the mean LDL concentration for all patients was 60.8 ± 0.89 mg/dl (± standard error). The mean change with regard to percent atheroma volume over the entire pull-back territory after 2 years was −0.98% (P < 0.001) with an even more significant regression of atheroma volume by −9.1% in the 10-mm segment with the greatest disease severity [14].

Are only statins capable of inducing coronary atherosclerosis regression? Early in the atherosclerosis regression research it became evident that HDL has a unique role for reverse cholesterol transport – from the vascular plaque back to the liver. Therefore, the role of a recombinant HDL (ApoA-I Milano) was also assessed with regard to plaque regression [11]. In this trial, a recombinant highly active variant of HDL (ApoA-I) was administered to 57 patients once a week for 5 weeks. Of these patients, 47 had complete serial IVUS data available. Patients treated with recombinant ApoA-I Milano HDL (ETC-216) showed a consistent 14.1 mm³ reduction in total coronary atheroma volume (P < 0.001). Published in 2003 as one of the first IVUS-based studies on coronary atherosclerosis regression, this study was limited by its small size but sparked the larger multicenter trials cited above.

Putting the results from statin-based regression studies with IVUS into perspective, Nissen pointed out that regression of atherosclerosis could be achieved by lowering LDL-C below 75 mg/dl (Fig. 1) [15].

Mechanisms of coronary atherosclerosis regression
Three major mechanisms are thought to be involved in the reversal of coronary atherosclerosis: (i) lipid lowering, (ii) anti-inflammatory interventions, and (iii) increasing laminar shear stress on the vascular endothelium.

The lipids as a target – aggressive pharmacological LDL lowering and HDL increase
A major breakthrough in establishing regression of atherosclerosis as a therapeutic target was the concept of reverse cholesterol transport (RCT). The idea that the intravascular deposition of cholesterol is not an irreversible process but extrahaepatic cholesterol can be returned to the liver for excretion in the bile was first described by Glomset in 1968 [16]. Together with Ross [17], he hypothesized that atherosclerotic lesions grow whenever there is an imbalance between arterial cholesterol deposition and its removal. Stimulated by the striking observation of

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**Fig. 1**

A correlation analysis of major atherosclerosis regression trials using intravascular ultrasound to quantify changes in atheroma volume indicates that LDL levels of less than 75 mg/dl must be reached to achieve atherosclerosis regression. ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; REVERSAL, Reversal of Atherosclerosis with Aggressive lipid Lowering. Reproduced with permission from [15].
the inverse relationship between plasma LDL levels and the prevalence of CV disease, Miller [18] proposed HDL as the peripheral cholesterol acceptor and argued that it should be a therapeutic target to increase LDL-C levels. HDL is synthesized in both the liver and the intestines.

However, RCT from the arterial wall differs considerably from RCT from other peripheral tissues, in the sense that cholesterol is trapped by macrophages. As a result of uptake of cholesterol-rich cell debris and modified lipoproteins, the vascular wall macrophages esterify cholesterol (CO) to cholesterol ester (CE) to escape cholesterol cellular toxicity. As CEs are hydrophobic in nature, they are stored in intracellular lipid droplets leading to the transformation of macrophages into foam cells.

The second mechanism by which macrophages try to escape cholesterol toxicity is cholesterol efflux, which occurs both as passive diffusion and through the active cholesterol efflux pathways ABCA1 and ABCG1. Mice which were transplanted with bone marrow from ABCA1 knock-out mice had significantly accelerated atherosclerosis progression [19]. The cholesterol excreted from the macrophages is unesterified cholesterol, which is again esterified by the HDL lecithin:cholesterol acyltransferase. During its transport to the liver, HDL can move CE to VLDL and LDL through the CE transfer protein. The HDL surface receptor scavenger receptor class B type I (SR-BI) is expressed in a number of cells and tissues including macrophages and the liver. The SR-BI receptor mediates selective HDL uptake by the liver of both CE and CO. Notably, SR-BI/ApoE double knock-out mice develop complex CAD and MI indicating the relevance of SR-BI for reverse cholesterol transport [20]. Both esterified and unesterified cholesterol can be efficiently taken up by the liver for further metabolism and excretion through the bile (Fig. 2) [21].

To promote RCT, two basic approaches have been investigated in humans: (A) to increase HDL concentrations, and (B) to reduce LDL concentrations to levels at which the normal RCT exceeds the LDL-mediated cholesterol influx into the plaque resulting in a net regression of atheroma volume.
HDL levels ( > 7.5% relative increase) had a greater reduction in arterosclerosis regression compared to patients with lower HDL levels (relative HDL increase > 7.5%) [22]. A recent meta-analysis investigating the correlation between changes in HDL levels and arterosclerosis regression in major IVUS regression trials revealed that out of patients within each group of LDL serum levels, those patients with higher HDL concentrations (relative HDL increase > 7.5%) had a significantly better attenuation on arterosclerosis progression (Fig. 3) [23].

The major studies for arterosclerosis regression with statins using IVUS as an imaging technique have already been presented above.

**Vascular inflammation and oxidative stress as therapeutic targets**

The process of lipid accumulation, generation of oxidized LDL in the vascular wall, and phagocytosis by activated macrophages initiates a process of local vascular inflammation. A number of large-scale epidemiological studies have confirmed the prognostic role of inflammatory markers for future CV events: Ridker [24–26] identified tumor necrosis factor-α, IL-6, soluble p-selectin, and C-reactive protein (CRP) as indicators of an elevated risk for CV events. Of all proinflammatory markers of arterosclerotic disease activity, high-sensitivity CRP (hs-CRP) has evolved as the most potent and reliable predictor of adverse CV events and CV death. In a cohort of 27,939 healthy women with 10-year follow-up, hs-CRP surpassed even LDL as the best predictor for future CV events [27].

Which anti-inflammatory treatment options are available for CAD? Two therapeutic principles have to be distinguished: (A) secondary anti-inflammatory agents of statins as part of their pleiotropic effects, and (B) primary anti-inflammatory interventions based on pharmacological interference with proinflammatory mediators.

(A) In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (TIMI 22 trial study), statin-treated patients who had achieved a target level of hs-CRP ≤ 2.0 ml/l had a significant improvement in the event-free survival – an effect independent of achieved levels of LDL cholesterol or cholesterol reduction [28]. These results were corroborated in the Aggrastat-to-Zocor study [29]. For the prevention of acute coronary events, a target value of hs-CRP less than 2.0 mg/l was recommended. For the prevention of acute coronary events a target value of hs-CRP less than 2.0 mg/l was recommended. In a proof-of-concept study (JUPITER study), the clinical effects of statin therapy as an anti-inflammatory intervention in patients with acceptable LDL levels (< 130 mg/dl) and elevated levels of hs-CRP (> 2.0 mg/l) were studied. Rosuvastatin therapy was effective in reducing hs-CRP concentrations by 37%, resulting in a 44% reduction in the primary endpoint of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes [30]. Unfortunately, a treatment arm enrolling patients with low CRP levels was not included, making it impossible to distinguish whether the reduction of CV risk was because of anti-inflammatory properties of statins or cholesterol lowering.

(B) In a nonrandomized observational study of patients with rheumatoid arthritis, patients treated with methotrexate had a 70% reduction in CV deaths indicating the potential of anti-inflammatory interventions to prevent acute CV events [31]. However, novel anti-inflammatory drugs such as CRP inhibitors (1,6-bis(phosphocholine)-hexane), IL-6 inhibitors, and tumor necrosis factor-α inhibitors have not yet entered the clinical arena.

Despite the impressive effects of anti-inflammatory interventions on cardiac event rate, no experimental or human data are yet available, which can prove that isolated...
The arterial tree, and laminar shear stress as a result of the blood pressure wave that is propagated along the arterial tree, and laminar shear stress as a result of pulsatile continuous blood flow is a potent survival signal for endothelial cells and has effects on multiple signalling pathways, which include the phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase 5 [ErK5; also known as mitogen-activated protein kinase 7 (MAPK7)], and NO pathways [38]. Endothelial cells must therefore express specific mechanotransducers that convert physical stress into biochemical signals. The cytoskeleton plays an important role in the sensing of shear stress, and high strain is observed at the luminal and basal membrane. In addition, cellular adhesion protein such as PECAM1, VE-cadherin, and the transmembrane tyrosine kinase vascular endothelial growth factor receptor (VEGFR2 = KDR) were found to mediate biochemical responses to flow. VEGFR2 activates PI3K, which is essential for Akt-mediated phosphorylation and activation of eNOS [39,40].

In contrast to laminar shear stress, the atherogenic flow patterns include turbulent or disturbed flow, low flow, gradients, and flow reversal. These conditions are associated with high rates of endothelial cell proliferation and apoptosis, increased production of reactive oxygen species, and increased expression of inflammatory markers inducing a preatherosclerotic vascular phenotype [38]. In the presence of additional atherogenic risk factors, such as hypertension, dyslipidemia, and diabetes, atherogenesis is significantly accelerated.

### Exercise-related mechanotransduction of laminar shear stress to improve endothelial function

Although regular physical activity in healthy adults can retard the development of age-associated endothelial dysfunction, it is even more important in the manifestation of CV disease; four weeks of aerobic endurance exercise training improves coronary endothelial function in patients with CAD [41]. In a sequel to this study, in patients waiting for elective coronary artery bypass grafting, LIMA tissue was harvested during surgery for molecular analysis. A significantly elevated eNOS expression and eNOS activity were confirmed after the training program [42]. In addition, a reduction in ROS generation and ROS-generating enzymes could be observed [43].

Patients with CV disease also exhibit an impairment of vascular regenerative capacity, as evidenced by a reduced number and migratory activity of bone marrow-derived circulating endothelial progenitor cells [44]. It has recently been shown that physical activity is able to enhance number and functional capacity of these cells in patients with peripheral and CAD [45].

Besides its positive effects on endothelial function, exercise training has the potential to modify several CV}

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**Table 1 Inflammatory processes involved in the progression of stable atherosclerosis**

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<tr>
<th>Process</th>
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<tr>
<td>Macrophage activation</td>
<td>TNF-α</td>
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<td>Mast cell activation</td>
<td>Metalloproteinate expression</td>
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ICAM, inter-cellular adhesion molecule 1; TNF, tumor necrosis factor; VCAM, Vascular cell adhesion molecule 1.

anti-inflammatory interventions are effective in modifying the progression of atherosclerosis. Therefore, their role as an antiatherogenic therapy is still unclear (Table 1).

Antioxidative therapeutic strategies have suffered a similar fate. In contrast to the promising results from small pilot studies, recent large-scale multicenter trials investigating antioxidative agents showed no beneficial prognostic effects [32].

**The endothelium as a therapeutic target**

Vascular function is closely related to the structural and functional integrity of the endothelium. During the last three decades it has become evident that the disturbance of endothelial function (termed endothelial dysfunction) is a condition sine qua non for atherogenesis [33].

Coronary endothelial dysfunction can be visualized as a paradoxical vasoconstriction after administration of acetylcholine [34] but may also occur under physiological conditions during mental stress or physical exertion.

A key component of intact endothelial function is a functional endothelial NO-Synthase (eNOS) located in the luminal endothelial cell membrane, which produces nitric oxide from l-arginine. By diffusion, the short-lived NO reaches the vascular smooth muscle cells in the media and causes relaxation through cGMP-dependent pathways. Potential mechanisms of endothelial dysfunction are as follows: (i) a reduction of l-arginine levels, (ii) an increase of competitive eNOS-inhibitor asymmetric dimethyl-arginine (which has evolved as a surrogate serum parameter for endothelial dysfunction) [35], (iii) a reduced quantity and activity of eNOS and inactivation of nitric oxide by reactive oxygen species (ROS) [36]. Another important mechanism for endothelial integrity has been extensively studied in the last decade, the regeneration of diseased endothelium by endothelial progenitor cells (EPCs) [37].

**Flow conditions and the development of endothelial dysfunction**

Arteries are exposed to two main forces: radial strain as a result of the blood pressure wave that is propagated along the arterial tree, and laminar shear stress as a result of the frictional forces caused by antegrade blood flow. Although increased radial strain, for example, as a result of arterial hypertension increases the atherogenic risk, laminar shear stress as a result of pulsatile continuous blood flow is a potent survival signal for endothelial cells and has effects on multiple signalling pathways, which include the phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase 5 [ErK5; also known as mitogen-activated protein kinase 7 (MAPK7)], and NO pathways [38]. Endothelial cells must therefore express specific mechanotransducers that convert physical stress into biochemical signals. The cytoskeleton plays an important role in the sensing of shear stress, and high strain is observed at the luminal and basal membrane. In addition, cellular adhesion protein such as PECAM1, VE-cadherin, and the transmembrane tyrosine kinase vascular endothelial growth factor receptor (VEGFR2 = KDR) were found to mediate biochemical responses to flow. VEGFR2 activates PI3K, which is essential for Akt-mediated phosphorylation and activation of eNOS [39,40].

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Besides its positive effects on endothelial function, exercise training has the potential to modify several CV
risk factors such as glucose metabolism, obesity, hypertension, and dyslipidemia. Current literature recommends physical activity together with other lifestyle modifications for the prevention of occurrence or progression of CV disease. At least 30-min moderate physical activity a day on most days of the week seem to be necessary to gain the above-mentioned effects [46].

**Pharmacological approaches to improve endothelial function**

Cardioprotective drugs such as statins and angiotensin-converting enzyme inhibitors (ACE-I) exert many of the beneficial effects by improving endothelial function:

Statins increase the stability of eNOS mRNA in endothelial cells and promote eNOS phosphorylation and activation through a protein kinase B/Akt-dependent pathway. In addition, they improve the antioxidative defense of the endothelium by upregulating the thioredoxin system. Dimmel and colleagues [47] were among the first to describe the proangiogenic properties of statins and their important influence on the reendothelialization after vessel injury. Statins mobilize EPCs from the bone marrow and improve differentiation and survival of EPCs – especially in the presence of CV risk factors.

The cardioprotective role of ACE-I in the setting of stable CAD has long been discussed. Today, data from recent clinical studies support a primary atheroprotective effect of ACI-I in CAD. In a substudy of the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), the PERindopril-Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial (PERTINENT) study, Human Umbilical Vein Endothelial Cells (HUVEC) were incubated with serum from placebo and perindopril-treated patients. Serum from perindopril-treated patients induced a 19% increase in eNOS protein expression and a 27% increase in eNOS activity. Endothelial apoptosis was reduced and NO production increased [48]. These results confirm a direct vasculo-protective effect of ACE-I in stable CAD.

**Conclusion**

Optimal medical therapy and coronary interventions are not mutually exclusive treatment strategies; over the last few decades both have proved to be effective in significantly reducing the CV mortality in the Western world. However, risk factor modification contributed half the effect to the reduction in CV mortality! [49] This figure provides an estimate of what could be achieved if we were to take risk factor modification more seriously – especially in the acute care setting.

Today we have a better understanding on how to stop progression and even induce regression of atherosclerosis. Much research still needs to be carried out and will be done. In the meantime, however, our primary focus should be implementing what is already known. In addition, it is essential not just to treat CV risk factors, but also to treat them to achieve the target values as set by the ESC guidelines.

**References**


