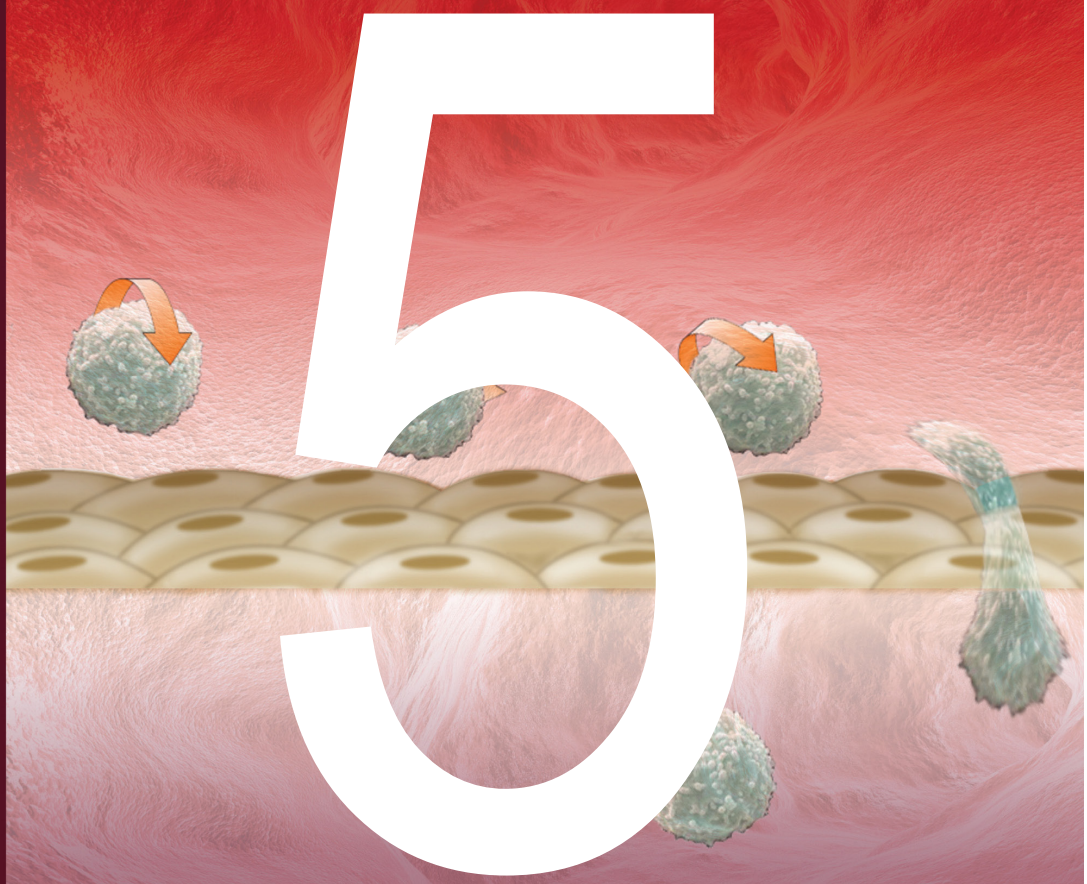
Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists



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Mechanisms of Vascular Disease

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A Reference Book for Vascular Specialists

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Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

5 • Current and Emerging Therapies in Atheroprotection

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BACKGROUND

The global epidemic of cardiovascular disease (CVD) continues to rise, with atherosclerotic CVD remaining the lead cause of morbidity and mortality worldwide, comprising of 29% of all global deaths in 2003. A majority of these deaths were directly caused by coronary artery disease (CAD) or strokes.[1] It is estimated that up to 50% of all deaths and disability due to CAD and strokes could be curtailed by a number of lifestyle and therapeutic approaches that directly target major cardiovascular risk factors.

Atherosclerosis is a systemic disease process involving multiple vascular territories. The presence of established vascular disease, regardless of the territory involved, portends the greatest risk of incident cardiovascular events. The prevalence of asymptomatic coronary stenoses of greater than 50% angiographic severity in non-disabling ischaemic stroke patients has recently been estimated to be 20%,[2] and those patients afflicted with peripheral arterial disease have a probability of death due to CAD and stroke of 55% and 11% respectively.[3] Given the significant systemic plaque burden in these patients coupled with corresponding high event rates, various anti-atherosclerotic and vascular protective therapies have the potential to significantly lower absolute clinical event rates.

PATHOLOGY

Atherosclerosis is a chronic inflammatory condition, characterised by the accumulation of inflammatory cells, lipid and apoptotic material within the arterial wall. The endothelial cell layer, a single cell layer lining the lumen of the vasculature, serves to regulate permeability of the arterial wall, vascular tone and tendency for thrombus formation. Endothelial dysfunction therefore results in altered permeability of the vessel wall, increased vascular reactivity with vasoconstriction and the promotion of a number of prothrombotic substances. Such abnormalities are inherently promoted by the reduced bioavailability of nitric oxide, the principal product of the endothelium. Following transmigration across the endothelial layer, migrated monocytes transform into macrophages, which engulf extracellular lipid to become foam cells, which accumulate to form a fatty streak, considered the earliest macroscopic evidence of atherosclerosis.[4] Local smooth muscle cell migration results in collagen production, forming a fibrous cap, which separates the enlarging inflammatory and lipid milieu from the circulating blood stream. The ongoing accumulation of inflammatory cells, lipid and apoptotic material covered by a strong fibrous cap represents a mature atherosclerotic plaque.[4] Many

atherosclerotic plaques remain clinically quiescent, however some plaques may progress to an advanced stage, characterised by progressive lumen encroachment, aneurysm formation and plaque rupture. The latter two processes are mediated by the degeneration of the extracellular collagen matrix, which in turn is driven by activated matrix metalloproteinase enzymes.[5] Furthermore, plaque neovascularisation (with the adventitial proliferation of vasa-vasorum) leading to repeated intraplaque haemorrhage is now widely recognised as an important mediator of plaque progression and instability.[6]

The degradation of collagen within the fibrous cap leads to a reduction in the tensile strength, which appears more pronounced at the shoulders regions of the plaque. Higher shear stress at these shoulder region, further predispose the thinned fibrous cap to erosion or rupture. This exposes plaque components (including the highly thrombogenic tissue factor) to the circulating blood stream, culminating in the activation and aggregation of platelets and the coagulation cascade, leading to local thrombus formation. This thrombus may embolise downstream, or result in local occlusion of the arterial lumen to blood flow, with resulting acute ischaemia.[7]

Anti-atherosclerotic therapies are administered for either the primary prevention of cardiovascular events, or to prevent the recurrence of events in those patients with established vascular disease. This chapter will review the role of various strategies that have shown clinical evidence of their atheroprotective effects for the prevention of cardiovascular disease.

RISK FACTOR MODIFICATION

Population studies have established an association of the presence of a number of modifiable cardiovascular risk factors with increased risk for the development of CVD.[8,9] These risk factors include: (1) elevated plasma concentrations of various atherogenic lipoproteins, which include low-density lipoprotein cholesterol (LDL-C), lipoprotein (a) and triglycerides (TGL); (2) reduced plasma concentrations of high-density lipoprotein cholesterol (HDL-C); (3) hypertension; (4) diabetes; (5) smoking; and (6) obesity and the associated metabolic syndrome. Mechanistic studies, primary and secondary prevention clinical studies and atherosclerosis imaging studies, have demonstrated significant benefits following the reduction of pro-atherogenic lipoproteins, elevation of HDL-C and treating hypertension, whilst the aggressive glucose lowering for reducing cardiovascular events remains controversial.

TABLE 5.1: Modifiable atherogenic risk factors

- Elevated atherogenic lipoproteins:
  - *LDL-C*
  - *TGL levels*
  - *Lipoprotein (a)*
  - *Chylomicron remnant particles*
- Reduced HDL-C levels
- Hypertension
- Diabetes mellitus
- Obesity
- Smoking

Statins, LDL lowering and C-Reactive Protein

In population studies with extensive follow-up, plasma concentrations of LDL-C have been shown to be a strong and independent predictor of future cardiovascular disease.[8] Established therapies to lower LDL-C levels include hydroxymethylglutaryl Co-A reductase inhibitors (statins), bile acid sequestrants, ezetemibe, LDL-C apheresis

and ileal bypass surgery. Statins however remain the predominant means of successful LDL-C lowering with an abundance of clinical and mechanistic evidence of the favourable impact these agents have upon atherosclerosis regression, and primary and secondary prevention.

Hydroxymethylglutaryl Co-A reductase is the rate limiting enzyme in the pathway leading to the endogenous synthesis of cholesterol by the liver. Inhibition of this enzyme results in the up-regulation of hepatic LDL receptors, with the subsequent removal of LDL from the circulation. Statins are well tolerated, and result in substantial inhibition in plasma LDL-C levels, coupled with modest elevations in HDL-C levels. A minority of patients develop elevations in hepatic transaminases and myositis, while rhabdomyolysis is exceedingly rare.

Statins have resulted in relative risk reductions of 20-40% of both primary[10-12] and secondary cardiovascular events.[13-17] The West Of Scotland Coronary Prevention Study (WOSCOPS) was the first primary prevention study that highlighted a 31% and 33% reduction of fatal and non-fatal coronary events respectively in 6595 randomized middle aged males (whose total cholesterol was greater than 6.5 mmol/L) who took pravastatin for 5 years.[10] Following WOSCOPS, the AFCAPS/TexCAPS trial randomized 6605 patients with a mean total cholesterol level of 5.7 mmol/L to lovastatin or placebo. After 5 years follow-up, lovastatin reduced the combined end point of sudden death, myocardial infarction and unstable angina by 33%.[11] More recently, the JUPITER study randomized 17802 individuals without hyperlipidaemia (mean LDL-C less than 3.4 mmol/L) but with an elevated high-sensitive C-reactive protein (hsCRP) of greater than 2 mg/L to daily rosuvastatin 20 mg or placebo. The trial was halted prematurely after a median follow-up of 1.9 years due to the rosuvastatin group experiencing a 23% relative risk reduction in the combined primary endpoint of myocardial infarction, stroke, arterial revascularisation, hospitalisation for unstable angina or death from cardiovascular causes.[12] This trial therefore highlighted the primary benefit of LDL-C lowering in patients with systemic inflammation.

The Scandinavian Simvastatin Survival Study (4S) randomized 4444 patients with established coronary artery disease and fasting total cholesterol between 5.5 to 8 mmol/L to treatment with simvastatin or placebo. After 5.4 years, the primary end point of all-cause mortality was reduced by 30% with simvastatin, with similar reductions in myocardial infarction and stroke.[13] Similar magnitudes of reduction in mortality and myocardial infarction were seen in the Cholesterol and Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies, which together evaluated the benefit of pravastatin versus placebo in over 13000 patients with prior myocardial infarction over a 5-year period.[14,16] Additionally, the Heart Protection Study (HPS) randomized 20536 patients with established atherosclerotic CVD (or high-risk equivalents on the basis of diabetes mellitus) and total cholesterol greater than 3.5 mmol/L to treatment with simvastatin or placebo.[15] Significant reductions in all-cause mortality (13%), cardiovascular mortality (17%), coronary events (27%) and stroke (25%) were found in the simvastatin group.

Regression of atherosclerosis within the coronary vasculature is a validated surrogate end-point of the clinical event reductions seen with statin therapies. Studies employing intravascular ultrasound (IVUS) have also highlighted the benefits of LDL-C lowering upon the coronary vessel wall. A consistent finding observed in the IVUS trials is the strong linear relationship between

mean LDL-C levels achieved on statin therapy and the median progression-regression rate of atherosclerosis. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, halting of disease progression was achieved with aggressive LDL-C lowering to 2.0 mmol/L with atorvastatin (80 mg/day), as compared with plaque progression seen in those patients randomized to moderate LDL-C lowering with pravastatin 40 mg/d who achieved a mean LDL-C of 2.9 mmol/L.[18] The ASTEROID (A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound –Derived coronary atheroma burden) study was the first large scale trial to show that plaque regression could be achieved by intensive LDL-C lowering to levels lower than achieved in REVERSAL. Rosuvastatin 40 mg/d lowered LDL-C levels to 1.6 mmol/L, and reductions in all volumetric measures of plaque burden was achieved.[19] More recently, a pooled analysis of more than 4000 patients who underwent serial IVUS coronary imaging in 6 trials has demonstrated a direct relationship between the baseline plaque burden, its progression and major adverse cardiovascular events.[20]

Although the clinical benefit seen in statin trials is able to be predicted from the degree of LDL-C lowering, statins are thought to exert vasculoprotective effects mediated by a variety of mechanisms other than direct LDL-C lowering. These suggested pleiotropic mechanisms include anti-thrombotic, anti-inflammatory, antioxidant, vasodilatory and anti-proliferative effects. Although such effects have been studied previously, only the anti-inflammatory CRP-lowering effects have been systematically evaluated in large scale clinical trials.

A major benefit of statin therapy is found in those patients with a high inflammatory state. Post hoc analyses of the CARE study found that those subjects with circulating biomarkers greater than the 90th percentile had the greatest risk of recurrent events, and the greatest benefit from pravastatin occurred in this group.[21] Further insights from REVERSAL revealed the superior CRP-lowering effects of atorvastatin over pravastatin. It is likely that this greater degree of anti-inflammatory effects exerted by atorvastatin contributed to a halting of atherosclerosis progression,[22] whereby the CRP reductions correlated directly with changes in atheroma volume seen with IVUS. The PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) study complimented the imaging findings from REVERSAL using the identical regimen of statin therapy in a large cohort of patients following an acute coronary syndrome (ACS), with the atorvastatin group experiencing significantly reduced clinical event rates.[23] It is yet to be shown as to whether CRP exerts direct effects upon plaque biology, and appropriately designed clinical trials will need to be undertaken to study the clinical effects of new molecules that directly target CRP.

The pleiotropic effects of statins have been postulated to result in plaque stabilisation, which renders the plaque less likely to rupture to cause clinical events. Modulation of endothelial dysfunction and the anti-inflammatory properties of statins have been demonstrated within a few hours following statin administration. As a result, the effects of statins have been studied early in the setting of ACS or prior to elective percutaneous coronary intervention (PCI) in stable patients. Patients with ACS present a relatively high risk of recurrent adverse cardiovascular events. Hence, the early intensive use of statins may improve clinical outcomes and as such, statins have recently been included in the treatment guidelines for ACS.[24] The early benefit of statin therapy following ACS was demonstrated in The Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study.[25] This trial enrolled

3086 patients with ACS and randomized this group to atorvastatin 80 mg/d or placebo commenced within 24-96 hours following randomization. After 16 weeks, the atorvastatin group demonstrated a 14% relative risk reduction in the composite clinical endpoint of death, myocardial infarction, resuscitated cardiac arrest or admission for suspected ischaemia. Two recent meta-analyses of randomized controlled trials which evaluated for benefits of statins compared to placebo or usual care following ACS have highlighted that the real benefit of early statin therapy takes at least 4-6 months to become evident, with the significant benefits predominantly limited to reductions in unstable angina.[26]

A number of studies have also investigated the effects of high-dose statin loading upon the incidence of periprocedural myocardial infarction in the setting of PCI. A large series of patients undergoing elective PCI (n = 5052), found that patients treated with statins at the time of procedure had a significant mortality reduction at 30 days (0.8% vs 1.5% in statin naive patients; p = 0.048); with this benefit being maintained at 6 month follow-up (2.4% vs 3.6%; p = 0.046).[27] Furthermore, in a series of 1552 patients, those patients that had initiated statin therapy prior to the procedure (39.6% of the study group) had a significantly lower incidence of periprocedural myocardial infarction (5.7% vs 8.1% in statin naive; p = 0.038) with a mortality benefit seen at 1 year (3.4% vs 6.9%; p = 0.003).[28] Statin pretreatment was predictive of survival chiefly in patients within the highest CRP quartile. The Atorvastatin for Reduction of Myocardial Damage During Angioplasty (ARMYDA) trial was the first randomized prospective, placebo controlled, double-blind study that demonstrated a beneficial effect of statin pretreatment in preventing myocardial damage following PCI.[29] Patients with chronic stable angina (n = 153) were randomized to atorvastatin 40mg/d commencing 1 week pre-procedure versus placebo. Periprocedural myocardial infarction was detected in 5% of atorvastatin-treated patients compared to 18% in the placebo arm (p = 0.025). The ARMYDA ACS trial randomized 171 patients with ACS to receive placebo or atorvastatin loading (80 mg 12 hours before coronary angiography and a 40 mg dose 2 hours before intervention).[30] The primary composite endpoint of 30 day death, myocardial infarction and need for repeat target vessel revascularisation occurred in 5% of the treatment group compared to 17% of the placebo group (p = 0.04), with multivariate analysis indicating that atorvastatin pretreatment was associated with an 88% relative risk reduction of 30-day events. Furthermore, the ARMYDA RECAPTURE study showed that acute statin preloading prior to PCI in patients on chronic statin therapy had a protective effect with the combined endpoint of 30 day death, myocardial infarction and target vessel revascularisation occurring in 3.7% of patients in the re-load group vs 9.4% in the placebo group (p = 0.037); a 50% relative risk reduction on multivariate analysis.[31] Both the ARMYDA ACS and ARMYDA RECAPTURE trial 30 day combined endpoints were largely driven by a significant reduction in periprocedural myocardial infarction. Collectively, this data highlights that statin pretreatment is a low risk yet highly effective therapy of 'plaque' and 'vessel' stabilisation, mediated perhaps via a number of pleiotropic effects, in both stable and unstable patients undergoing coronary intervention, regardless of whether patients are statin naive or not.

The vasculoprotective effects of statins also extends to the perioperative period during noncardiac surgery. A retrospective case-control study of 2816 patients who underwent major non-cardiac vascular surgery was the first study to show a 4-fold

significant reduction in all-cause mortality during the perioperative period.[32] Soon after, the first prospective, placebo-controlled, blinded, randomized controlled trial evaluating the effects of 2 months of statin treatment upon perioperative cardiovascular complications after vascular surgery showed that the combined primary endpoint (cardiac death, nonfatal myocardial infarction, stroke or unstable angina) at 6-months was 3-fold higher with placebo than with atorvastatin 20 mg/d.[33] A number of retrospective studies have also evaluated the effects of statin therapy upon perioperative complications in patients undergoing noncardiac surgery. A large cohort (n = 780591) of patients undergoing noncardiac surgery found that in those 70159 statin users, there was a significant 1.4-fold reduced risk of in-hospital mortality.[34] The Statins for Risk Reduction in Surgery (STARRS) study assessed the effect of statins on cardiac complications in 1163 patients undergoing vascular surgery.[35] This study found a significantly lower perioperative complication rate in the statin group compared to statin non-users (adjusted OR 0.52, 95% CI 0.35-0.77). Furthermore, the long-term benefit of statins was observed in 510 patients undergoing successful abdominal aortic aneurysm surgery, with a significant reduction in all-cause mortality (18% vs 50%; p<0.001) seen in statin users compared to non-statin users over a median period of 4.7 years.[36] Although a risk of statin-induced myopathy exists in the surgical group of patients taking statins, this risk is considered relatively modest compared to the benefits of statins in reducing perioperative cardiac events. Also noteworthy is the evidence that suggests that statin therapy should remain uninterrupted (if possible) during the perioperative period. Due to the lack of availability of intravenous formulations, statin interruption, however, is common and usually unintended.

TABLE 5.2: LDL-C lowering summary points

- Statins are the most effective means of LDL-C lowering
- Statins inhibit the rate limiting enzyme in cholesterol synthesis
- Statins also achieve minor elevations of HDL-C, modest reductions of TGL levels
- 20%-30% reduction of events in primary prevention studies
- 30%-40% reduction of events in secondary prevention studies
- Clinical benefit proportion to degree of LDL-C lowering
- Regression of coronary atherosclerosis achievable with substantial LDL-C lowering
- Pleiotropic benefits of statins may contribute to benefit seen during ACS, peri-procedural administration during PCI, and peri-operatively for non-cardiac surgery

The complexity of HDL

Although the unequivocal benefit of LDL-C lowering has been demonstrated in a number of clinical trials, reductions in event rates by no more than 40% suggest that additional mechanisms are involved in mediating cardiovascular events, and that complementary strategies are required to achieve greater efficacy in cardiovascular risk reduction. HDL-C is emerging as an important therapeutic target for modulation of cardiovascular risk. Observational studies have suggested that the prevalence of low HDL-C levels (< 40 µg/dL, or 1.0 mmol/L) is greater in patients with established CAD, with numerous population studies also demonstrating an inverse relationship between HDL-C levels and prospective risk of CAD, regardless of the corresponding level of LDL-C.[37] HDL-C was found to be the strongest biochemical predictor of cardiovascular outcome in the Framingham study.[38] A pooled meta-analysis of four

population studies subsequently estimated that each 1 μg/dL rise in levels of HDL-C was associated with a 2% to 3% reduction in cardiovascular risk.[39]

High-density lipoprotein cholesterol possesses numerous anti-atherosclerotic properties, including the promotion of reverse cholesterol transport, protection of both LDL-C particles and endothelial cells from oxidative changes, inhibition of cytokine induced expression of endothelial cell surface adhesion molecules and the inhibition of the prothrombotic milieu associated with atheroma. Animal studies have provided support of these protective effects of HDL. Early studies showed that HDL infusions not only retard lesion formation but also promoted regression of established atherosclerotic plaque, with favourable effects also seen upon plaque composition.[40] These studies therefore provided robust pre-clinical evidence that raising HDL-C levels might be beneficial in humans.

There are a number of strategies that increase HDL-C levels. Non-pharmacological methods include weight loss, smoking cessation and mild alcohol consumption. Established pharmacological strategies include fibrates, statins and nicotinic acid, which raise HDL-C levels by 10-35%, 5-15% and 15-35% respectively. Fibrates have been shown to reduce clinical event rates in studies of primary and secondary prevention. The Helsinki Heart Study (HHS) demonstrated that an 11% increase in HDL-C independently predicted the 34% reduction in myocardial infarction and cardiovascular death with gemfibrozil. Each 1% increase in HDL-C was associated with a 3% reduction in cardiovascular risk.[41] A similar benefit with gemfibrozil was observed in patients with established CAD and low HDL-C levels in the VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial), whereby the 6% rise in HDL-C predicted the 22% reduction in myocardial infarction or cardiovascular death.[42]

Apart from LDL-C lowering, statins modestly raise HDL-C levels. In a pooled analysis of four clinical studies, raising HDL-C was found to be an independent predictor of the benefits of statins in slowing progression of coronary atherosclerosis, with incremental benefit regression observed within those patients whose HDL-C rose by 7.5%, despite intensive LDL-C lowering.[43]

Niacin is the most effective current method of raising HDL-C levels. Several studies have demonstrated that the use of niacin in combination with other lipid-modifying agents, had a substantial effect upon relative risk reduction and disease progression. The HATS (HDL in Atherosclerosis Study) showed that simvastatin and niacin raised HDL-C by 24%, lowered LDL-C by 42% and promoted regression of angiographically detectable CAD. Moreover, there was a profound 60% relative risk reduction in major adverse cardiac events.[44] The benefit of adding extended release niacin to statin therapy was also seen in the ARBITER-2 (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2) study, whereby an increase in HDL-C levels of 0.21mmol/L slowed progression of carotid intimal-media thickness (CIMT) in patients with HDL-C levels below 1.2 mmol/L.[45] More recently, the addition of niacin (for HDL-C augmentation) was found to be superior to the addition of ezetemibe (for further LDL-C lowering) in a group of patients already on chronic statin therapy for CAD, whereby the niacin/statin group experienced significant regression of CIMT compared to the ezetemibe/statin group.[46] Intolerance due to flushing, which is mediated by activation of epidermal prostanoid receptors, continues to limit the widespread clinical use of effective doses of niacin. However, pharmacological strategies to inhibit these

epidermal prostanoid receptors in combination with the delivery of niacin therapy may hold promise for future trials employing niacin as an effective and well-tolerated anti-atherosclerotic therapy. Enthusiasm also exists for significantly raising HDL-C levels via the inhibition of cholesteryl ester transfer protein (CETP). In humans, CETP inhibition is capable of raising HDL-C levels by greater than 50% and reducing LDL-C levels by 20%. However the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial was prematurely halted due to a higher clinical event rate seen in the patients administered Torcetrapib (CETP inhibitor).[47] These unexpected effects have been postulated to arise from activation of the renin-angiotensin system as well as a direct, unfavourable molecule-specific vasculotoxic effect of Torcetrapib itself.[48] The recent report of the safety of Anacetrapib, a next generation CETP inhibitor, has raised hopes that significant elevations in HDL-C levels via CETP inhibition will regress atherosclerosis and eventually result in reduced clinical event rates.[49]

HDL comprise a heterogenous group of particles, which vary in size, shape and content of both lipid and protein. Normal or elevated levels of HDL are not always atheroprotective in humans. The finding that greater than 40% of the clinical events observed in the Framingham cohort occurred in subjects with serum HDL-C levels greater that 1.01 mmol/L suggests that their HDL failed to possess the appropriate levels of protective properties.[50] The observation that HDL, isolated from subjects with CAD despite high HDL-C serum levels, promotes rather than inhibits monocyte chemotaxis in response to oxidised LDL-C, provided mechanistic evidence that HDL may be proatherogenic in some individuals.[51] It remains to be established whether the size and composition of HDL particles bears influence upon their functional properties. Contrasting reports from population studies have demonstrated that HDL particle size may influence prospective clinical risk. Furthermore, a potential relationship between HDL subclasses and cardiovascular risk has been reported to contribute to the relative benefit of various lipid-modifying therapies. In an exploratory analysis of VA-HIT, the generation of small HDL particles with gemfibrozil was demonstrated to independently predict protection from cardiovascular events.[52] This may explain why a relatively small rise in HDL-C levels was associated with clinical benefit. The observation of benefit by raising levels of lipid-deplete HDL particles is consistent with their ability to remove excess cellular cholesterol, prevent LDL-C oxidation, rapidly improve endothelial function, and promote plaque regression in humans.[53]

HDL therefore remains an attractive target for modification by therapies aimed to promote cardiovascular risk reduction. However, the complexity of HDL presents a major challenge in determining the optimal therapeutic approach. Although a number of groups have proposed specific HDL-C targets for treatment, there is no current evidence that treating to a particular target results in clinical benefit. At the minimum, it would seem that attempts to raise HDL-C levels above levels considered to be associated with an increase in cardiovascular risk (1.01 mmol/L in men and 1.28 mmol/L in women) would be prudent. However the emergence of the functional quality of HDL, rather than absolute HDL levels, is currently presenting a major challenge for future drug development programs. It is likely that raising the right type of HDL-C may have the greatest impact upon cardiovascular disease prevention.

TABLE 5.3: HDL-C cholesterol summary points

- Strongest independent predictor of events
- Numerous atheroprotective properties:
  - *Promotes cholesterol efflux*
  - *Anti-inflammatory actions*
  - *Reduces oxidation of LDL-C*
  - *Inhibits thrombogenecity*
- Elevated by weight loss, smoking cessation and mild alcohol consumption
- Therapeutically elevated by fibrates and nicotinic acid
- Novel therapeutic agents that elevate HDL-C levels and promote HDL-C functionality are currently being trialled in humans

The controversy of triglycerides

Despite extensive research, in the setting of clinical trials and epidemiologic studies, the exact role of serum TGL levels as an independent risk factor for CAD remains uncertain. Observational studies have produced data in support of the independent predictive value of fasting TGL levels for incident CAD. Graziano et al. investigated the interrelationships between fasting TGL and other lipid parameters, along with non-lipid risk factors, against the risk of myocardial infarction in 340 cases and 340 age-, gender- and community-matched controls. The relative risk of myocardial infarction was found to have a strong association with elevated fasting TGL levels that remained unaltered after controlling for other non-lipid risk factors; however despite remaining statistically significant, the strength of this association was attenuated somewhat after controlling for HDL-C.[54] Following this study, Jeppesen et al. examined the relationship between fasting TGL levels and ischaemic heart disease (IHD) risk in over 2,900 males in the Copenhagen Male Study, with 8-years of follow-up. Following adjustment of both lipid and non-lipid risk factors, men in the middle and highest tertile of TGL levels had relative risks of IHD of 1.5 (95% CI, 1.0-2.3; $p = 0.05$) and 2.2 (95% CI, 1.4-3.4; $p < 0.001$) respectively, when compared with men in the lowest TGL tertile.[55] When TGL levels were stratified by HDL-C levels, the risk of IHD increased with increasing TGL within each HDL-C level. Similarly, the larger Prospective Cardiovascular Munster study involving 4,849 middle-aged men who were followed for 8-years found TGL levels to be an independent risk factor for CAD irrespective of HDL- or LDL-C levels.[56]

Therefore there is no clinical trial that has been designed to specifically address the issue of TGL lowering upon incident cardiovascular events. Although patients enrolled in the HHS experienced a 35% reduction in TGL levels, it was the 11% increase in HDL-C levels that predicted the 34% relative risk reduction in the rate of myocardial infarction.[41] Limited data therefore exists from clinical trials to suggest that the specific lowering of TGL levels, independent of concomitant HDL-C raising/LDL-C lowering, will result in reduced clinical event rates within patients with normal or elevated LDL-C levels. Although current guidelines do not mandate screening for elevated TGL levels within the general population, TGL levels in patients afflicted with CAD (or CAD risk equivalent) may provide valuable prognostic information for therapeutic decision-making. At this point the presence of mild to moderate hypertriglyceridemia identifies a patient who requires more intensive management of LDL-C, with treatment guidelines advocating initiation or intensification of statin therapy as first line treatment.

Hypertension

Epidemiologic studies have established a direct relationship between both systolic and

diastolic blood pressures and cardiovascular events. The strongest relationship lies between hypertension and cerebrovascular disease. Framingham data predict the lifetime risk of developing hypertension to be about 90% by the age of 65 years.[57] The Multiple Risk Factors Intervention Trial (MRFIT) demonstrated a continuous and graded relationship between both systolic and diastolic blood pressures and death due to both CAD and stroke,[58] with the strength of this relationship greatest for systolic blood pressure. In addition, isolated systolic hypertension, the commonest form of hypertension, portends a 2.5-fold greater risk of cardiovascular disease compared with matched, normotensive patients.

Hypertension alters shear forces within the vascular lumen. Steady laminar flow stimulates endothelial cellular functions which maintain vascular tone, thrombogenecity and regulated permeability. The mechanotransduction of these altered shear-stress signals arising from the endothelial surface result in a number of changes contributing towards atherogenesis, including altered gene expression, as well as changes to vascular regulatory substances including nitric oxide, endothelin and angiotensin II.

The use of anti-hypertensive therapy for primary prevention reduces cardiovascular events. A meta-analysis of randomised controlled trials involving the reduction of systemic hypertension in primary prevention revealed a 21% risk reduction in events attributed to CAD and a 37% reduction in the incidence of stroke.[59] The Hypertension Optimization Trial (HOT) randomised patients with hypertension to therapy aimed at three groups of blood pressure targets. Analysis revealed the lowest incidence of cardiovascular events in those with a mean diastolic blood pressure of 82.6 mmHg, supporting aggressive lowering of blood pressure into the 'normal' range.[60]

The Heart Outcome Prevention Evaluation (HOPE) study supports the use of angiotensin converting enzyme (ACE) inhibition in all high risk patients. Despite the minimal blood pressure reduction seen in the ramipril arm, the use of an ACE inhibitor reduced the composite vascular end point by 22%, supporting the critical role played by the renin-angiotensin system in the promotion of atherogenesis.[61] The second Australian National Blood Pressure Study also highlighted the benefit of an ACE inhibitor-based anti-hypertensive regimen significantly lowering cardiac death in the elderly population as compared to a diuretic-based regimen.[62] The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) reported no overall differences in CAD outcome among patients treated with a diuretic-based compared to a calcium channel blocker- or an ACE inhibitor-based treatment program.[63] However, patients in the diuretic group experienced fewer episodes of heart failure than in the calcium channel blocker group. Although The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (National Heart, Lung, and Blood Institute. National Blood Pressure Education

TABLE 5.4: Hypertension summary points

- Strong independent risk factor
- Small reductions in blood pressure result in marked reduction in clinical events
- Reduction of blood pressure to the normal range results in the least number of clinical events; further reductions may be deleterious
- Blood pressure lowering per se is of utmost importance, irrespective of the choice of anti-hypertensive agent
- ACE inhibition reduces cardiovascular events in all high-risk patient groups, regardless of baseline blood pressure

Program, 2003) supports thiazide diuretics as first-step drug of choice in most hypertensive patients, what is clear from the wealth of trial data is that blood pressure lowering per se is of greater importance in reducing cardiovascular event rates rather than the choice of agent(s) used.

RISK FACTOR MODIFICATION IN THE DIABETIC PATIENT

Glycaemic Control

The incidence of diabetes continues to increase worldwide, predominantly due to the significant rise in the prevalence of type 2 diabetes mellitus, which now accounts for over 90% of all diagnosed cases. The major cause of morbidity and mortality in subjects with diabetes is attributed to atherosclerosis, particularly CAD. In subjects with type 2 diabetes, it is well established that there is a two- to four-fold increased risk of CAD, peripheral arterial disease and cerebrovascular disease than compared with matched non-diabetic controls. This persists despite accounting for other traditional cardiovascular risk factors such as hypertension, smoking and dyslipidaemia. Accordingly, treatment guidelines now consider the presence of diabetes to be an atherosclerosis equivalent, and suggest that diabetics should be treated in a similar fashion as those with established clinical cardiovascular disease in terms of risk factor control.[64]

A number of direct and indirect pathways contribute towards atherogenesis in diabetics. Indirect pathways that are promoted by hyperglycaemia include worsening of dyslipidaemia (development of atherogenic dyslipidaemia; small dense LDL-C particles, reduced HDL-C levels and elevated TGL levels), sympathetic nervous system dysfunction and the development of renal dysfunction. Direct pathways (directly pertaining to chronic hyperglycaemia) result in the overall reduction in the bioavailability of nitric oxide. The resultant endothelial dysfunction promotes vasoconstriction, pro-inflammatory and prothrombotic tendencies that contribute towards the progression of atheroma and subsequent atherothrombosis. Cholesterol and blood pressure lowering trials have demonstrated benefit in diabetic patients. Given the implicit relationship between hyperglycaemia and virtually all stages of atherogenesis, one would expect that the strict control of blood sugar levels would cause corresponding reductions in atherosclerotic cardiovascular disease. However clinical trials evaluating the impact of chronic, intensive glycaemic control upon cardiovascular disease have produced conflicting results, reflecting a complex interaction between glycaemic control and the atherosclerotic disease process.

Observational studies have tended to show a linear relationship between hyperglycaemia and cardiovascular mortality.However for levels of glucose at or below the threshold for the diagnosis of diabetes, the relationship with cardiovascular mortality is less clear-cut.[65,66] Recently, the results of large-scale intervention trials examining the relationship between intensive glucose control and cardiovascular outcomes have been published. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial examined the effect of intensive glucose control (target HbA_{1c} under 6.0%, but achieving a mean level of 6.4%) versus standard therapy (targeting HbA_{1c} between 7.0-7.9%, achieving a mean level of 7.5%) in over 10,000 established type 2 diabetics.[67] An unexpected finding of a higher rate of cardiovascular mortality (34%, $p = 0.02$) and all-cause mortality (22%, $p = 0.04$) within the intensive glycaemic arm resulted in a premature halting of this study after a mean follow-up period of 3.5 years. Despite these

mortality rates, there was a non-significant trend towards a reduction in the primary outcome of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Although the exact mechanisms of the resultant increase in mortality in this trial are unknown, an association between higher rates of severe hypoglycaemia within the intensive glycaemic control arm was reported, with patients with the highest baseline HbA_{1c} levels at greatest risk of hypoglycaemia compared to those with superior initial glycaemic control. In contradiction to ACCORD, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial randomised over 11,100 type 2 diabetics to either intensive glucose control (achieving a mean HbA_{1c} of 6.5%) or standard control (achieving a mean HbA_{1c} of 7.3%).[68] After a mean follow-up period of 5 years, the composite primary endpoint of combined macrovascular and microvascular events was significantly attenuated in the intensive glucose control group. However this result was primarily driven by the significant reduction in microvascular endpoints, whereas there was no significant reduction in cardiovascular events.

In the United Kingdom Prospective Diabetes Study (UKPDS), 3,867 newly diagnosed type 2 diabetics were randomised to an intensive glycaemic control compared with conventional treatment policy.[69] Over the ensuing 10-year period of the trial, the intensively treated patients achieved a mean HbA_{1c} of 7.0% compared to a mean HbA_{1c} level of 7.9% in the conventionally treated group. The intensively treated patients experienced a 16% relative risk reduction of myocardial infarction which just failed to achieve statistical significance ($p = 0.052$) compared to the conventionally treated group. However the intensively treated group did experience a significant 25% reduction in microvascular complications ($p = 0.01$). A sub-group of overweight individuals within the UKPDS study who were placed on metformin as part of their intensive glucose control regimen did experience a significant 39% reduction in myocardial infarction ($p = 0.01$) and a 36% reduction in all-cause mortality ($p = 0.01$). This data has been adopted to promote the use of metformin as a means of effectively reducing cardiovascular endpoints independently of glycaemic control. Following the publication of the UKPDS results, all surviving patients of this study entered into a post-trial monitoring program until 2007.[70] During this follow-up period, no attempts were made to continue the mode and intensity of glycaemic control according to their prior randomisation group. In the first year after entering the post-trial monitoring program, any differences in the HbA_{1c} between the previous 2 treatment groups was lost. Despite the rapid loss of glycaemic separation between the two groups in the post-trial follow-up program, a significant benefit of being previously randomised to an intensive glucose control regimen was still observed, whereby this group experienced a 15% lower rate of myocardial infarction ($p = 0.01$) as well as a 13% reduction in all-cause mortality ($p = 0.007$). Moreover, the prior reductions in microvascular endpoints as well as the benefits of metformin therapy were all maintained during this post-interventional follow-up study. These observations virtually mirror the results of the previously reported Diabetes Control and Complications Trial (DCCT); a 9-year trial highlighting the benefit intensive glycaemic control significantly delaying the development and progression of diabetes-related microvascular complications in type 1 diabetics, however failing to show any significant benefit upon cardiovascular events.[71] Following completion of the DCCT, subjects were then followed by the Epidemiology of Diabetes Interventions

and Complications (EDIC) study.[72] Again, differences in HbA_{1c} were quickly lost between the 2 treatment groups. The completion of the 11-year post trial observation period occurred in 2005, and despite the early loss in glycaemic separation between the prior 2 groups, the combined endpoint of cardiovascular events (non-fatal myocardial infarction, stroke or cardiovascular death) were reduced by 57% ($p = 0.02$) in the group of patients previously assigned to intensive glucose control.

The UKPDS follow-up study and the EDIC study suggest that the sustained, early intensive control of blood glucose levels eventually translates into a significant benefit upon the development of cardiovascular disease many years down the track. Mechanisms pertaining to this 'legacy' effect are currently unknown. At least 4 recently published meta-analyses (that have included the ACCORD and ADVANCE studies) have suggested that intensive versus standard glucose lowering reduces cardiovascular events without increasing cardiovascular or all-cause mortality. [73-75] Therefore, an HbA_{1c} target of < 7.0% still remains an acceptable target for appropriate glucose control. However under certain circumstances, especially in the setting of newly diagnosed type 2 diabetes and in young patients without significant comorbidities, aiming for a lower HbA_{1c} level may represent an appropriate strategy to lower both microvascular and macrovascular complications.

Global risk factor reduction in diabetics

The greatest benefit for diabetic patients, in terms of cardiovascular risk factor reduction, has resulted from the aggressive modification of plasma lipoproteins and blood pressure. Diabetic dyslipidaemia, characterised by elevated TGL levels, reduced HDL-C levels and the presence of small, dense LDL-C particles, represents a potent atherogenic stimulus. Weight loss and aggressive glycaemic control leads to an improvement of this lipid profile.[64] Statin trials have demonstrated greater relative risk reductions in diabetic subgroups, as have trials employing gemfibrozil.[13,42] Although the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study did not show daily fenofibrate to significantly reduce the risk of the primary outcome of coronary events (death due to CAD or non-fatal myocardial infarction) in over 4800 type 2 diabetics, there was a primary reduction in the rate of coronary and non-coronary revascularisations as well as fewer non-fatal myocardial infarctions.[76] Moreover, fenofibrate therapy resulted in the improvement in a number of microvascular parameters. Furthermore, the ACCORD study group investigated whether combination therapy with statin plus fenofibrate, as compared with statin monotherapy, would further reduce the risk of cardiovascular disease in over 5,500 type 2 diabetics at high risk for cardiovascular events. The statin/fibrate combination did not reduce the rate of fatal cardiovascular events, non-fatal myocardial infarction, or non-fatal stroke as compared with statin therapy alone.[77] A recent meta-analysis (of 18 trials, over 45,000 patients) investigating the effects of fibrates on major clinical outcomes concluded that fibrates do reduce the risk of major cardiovascular events, largely driven by a 13% relative risk reduction (7-19) in coronary events ($p<0.0001$).[78] Collectively, these trials suggest that although statin therapy should remain the cornerstone of treating dyslipidaemia in diabetics, diabetics with reduced HDL-C and elevated TGL levels may derive some additional benefit with the addition of fibrate therapy.

Similarly, lowering blood pressure is of utmost importance in diabetics for enhanced

cardiovascular risk reduction, portending a greater risk benefit in diabetics compared with non-diabetics. The blood pressure lowering sub-study of UKPDS confirmed a significant reduction in strokes (as well as microvascular endpoints) in those with aggressive blood pressure control (mean on-treatment blood pressure of 144/82 mmHg) compared with the group assigned less tight control (who achieved a mean blood pressure of 154/87 mmHg).[79] A similar observation was noted within the HOPE (Heart Outcomes Prevention Evaluation Study) study, with the benefit of ramipril seen in diabetic patients compared to those with established vascular disease.[61] However, more recent attempts to define the optimum level of blood pressure control in diabetics has highlighted the complex relationship between blood pressure levels in diabetics and cardiovascular event rates. Until recently, it was widely felt that aggressive lowering of systolic blood pressure below 135 mmHg in diabetics would be of further clinical benefit. However the results of the ACCORD study group collaborators found that in type 2 diabetics at high risk for cardiovascular events, intensive systolic blood pressure lowering to levels below 120 mmHg, as compared to less than 140 mmHg, did not reduce the rate of composite outcome of fatal and nonfatal major cardiovascular events.[80] Moreover, the patients assigned to intensive blood pressure lowering experienced significantly higher adverse event rates attributed to the antihypertensive treatment. This trial reinforced the notion that aggressive blood pressure lowering in diabetics to values below 130-135 mmHg may be problematic.

TABLE 5.5: Diabetes summary points

- Diabetes and insulin resistance are both strong risk factors for cardiovascular events
- Glycaemic control correlates with clinical outcome
- Aggressive glycaemic control reduces microvascular complications
- There is a more complex relationship between aggressive glycaemic control and reduction of macrovascular events
- Early, aggressive glycaemic control may have a longer term 'legacy' effect upon reduction in macrovascular events
- Metformin use in obese diabetics significantly lowers rate of myocardial infarction
- Statins remain the cornerstone of lipid management in diabetics
- Control of blood pressure equally important in diabetics; however aggressive lowering of systolic blood pressure to levels < 120 mmHg may be detrimental

The metabolic syndrome

The metabolic syndrome refers to the co-existence of an atherogenic lipid profile, elevated blood pressure, and elevated plasma glucose, associated with abdominal obesity and insulin resistance.[64] Although a number of definitions exist, the most recent consensus from the International Diabetes Federation defines metabolic syndrome as the presence of central obesity (defined as waist circumference with ethnic specific values, or if body mass index exceeds 30 kg/m^2, then central obesity can be assumed) and any two of the following: (1) raised TGL levels (> 1.7 mmol/L), (2) reduced HDL-C levels (< 1.03 mmol/L in males and 1.29 mmol/L in females), (3) raised blood pressure (systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg), (4) raised fasting plasma glucose level (> 5.6 mmol/L).[81]

Numerous studies have investigated the cardiovascular risk associated with metabolic syndrome, with ongoing debate regarding the prognostic significance of the metabolic syndrome for cardiovascular outcomes. A recent meta-analysis was conducted of

the cardiovascular risk associated with the metabolic syndrome (as defined by the National Cholesterol Education Program), which found the presence of metabolic syndrome to be associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality.[82] It remains unclear, however, as to the relative contribution of the individual components of the metabolic syndrome towards the mediation of cardiovascular risk. A recent study analysing the risk of myocardial infarction conferred by the metabolic syndrome and its individual components in multiple ethnic populations was recently undertaken. It was found that the risk of metabolic syndrome upon myocardial infarction is generally comparable to that conferred by some, but not all, of its component risk factors, whereby the association with myocardial infarction being similar to that of diabetes mellitus and hypertension.[83] Accordingly, a recent analysis of over 3450 patients who participated in 7 clinical trials that monitored coronary atheroma progression with IVUS found accelerated disease progression in those patients with the metabolic syndrome. However, after adjusting for its individual components, the presence of the metabolic syndrome itself was no longer found to be an independent predictor of disease progression.[84] Infact, further analysis of the same patient cohort found that patients with diabetes mellitus had greatest coronary plaque burden, greater plaque progression and lumen constriction than those categorised as having metabolic syndrome.[85] Further studies will need to be conducted to ascertain the candidate mechanisms by which metabolic syndrome mediates cardiovascular risk. However given the strong relationship between the presence of its component risk factors, the ideal anti-atherosclerotic approach tackling the metabolic syndrome would appear multi-factorial, in addition to weight loss and life-style measures.

FUTURE TARGETS

The current generation therapeutic approach for atherosclerotic cardiovascular disease prevention is essentially aimed directly at the modulation of known cardiovascular risk factors. Although these approaches have been successful in risk reduction, a substantial residual risk remains. Given our understanding of the implicit role of oxidative and inflammatory pathways in atherogenesis, therapies directly targeting these pathologic substrates represents a potential future challenge in achieving further risk reduction in the population. As a result, various novel therapeutic agents are undergoing clinical development. These include a number of anti-oxidant and anti-inflammatory therapies. It is likely that these therapeutic approaches will find their way into clinical practice.

CONCLUSION

Atherogenesis represents the culmination of a complex series of humoral events that promote the inflammatory cascade and thrombogenicity. The optimal therapeutic approach for both primary and secondary prevention of atherosclerosis still involves the traditional approach of global risk factor modification. However emerging therapies targeting novel markers of disease will be needed to tackle the residual burden of clinical events attributable to atherosclerosis despite contemporary anti-atherosclerotic therapies. Furthermore, emerging imaging and serum markers of atherosclerosis and its inflammatory content will enhance our risk prediction capabilities for cardiovascular events, as well as the ability to monitor response to anti-atherosclerotic therapies.

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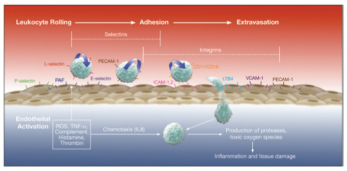

Cover diagram by David Heinrich of the *Medical Illustration and Media Unit, Flinders Medical Centre*. (See chapter 18)

Mechanisms of Vascular Disease

Edited by Robert Fitridge and Matthew Thompson

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