Chapter 6. Macrovascular complications

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Section A. Introduction

Diabetes mellitus is primarily a metabolic disorder associated with impaired glucose, lipid and protein metabolism as a consequence of impaired production, secretion or action of insulin. However, diabetes generates broader changes including vascular pathology. The entire vasculature is damaged by diabetes and both micro- and macrovascular complications develop. Microvascular changes are located mainly in capillaries and are manifested as diabetic retinopathy, nephropathy and neuropathy (*see also* Chapter 5). On the other hand, macrovascular disease manifested as atherosclerosis is located within the arteries. Macrovascular disease is more common in people with diabetes than in those without.

The presence of diabetes therefore increases the risk of vascular wall impairment. Development of cardiovascular and cerebrovascular disease is a typical consequence of the long-term effect of diabetes as a primary metabolic disorder. Acute myocardial infarction is at least three times, stroke five to ten times and ischaemic disease of the lower limbs nearly twenty times more common in patients with diabetes than in the non-diabetic population. In people with diabetes, vascular changes develop earlier and are more advanced than in those without and their development depends on the disease duration. Earlier manifestation is associated with vascular events occurring in a younger population than in people without diabetes. In addition, the multiple impairments of arteries create a more complicated course of the disease. Therefore, macrovascular complications contribute to significantly higher morbidity and mortality of people with diabetes compared to people without. In addition, the risk of macrovascular complications is increased by other factors such as arterial hypertension, dyslipoproteinaemia or obesity, which are frequently associated with diabetes. These 'risk factors' have both genetic and environmental backgrounds, which contribute to accelerated manifestation of cardiovascular disease.

The elucidation of pathogenetic interrelationships in development of macrovascular complications as well as early diagnosis may initiate both better prevention and proper treatment of atherosclerosis. Although the prognosis of patients with cardiovascular disease without diabetes has significantly improved during the past 20 years, this has not been the case for patients with diabetes. More complicated cases need intensive treatment, with associated higher costs of management. It then becomes clear why the budget allocated to diabetes treatment has increased during the last decade. More intensive and effective treatments have helped more patients with complications to survive, and those patients then need active medical follow-up.

The increasing number of patients with macrovascular complications associated with the 'diabetes epidemic' needs better understanding of all biological mechanisms, as well as active and more intensive prevention and treatment strategies mainly at earlier stages of diabetes. Early diagnosis of the initial stage of arterial disease, as well as elucidation of all risks including genetic predisposition, may indicate those people with diabetes who are candidates for macrovascular disease (atherosclerosis). Intensive management would diminish the development of atherosclerosis and would be therefore beneficial for their future life. Early intervention would be cost effective because it may save more money than late treatment of advanced stages of cardiovascular or peripheral arterial disease in patients with diabetes.

The biomedical research community does not currently have all necessary data to start immediately with these tasks and further research is still necessary.

Section B. Scientific advances and major challenges

The past 10 years have seen many improvements in treatment in the field of diabetic macrovascular complications such as atherosclerosis of coronary, cerebral and peripheral arterial walls. Acute myocardial infarction, stroke or lower limb amputation are typical consequences of this vessel wall impairment. Some pathogenetic mechanisms have been elucidated, and collection of clinical data from many studies on prevention and treatment of cardiovascular disease has significantly strengthened our understanding in this area. More patients with diabetes with vascular disease may be intensively treated, and their survival time has been extended. These patients live longer than before, and their wellbeing has improved. However, there are still gaps between the medical results obtained in treatment of patients with diabetes and those without. Not all details in development of atherosclerosis in diabetes have been elucidated, and data on effective treatment are still lacking. Despite positive results, macrovascular complications once manifest, accelerate and are the main cause of death in diabetes.

Macrovascular complications are not specific for diabetes but occur faster and more commonly compared to those in people without it. This is due to some pathogenetic mechanisms originating in advanced oxidative stress as a consequence of hyperglycaemia and dyslipidaemia as discussed here. However, this diabetes-specific pathophysiology is related only to development of more advanced vascular changes than in the non-diabetic population. Metabolic abnormalities associated with diabetes accelerate the ageing process, and consequently cardiovascular disease develops at an earlier age in all people with diabetes.

Elucidation of possible pathogenetic mechanisms of cardiovascular disease in diabetes

Oxidative stress

Oxidative stress is characterised by the presence of reactive oxygen species (ROS) (such as superoxide anions, hydrogen peroxide, hydroxyl radicals) created by different metabolic pathways. Some of them are highly active free radicals that damage proteins, lipids, saccharides or nucleic acids. ROS are quickly inactivated by different antioxidative mechanisms, including enzymes and other molecules (known as scavengers). The impaired balance between ROS overproduction and inactivation thus accelerates oxidative stress, which may be deleterious for molecules and consequently for cells and tissues. Advanced oxidative stress has been observed in different disorders, including diabetes. It has been shown to play a key role in the development of diabetic complications, including cardiovascular complications. *In vitro* and *in vivo* studies show that hyperglycaemia induces an excess generation of ROS. A unifying hypothesis suggests that free radicals are overproduced at the level of the mitochondria during hyperglycaemia.

Interestingly, not only chronic but also oscillating and postprandial hyperglycaemia seems to have this effect. Moreover, the deleterious long-lasting effect of hyperglycaemia has been identified as ‘glucose memory’. High glucose also causes a derangement in metabolic pathways by influencing gene regulation. This effect may be associated with changes in the cells and tissues (e.g. collagen production) creating abnormal amounts of structural molecules (quantitative changes) or abnormal molecules (qualitative changes). This effect persists even if normal glycaemia is then introduced and maintained, and genetically fixed abnormalities have been documented. Glucose memory explains the persistence of mitochondrial free radical overproduction even when glycaemia is normalised.

Advanced glycation end-products (AGEs)

Several important biochemical mechanisms are activated in the presence of high concentrations of glucose, which occurs in diabetes. Elevated glucose accelerates the formation of advanced glycation end-products (AGEs). A major pathway is thought to involve increased production of methylglyoxal that reacts to form non-enzymatically glycated proteins, which are further transformed into AGEs. These are biologically noxious complexes that act via their chief signalling receptor - the AGE-specific receptor (commonly abbreviated as RAGE). AGEs generate reactive oxygen species accelerating oxidative stress and activate inflammatory changes. Consequently, AGEs have key roles in the pathogenesis of diabetic complications and there is a growing body of evidence to indicate that this applies also to diabetic cardiovascular disease. Such observations suggest that the inhibition of AGE formation may be a promising target for therapeutic intervention in diabetic vascular complications.

Inflammation

Until recently, atherosclerosis was thought to be a passive process of lipid deposition in the arterial wall, followed by progressive occlusion of the lumen, and finally plaque rupture and thrombosis. Data suggest the contrary, that atherosclerosis is a dynamic process developing over many years, characterised by active uptake of lipids and smooth muscle cell proliferation, 'moulding' of plaque, and subject to the influence of many environmental and genetic factors. Central to these processes, both at initiation and propagation, there are factors associated with inflammation. Insulin resistance, one of the underlying causes of type 2 diabetes, is also associated with elevated levels of inflammatory factors, such as C-reactive protein (CRP), plasminogen activator inhibitor-1, and fibrinogen; these same factors have been shown to precede and predict diabetes. These findings have led to the notion of a strong association between insulin resistance and diabetes with cardiovascular disease possibly through inflammation pathways.

C-reactive protein (CRP) is an acute-phase response protein that is considered both a marker of inflammation and a predictor of cardiovascular events including myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death. Evidence indicates that CRP has a direct proatherogenic effect through up-regulation of angiotensin II type 1 receptors and the stimulation of other proinflammatory factors. This may play a role in the accelerated atherosclerosis of type 2 diabetes.

Endothelial dysfunction and initiating factors

The initial impairment in development of atherosclerosis (macrovascular disease) in diabetes is characterised by functional changes in the vascular wall. Endothelial dysfunction, with a lack of nitric oxide available for vasodilatation represents the first stage in this process, making early diagnosis important for decisions regarding prevention and treatment. This involves both pharmacological and non-pharmacological management improving endothelial function. Factors creating endothelial dysfunction involve oxidative stress associated with either hyperglycaemia or higher concentrations of free fatty acids. Indeed, macrovascular disease in diabetes is a consequence of several factors besides hyperglycaemia, such as dyslipidaemia, arterial hypertension, impaired fibrinolysis and adipose tissue hormones/factors among others. A role for genetic factors is proposed, but information is still limited. Treatment of the patient in the stage of endothelial dysfunction, which is more reversible than already developed atherosclerosis, may prevent vascular wall changes and, consequently, disorders such as myocardial infarction, stroke or peripheral artery disease.

Functional methods, such as flow-mediated vasodilation estimated most frequently on the brachial artery, together with evaluation of carotid artery intima-media thickness (IMT) measured by ultrasound, have been used in clinical studies to measure the effects of pharmacological treatment in follow-up clinical trials. Such non-invasive techniques bring lesser risks to the patient, are painless, more comfortable and easier to perform.

Role of arterial hypertension in vascular disease

In the past 5 years, clinical trials have contributed to the investigation of the role of anti-hypertensive treatments in diabetes. Before 2003, few studies were focussed specifically on the clinical issue of hypertension and diabetes. Other studies consisted mainly of the analysis of diabetic sub-groups of large trials where the diabetic population was often poorly characterised. Studies focussing specifically on diabetic populations, including the Steno 2 Study, with multifactorial intervention have provided important data in the past 5 years. The studies concluded that in patients, intensive antihypertensive treatment prevents development of vascular disease and diminishes the progression of already established cardiovascular disease. Lowering of blood pressure to normal values thus improves the prognosis of patients with diabetes. In addition, some groups of drugs (e.g. blockage of the renin-angiotensin-aldosterone-system) were found to have more beneficial effects than the others because they prevent vascular wall impairment. A new drug from this group has now been brought to the market: aliskiren, the first direct inhibitor of renin that acts upstream of presently used drugs, offering the hope of greater efficacy.

Different factors have been suggested as pathogenetic mechanisms, such as: a) genetic predisposition; b) role of the pro-renin and the renin-angiotensin-aldosterone system; c) membrane cation transport abnormalities; d) altered adrenoreceptor responsiveness and role of autonomic dysfunction; e) role of increased sodium sensitivity in the vasculature; f) neurohormonal changes; g) insulin resistance as an initiator. However, none of these possible mechanisms have been confirmed in type 2 diabetes as one of the initial pathogenetic events leading to hypertension of diabetes.

Dyslipidaemias
In the last 5 years, treatment of dyslipidaemias has shown that intensive lowering of blood cholesterol (mainly LDL-cholesterol) prevents atherosclerosis in patients with diabetes. There are two research challenges in people with diabetes: one is the increased (higher than desired) LDL cholesterol level, which belongs to modifiable risk factors. Interventional and epidemiological studies identified the therapeutic goal for LDL cholesterol level in patients with diabetes to be as low as under 2 mmol/L. A second challenge is diabetic dyslipidaemia (dyslipidaemia of the metabolic syndrome) characterised by increased accumulation of VLDL in the liver (fatty liver) and increased production of VLDL particles by the liver resulting in hypertriglyceridaemia, which consequently affects both HDL metabolism leading to reduced HDL cholesterol, and LDL metabolism resulting in an increase of atherogenic small, dense LDL particles.

While several studies have reported that statins showed some benefit in reducing LDL cholesterol to less than 2 mmol/L, less convincing results were observed in the treatment of diabetic dyslipidaemia both by fibrates or niacin. However, positive side effects have been observed with fibrates (beneficial effect on retinopathy) in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. Treatment of dyslipidaemia improves plasma lipid concentrations and reduces the risk of atherosclerosis.

Ischaemic heart disease
Ischaemic heart disease is the most frequent complication of type 2 diabetes. Mortality in post myocardial infarction is higher in people with diabetes when compared with the general population for both type 1 and type 2 diabetes. Combination of antihypertensive, hypolipidaemic and glucose-lowering drugs together with non-pharmacological management (increased physical activity and dietary regimen) influencing several risk factors is more effective than the treatment of individual risk factors. Therefore, such multifactorial intervention (e.g. Steno 2 study) reduces the risk of this complication by 50 percent. Simple measurements, such as albumin excretion rate, blood lipids, blood pressure or central obesity, identify patients at high risk. Well-established preventive treatment for type 2 diabetes includes addressing blood glucose, blood pressure, dyslipidaemia and body weight. Treatment of all risk factors in parallel brings greater benefit than improvement of only one or two factors.

Lower limb disease
Diabetes has been shown to accelerate the atherogenic process, which is reflected in a higher prevalence of lower limb disease in a group of people with type 2 diabetes. Untreated lower limb disease is a cause of ischaemia, ulcers, gangrene and amputation of foot or leg. Limited mobility, disability, necessity of help from another person, as well as loss of employment with financial and social problems, are the main consequences of advanced atherosclerosis in lower limbs. Lower limb ischaemic disease is diagnosed late, and treatment is insufficient. Strategies for prevention, including diabetes management and foot care, are therefore necessary. However, the conclusions are still under discussion, and different strategies require investigation.

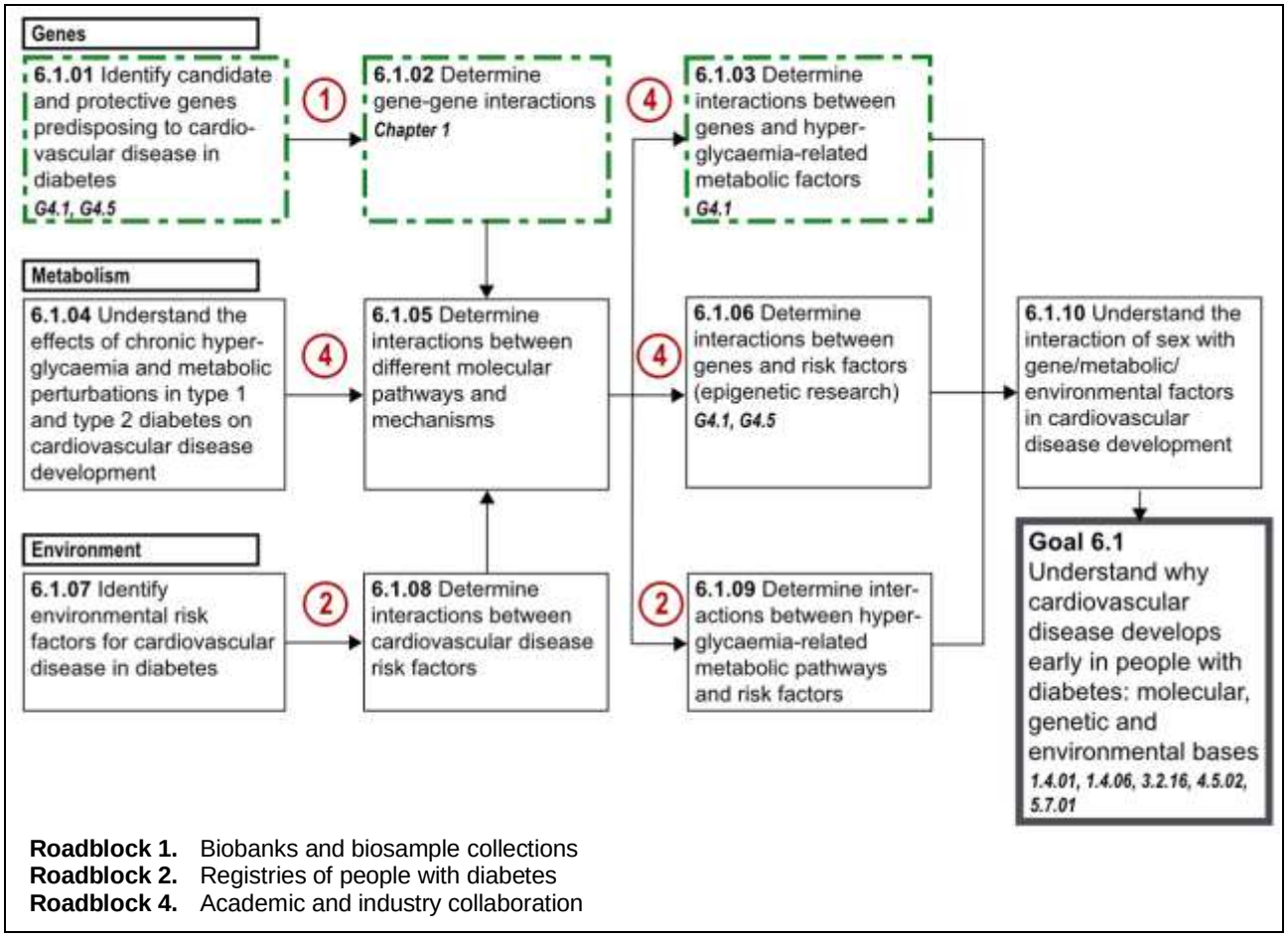
Conclusion
The last 10 years have seen much progress in treatment for macrovascular disease in diabetes. This progress has opened new research pathways in pathogenetic mechanisms to understand underlying processes, and in genetics and epidemiology to develop more evidence-based treatments. Reports from genome-wide association studies initiated the search for candidate genes associated with vascular disease in diabetes but this is still at very early stages. Elucidation of mechanisms of macrovascular disease helped to initiate the studies with intensively treated patients with diabetes. They showed that combined treatment of all risk factors brings better prognosis to the patient. The idea that people with diabetes have to be examined and treated for all risk factors as early as possible and more intensively is now generally accepted because it may diminish disability and morbidity and thus extend wellbeing. In addition, early risk detection and intervention may be cost effective by eliminating the need for expensive treatment of advanced macrovascular complications.

However, much more research is needed in order to improve the lives of people with diabetes suffering from or likely to develop macrovascular complications. This includes understanding better the underlying pathology, timecourse and specificity of the macrovascular complications of diabetes, developing diagnostic tools to allow for earlier intervention, validating new treatment modalities including a personalised approach to therapy, and ultimately preventing diabetic CVD.

Section C. Road maps reports

Links between Goals and Milestones in the DIAMAP report are noted within the text and also in the diagrams in *italic*s. Roadblocks are listed below the diagrams and described at the end of the chapter. Goals and Milestones considered a priority are indicated with a broken green line.

Goal 6.1. Understand why cardiovascular disease develops early in people with diabetes: molecular, genetic and environmental bases



Roadblock 1. Biobanks and biosample collections
Roadblock 2. Registries of people with diabetes
Roadblock 4. Academic and industry collaboration

Introduction and background

Diabetes creates specific conditions (a high glucose concentration with multiple metabolic effects) for macrovascular complications to develop that are characterised by atherosclerosis appearing earlier and at a more advanced stage than is seen in people without diabetes. However, it has not been established whether cardiovascular disease (CVD) in diabetes has specific features (e.g. biochemical changes within the vessel wall), which may differentiate it from CVD in patients without diabetes: an analysis of all possible factors and their interactions will be required to eludicate this. A deeper understanding of pathogenetic mechanisms is a prerequisite for an improvement in early diagnosis and treatment, as well as eventually preventing CVD in diabetes. As CVD develops during the early stages of diabetes, frequently even before diagnosis, it should be investigated also in the prediabetic state and in the metabolic syndrome. Epidemiological studies evaluating risk factors should be undertaken in patients with diabetes and prediabetes.

Development of CVD in diabetes may be influenced by interactions between genetic and metabolic risk factors, as well as risk factors that facilitate functional (e.g. endothelial dysfunction) and morphological (atherosclerotic plaques) changes of the vascular wall. All of these factors may be modified by sex and ethnic differences.

The early stage of vascular disease is mostly asymptomatic, and the patient is without any problems. However, CVD develops progressively and, therefore, it needs to be discovered as early as possible (*see also* Milestones 1.4.01, 1.4.06, 4.5.02, 5.7.01).

Track 1: Genes

Milestone 6.1.01. Identify candidate and protective genes predisposing to cardiovascular disease in diabetes

Genetic predisposition to vascular disease has been repeatedly postulated, but no significant data exist to confirm this hypothesis. Only single genes and limited numbers of their polymorphisms have been studied with no firm conclusion to support their possible role in vascular wall impairment. However, several genes contribute to development of CVD (indicating the 'polygenic' nature of vascular disease), and their different combinations ('mosaic interplay' between the genes) is highly probable. To fulfil the aim of this Milestone, large biobanks of genetic material are needed to obtain data from different populations. The information on candidate genes (genes contributing to the respective disease) participating in development of CVD is lacking, and only genetic analyses of large cohorts (with and without diabetes as well as with and without vascular disease) may provide such data. In addition, the role of genes and their contribution to CVD may be different in various populations, and thus investigation needs to be done in ethnically defined individuals. Epidemiological studies comparing genotype-phenotype relationships are needed. Genes (or more precisely gene variants) protective for CVD should be analysed by studying centenarians or older adults without any signs and symptoms of CVD (*see also* Goal 4.5). The European Platform for Clinical Diabetes Research (EPCRD) will be instrumental in facilitating such largescale studies (*see also* Goal 4.1).

Milestone 6.1.02. Determine gene-gene interactions

Clusters of genes have been suggested to act jointly in diabetic vascular disease but neither individual genes nor their interplay has yet been elucidated. By identifying gene-gene interactions in well-defined populations their role in atherogenesis can be clarified. New techniques are required to allow large numbers of different gene polymorphisms to be combined and to understand the interactions that may accelerate development of vascular wall pathology in diabetes or may have a protective role. Research into the role of genes and their interactions in CVD development will increase our knowledge on the contribution of genes to vascular disease, and it will stimulate further investigation. Research in this area would facilitate genetic screening in relevant patients in the future, allowing evaluation of their genetic risk of CVD. Patients with higher genetic risk could be treated more intensively (aggressively) than those with lower risk (*see also* Chapter 1).

Milestone 6.1.03. Determine interactions between genes and hyperglycaemia-related metabolic factors

Clusters of factors (*see also* Milestones 6.1.02 and 6.1.05) have not been fully specified, but the vascular wall is affected by their interaction. This means that vascular wall disease develops under the influence of several genes and hyperglycaemia-related metabolic factors (such as reactive oxygen species, oxidised lipids, glycated proteins, among others), which are not isolated but may act together with accelerating effects. Animal strains with genes protecting the vascular wall (*see* Milestone 6.1.01) should be studied while they are in the hyperglycaemic state. Research on the isolated effect of the diabetic state on development of atherosclerosis in genetically protected animals (such as minipigs) may generate new information on metabolic risk factors. It would further elucidate the role of glucose memory in different genetic animal strains. Similar data can be obtained with other CVD risk factors used in genetically protected animals. Pursuing this Milestone will reveal the contribution of genetic and metabolic factors to development of atherosclerosis in experimental animal studies. It will create new lines of research because we do not yet have information on interactions between metabolic changes and genes specific for macroangiopathies. In humans, cross-sectional and follow-up studies are required in well-characterised groups with confirmed genetic background for gene variants (the balance of protective and risk alleles) known to play a role in vascular wall pathology or altered CVD risk.

Patient registries and collaborative clinical research networks are fundamentally important to this Milestone (*see also* Goal 4.1). Genetic analyses need data from large cohorts because gene clusters may interact differently with various combinations of metabolic factors. One research centre is insufficient for obtaining such endpoints, but networks of centres may offer valuable results from thousands of patients with statistically significant power. Clinical characteristics and data from laboratory analyses have to be included, making registries necessary. The investigation carried out in this Milestone will help patients in estimating the risk of their genetic and metabolic factors contributing to CVD development. Such research may further justify the need for intensive treatment.

Track 2: Metabolism

Milestone 6.1.04. Understand the effects of chronic hyperglycaemia and metabolic perturbations in type 1 and type 2 diabetes on cardiovascular disease development

A high concentration of glucose accelerates oxidative stress, inflammation and other pathogenetic mechanisms that play a role both in functional and morphological disturbances of the cells and extracellular matrix in the vascular wall. In addition, 'glucose memory' (i.e. the long-term consequences in an individual of an historical period of good or poor glucose control) may influence how genes are expressed within these cells. It also modifies the internal structure of the blood vessel walls.

In vitro or animal experiments are necessary to understand glucose-tissue interactions. Glucose as a reactive molecule modifies proteins and lipids and thus may induce structural changes in connective tissue of the vessel wall. Interrelation between different pathogenetic pathways needs to be investigated to establish what role this plays, and models of glucose memory (in animals or human tissue) are still lacking. Two separate investigations are necessary: a) into type 1 diabetes characterised by hyperglycaemia and insulin deficiency and b) into type 2 diabetes covering mostly 'clusters' of metabolic and other risk factors. Research in this area may strengthen treatment of patients with diabetes and help scientists to look for new drugs influencing investigated pathways. Benefit to both basic science and patient are evident.

Milestone 6.1.05. Determine interactions between different molecular pathways and mechanisms

Chronic hyperglycaemia stimulates different pathogenetic pathways (non-enzymatic glycation, protein kinase C activation and oxidative stress pathways) all of which contribute to changes both in connective tissue and within the cells of the vascular wall. Some of these pathways have already been characterised, but a specific link between them has only been hypothesised. Their interrelationships have to be studied in specific animal models (e.g. minipigs), as well as in humans. Pathways and mechanisms may have different power to create CVD when acting separately or in combination. Glucose memory may be amplified by other mechanisms generated as a consequence of hyperglycaemia. Research in pursuit of this Milestone is paramount for clarification of the multiple roles of hyperglycaemia in CVD.

Milestone 6.1.06. Determine interactions between genes and risk factors (epigenetic research)

The genetic background identified in Milestone 6.1.01 should be analysed when CVD risk factors are already present to investigate their effect on CVD development. The combination of risk factors that has the strongest effect on genes accelerating CVD needs to be determined. The entire spectrum of epigenetic research will be included in this analysis of interactions. Animal strains with genes predisposing to development of atherosclerosis need to be studied along with presenting CVD risk factors. The interaction of mixed genes and CVD risk factors will confirm how this combination accelerates the vessel wall pathology. This investigation must also be undertaken in humans (*see also* Milestone 6.1.03) with the need for patient registries and collaborative networks (*see also* Goal 4.1). Different combinations of genes and risk factors increase the need for testing in thousands of well-characterised patients with diabetes. Such analyses will require registries from different centres to strengthen statistical power in evaluation and confirm the usefulness of the complex genetic and risk factor analysis in single patients. Collaboration between researchers will therefore be necessary and success will depend on the EPCRD (*see also* Goal 4.1).

Important data could be obtained from separate analysis of the protective gene-environment interactions in studies in centenarians and older adults. Research on such populations that appear to be protected against diabetic CVD would elucidate possibilities for prevention (*see also* Goal 4.5).

Track 3: Environment

Milestone 6.1.07. Identify environmental risk factors for cardiovascular disease in diabetes

Diabetes is frequently associated with different risk factors that accelerate the development of atherosclerosis. These risk factors may be genetically determined, influenced by the metabolic disturbance of diabetes itself, or caused by lifestyle. Apart from known risk factors such as arterial hypertension, hyperlipoproteinaemia and obesity, there are others that are not fully confirmed and probably others still to be discovered. These metabolic and environmental factors, as well as their interaction with the immune/inflammatory system, should be studied together because they do not occur in an isolated fashion in all patients.

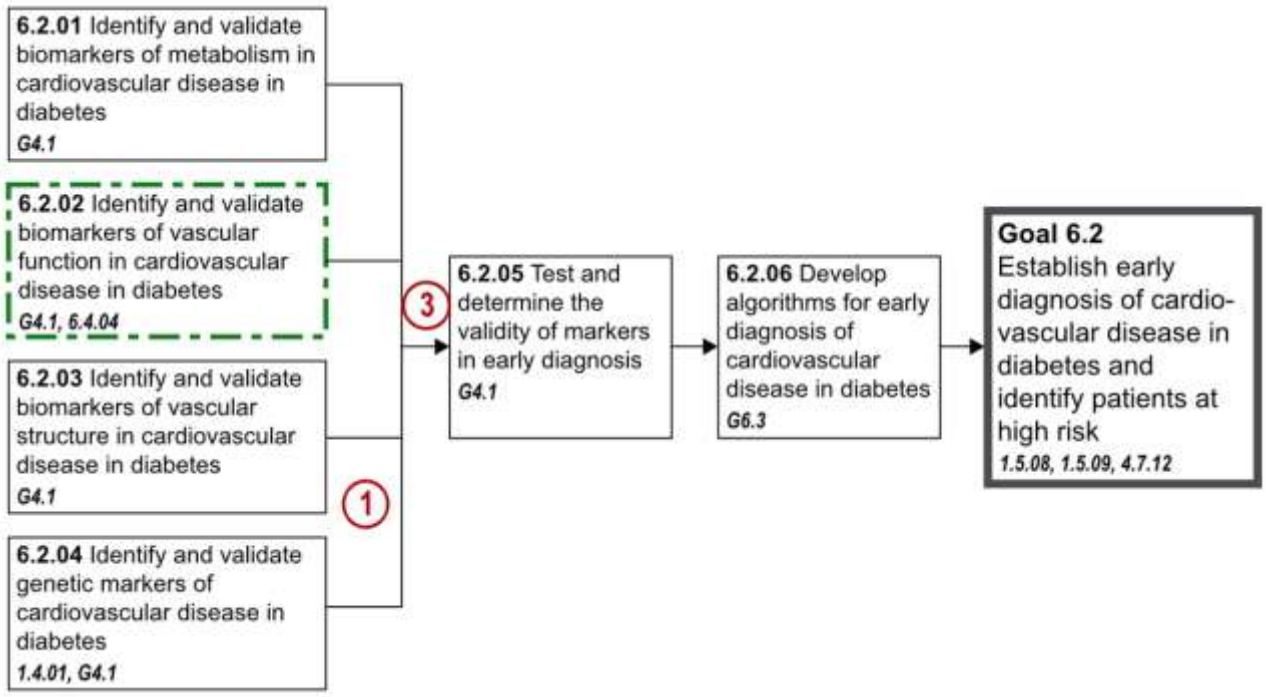
Estimation of individual clusters of metabolic and environmental factors may improve decisions and treatment options. Identifying all risk factors and determining their contribution to the development of vascular wall pathology is necessary because their different clustering (combination) causes altered risk of CVD development. For such an investigation, animal models of different CVD risk factors need to be developed in order that their specific impact on vascular wall changes can be identified, and data from large groups of well-characterised patients will need to be analysed because sufficient statistical power will be required.

Milestone 6.1.08. Determine interactions between cardiovascular disease risk factors
Different risk factors for CVD (e.g. overeating, salt intake, lack of physical activity) are frequently combined, and their effect is therefore amplified. Their separate roles, elucidated in Milestone 6.1.07, need to be used for understanding synergy when they are present in combination. Arterial hypertension, dyslipoproteinaemia and obesity form clusters together with other currently undetermined risk factors. Data obtained from animal models with defined CVD factors would serve to explain how the clusters of CVD factors contribute to vascular changes. Sex and ethnic differences also need to be evaluated and development of vessel wall changes will be identified. Similarly, human studies carried out on large well-defined population-based samples from patient registries are needed to contribute new data on CVD factors to determine the role of interactions between different risk factors for development of atherosclerosis in diabetes. Such investigations would offer a forecast to patients about their risk of CVD as a basis for personalised treatment.

Milestone 6.1.09. Determine interactions between hyperglycaemia-related metabolic pathways and risk factors
In diabetes, chronic hyperglycaemia does not occur in isolation, but it is frequently combined with different CVD risk factors. However, this interaction has not been fully explained. Determination of metabolic and non-metabolic CVD risk factor interactions is a major milestone in understanding their effects in combination. Animal studies using specific strains and human trials making use of cohorts from defined patient registries should be used (as in Milestones 6.1.07 and 6.1.08, taking advantage of the EPCRD). These studies would then explain why the severity and extent of vascular wall changes are so profound in diabetes.

Milestone 6.1.10. Understand the interaction of sex with gene/metabolic/environmental factors in cardiovascular disease development
Sex hormones influence CVD development. Higher prevalence of CVD in younger men than in women changes in older age. The lack of oestrogens in the menopause may accelerate CVD development in older women, and no difference between sexes is then apparent. The effect of sex on genetic, metabolic and environmental factors of CVD therefore needs to be investigated.

Goal 6.2. Establish early diagnosis of cardiovascular disease in diabetes and identify patients at high risk



Roadblock 1. Biobanks and biosample collections
Roadblock 3. Large-scale research networks

Introduction and background

Macrovascular disease presented by ischaemia in the heart, brain and lower limbs is manifested when advanced changes of the vascular wall are already developed. Its manifestation is frequently asymptomatic, and the patient may not visit a physician for some time. Diagnosis is therefore made when it is too late for treatment to be successful, limiting the likelihood of preventing organ failure. Late diagnosis of macrovascular disease in diabetes is therefore the cause of premature death of people with diabetes when compared to those without. Early diagnosis, before development of vascular changes, is therefore an important Goal. The patient can be intensively handled both pharmacologically and non-pharmacologically when morphological changes in the vessel wall have not yet developed, which may slow or prevent atherosclerosis.

Early diagnosis depends on being able to evaluate markers (e.g. biochemical indicators, mostly molecules of the initial vascular wall impairment) that indicate either predisposition to development of atherosclerosis or the presence of specific initial vascular wall activation, which is characterised by molecules associated with and produced by endothelial cells. They may be detected in body fluids, such as plasma. Early detection of atherosclerosis must be based on genetic predisposition together with metabolic, functional and structural biomarkers. These biomarkers represent molecules indicating the presence of endothelial dysfunction, which accelerates the effects of genetic background. It will be necessary to find more biomarkers than are presently available, and validate them (*see also* Milestones 1.5.08, 1.5.09).

Milestone 6.2.01. Identify and validate biomarkers of metabolism in cardiovascular disease in diabetes

Metabolic biomarkers require substantial further study to be more completely understood. They are influenced by the treatment used to control diabetes and by their relationship to subsequent vascular changes; therefore, they have to be validated. These biomarkers reflect rather the consequence of the initial vascular activation than a cause of the pathogenetic process itself. The relationship of biomarkers to endothelial dysfunction at an early stage of the vascular disease has yet to be confirmed. This Milestone involves identifying and validating metabolic biomarkers from cross-sectional studies and the validation of their usefulness to reflect acute and chronic metabolic

conditions. Such research may therefore initiate treatment directly helping the patient (*see also* Goal 4.1).

Milestone 6.2.02. Identify and validate biomarkers of vascular function in cardiovascular disease in diabetes
Functional biomarkers are based on the activity of blood vessels and endothelium. For example, endothelium is stimulated by molecules of advanced oxidative stress (reactive oxygen species), inflammation etc. This may induce an abnormal expression of vasoactive substances that influence vasodilatory properties of capillaries and arteries. Decreased availability of nitric oxide (NO) reduces the vasodilation response when measured by Doppler ultrasound. In this example, functional biomarkers would comprise both vasoactive substances (e.g. direct NO or endothelial NO synthase measurement, prostaglandins among others) and indicators (parameters) derived from Doppler ultrasound measurement (flow-mediated vasodilation) or from laser-Doppler fluxmetry.

New biomarkers are required, and this Milestone will allow them to be introduced into this field of research in collaboration with industry and further applied into clinical practice. The aim is to identify markers of vascular changes that characterise early stages of vascular disease before morphological impairment develops. These methods are non-invasive and painless, so not disturbing the patient who will benefit from early discovery of vascular changes (*see also* Milestone 6.4.04 and Goal 4.1).

Milestone 6.2.03. Identify and validate biomarkers of vascular structure in cardiovascular disease in diabetes
The third group of biomarkers consists of indicators that confirm the structural changes in the vessel wall. The initial stage of atherosclerosis is characterised by thickening of the intima-media (IMT) layer (inner and medial layers together) of the artery wall. Accurate determination of IMT is important for the process of measuring the stage of atherosclerosis. Development of new methods or examinations is necessary so that physicians can determine early structural changes in the arteries. The X-ray examination presently used to confirm late and advanced stages of atherosclerosis is not suitable for early diagnosis (*see also* Goal 4.1).

Milestone 6.2.04. Identify and validate genetic markers of cardiovascular disease in diabetes
Predisposition to macrovascular disease may arise from clusters of genetic factors. Some of the genes (more precisely gene variants impacting CVD risk) found by research undertaken for Milestone 6.1.01 might be useful as markers for the diagnostic process. Candidate genes specific for development of vascular wall changes or genes that determine risk factors playing a role in the atherosclerotic process may be present in diabetes and must be identified and characterised. The gene polymorphisms associated with impaired vascular morphology need to be determined and such an analysis will depend on newly developed or developing techniques to evaluate hundreds of genes, especially in combination, because multiple genes play a role in this process. Large numbers of samples will be needed to achieve the Goals and validate the appropriate genetic markers (*see also* Milestone 1.4.01 and Goal 4.1).

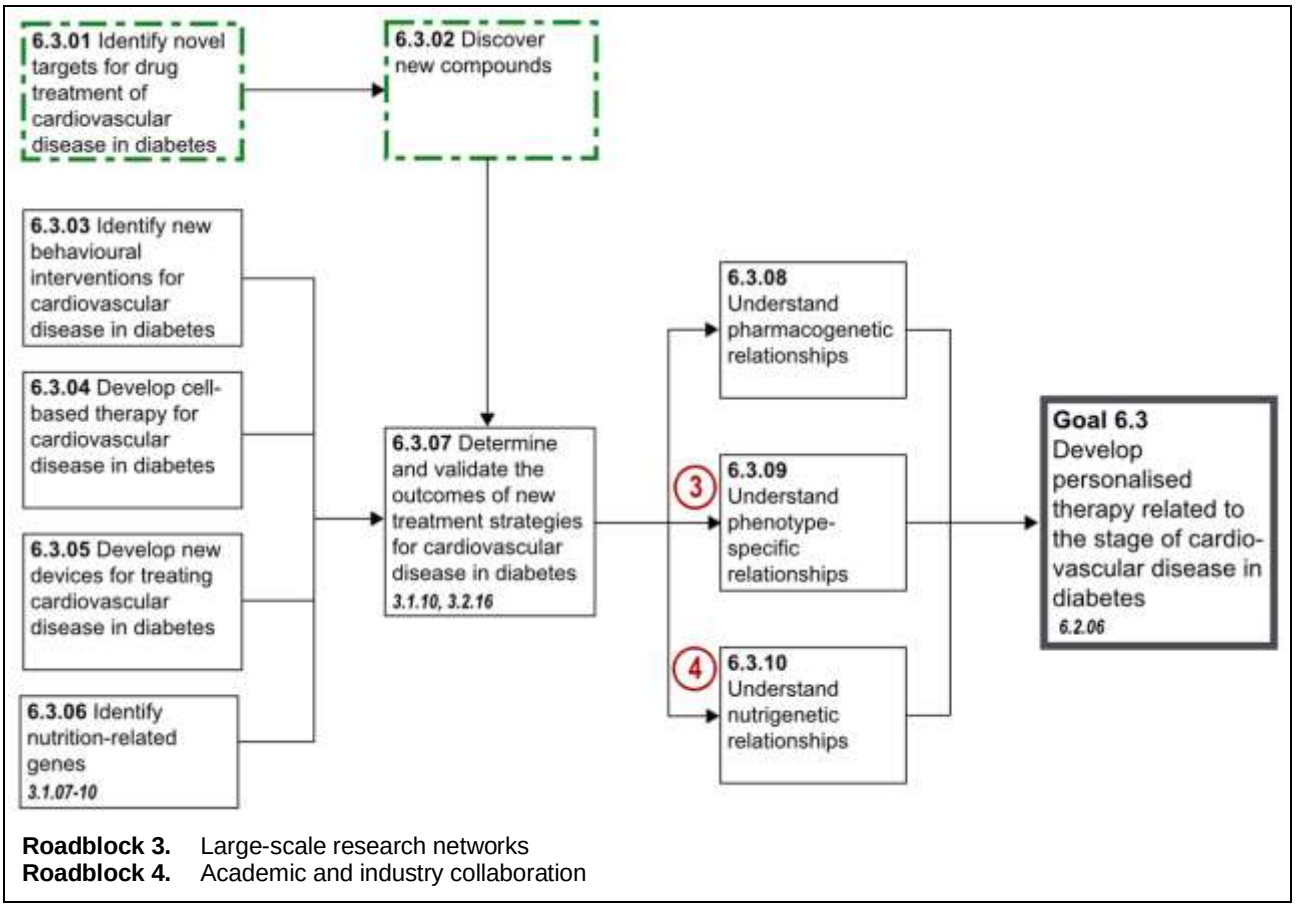
Milestone 6.2.05. Test and determine the validity of markers in early diagnosis
The main task in the evaluation of biomarkers is to undertake long-term follow-up clinical studies that will help to confirm the specificity and sensitivity of such indicators (true and false positive and negative values compared). Large long-term multicentre studies that use both genetic markers and biomarkers may produce information on time-dependent development of vascular disease. The evaluation needs to be done in a reliable number of patients providing sufficient statistical power, which cannot be obtained in a few centres alone, and several years are necessary for development of vascular changes. Genetic predisposition to vascular changes (e.g. represented by clusters of gene polymorphisms) compared to different biomarkers will provide valuable information regarding their influence on vascular wall impairment. More precise and well-validated information estimating risk of atherosclerosis development would help the patient to become involved in his/her treatment. These studies will be based on close collaboration of research groups at a European level and access to biobanks of material from well-characterised patients (*see also* Goal 4.1).

Milestone 6.2.06. Develop algorithms for early diagnosis of cardiovascular disease in diabetes
Research described in these Milestones will help scientists to find configurations of biomarkers that allow development of a scale from low to high risk. Relapsing CVD could then be evaluated with the specific view to biomarker combinations that increase the risk of vascular impairment. Grouping of metabolic, functional, structural and genetic biomarkers would contribute to recognising how this scale influences both diagnostic and therapeutic algorithms.

Before introducing general recommendations into clinical practice, diagnostic algorithms necessary for early diagnosis of macrovascular disease in

diabetes have to be developed. This process also needs to evaluate suggested biomarkers in large follow-up studies with significant statistical power at national and international levels, which will also reveal ethnic differences. Meta-analyses can help to confirm the place of the most important biomarkers in early diagnosis of macrovascular disease in patients with diabetes and their use in routine clinical practice. This will help the patient because precise diagnosis will be done earlier and more accurately than at present. Biomarkers could be used in clinical trials testing the effects of new drugs (*see also* Goal 6.3). This will create an opportunity for pharmaceutical industry research.

Goal 6.3. Develop personalised therapy related to the stage of cardiovascular disease in diabetes



Roadblock 3. Large-scale research networks
Roadblock 4. Academic and industry collaboration

Introduction and background
Successful diabetes treatment needs to restore the physiological regulation of metabolism and to normalise blood glucose concentrations, as well as to eliminate the risk factors that contribute to macrovascular disease. This cannot be achieved by currently available treatment strategies, and it is important to develop new, more effective routes to deliver treatment. This Goal will fulfil (include) both pharmacological and non-pharmacological interventions to improve quality of life and prognosis of patients with diabetes by preventing or diminishing development of CVD. New treatment strategies have to be oriented to the individual patient because individual responsiveness to treatment regimens must be taken into account.

New strategies are based on improved understanding of metabolism in diabetes and thus on modifications of metabolic impairment to become closer to the physiological state (*see also* Milestone 3.2.16). By combining efficient pharmacological/technical and non-pharmacological interventions, more effective results can be achieved. Tailored diabetes therapy may have a positive effect on other risks or co-morbidities (e.g. metformin protecting against cancer development).

Milestone 6.3.01. Identify novel targets for drug treatment of cardiovascular disease in diabetes
Metabolism is regulated by hormones and mediators acting by different target molecules (such as receptors or other binding compounds). Growth factors such as vascular endothelial growth factor are also relevant in the present context. Molecular mechanisms for a large number of currently used drugs are not yet defined. Intensive combined treatment may improve metabolic disturbance effectively with the consequence of reducing the risk of long-term vascular complications. Research to identify molecular mechanisms enables improved understanding of currently used drugs together with their interactions and side effects, as well as indicating new drug targets. More effective treatment will help the patient by preventing or reducing the risk of macrovascular disease.

Milestone 6.3.02. Discover new compounds
An improved understanding of physiological regulation including target molecules affecting metabolic pathways may open routes to discovery of new molecules. By connecting with Milestone 6.3.01, new drugs may be developed. Such research will be strongly industry based. The risks and benefits of drug therapies must first be evaluated in animal models when identification of the best compounds is carried out. More potent drugs with fewer side effects can be selected for experimental testing and then used in clinical trials. New modes of drug action will be the main area of interest. This would open new areas for research (e.g. use of new mechanisms of action) and offer more powerful treatment to the patient. Specific attention should be given to drugs for diabetes and their relationship to myocardial and vessel wall function (such as incretins, thiazolidinediones). Positive or negative effects need to be evaluated in clinical trials. Potential and/or novel CVD indications for established diabetes therapy should be identified (such as protective effects on myocardial function, protection against endothelial dysfunction).

Milestone 6.3.03. Identify new behavioural interventions for cardiovascular disease in diabetes
Non-pharmacological treatment is an integral part of any successful therapy because it significantly improves metabolic disturbances in diabetes. Addressing issues of lifestyle, diet and exercise is therefore a major challenge for clinicians and people with diabetes alike. The aim of Milestone 6.3.03 is to facilitate changes in lifestyle. Collaboration with psychologists will be necessary because their methods will enforce the effects of non-pharmacological treatment supporting further the effects of pharmacological interventions (6.3.01, 6.3.02) as well as of new technology developments (6.3.04). Better improvement of metabolic disturbance in patients with diabetes can be obtained by combining different strategies than by using pharmacological interventions alone.

Milestone 6.3.04. Develop cell-based therapy for cardiovascular disease in diabetes
New technologies may improve prognosis for patients with atherosclerosis and diabetes because they will prevent or diminish development of vascular wall changes. The properties of the vascular wall surface must be analysed in detail to identify the cells/tissue interactions. This will help to substitute the impaired layer of the endothelial/subendothelial part of the vessel wall either by artificial surfaces or by replacement of the layer with new endothelial cells. The development of new methodology and techniques is needed, thus creating new research fields. Patients would receive new opportunities for prevention and treatment of vascular disease. Investigation of vessel wall properties and metabolism is proposed at molecular/cellular/tissue levels as a basis for new cell-based therapies to be developed. This involves the *in vitro* investigation of human cell cultures, observation of cell viability and differentiation before implantation into the vessel wall, testing of cell-connective tissue interactions, safety issues including risk of tumours, etc. All these routes are new and need further research before application into human medicine. Animal experiments would therefore be the first step after *in vitro* research.

Milestone 6.3.05. Develop new devices for treating cardiovascular disease in diabetes
Established vascular changes that lead to progressive ischaemia (lack of oxygen supply to respective organ by atherosclerotically changed arteries) and eventually organ failure (e.g. heart failure) require treatment with newly developed artificial devices that can be introduced into the artery lumina in order to sustain the physiological properties of the inner vascular surfaces (e.g. new stents). Developments in technology would provide the source of the new materials (biochemically changed surfaces of the stents preventing thrombosis and atherosclerosis development). Collaboration between clinical researchers and industry may facilitate this investigation and further strengthen the research. Industry would develop and supply new materials for testing. This would facilitate development of artificial surfaces with new properties, which may improve survival as well as quality of life of the patient.

Milestone 6.3.06. Identify nutrition-related genes
Obesity expressed as a phenotype feature reflects interaction of dietary regimen with obesity genes. However, all obesity genes have not been discovered, nor has their relationship to energy intake been studied. Protective genes that prevent obesity development are still not known. Identification of gene-energy intake interactions is necessary to understand how appropriate dietary regimen may influence people with diabetes (*see also* Milestones 3.1.07-10).

Milestone 6.3.07. Determine and validate the outcomes of new treatment strategies for cardiovascular disease in diabetes
Novel drugs, new technologies and non-pharmacological interventions must be tested in properly defined and well-designed clinical studies (double-blind, multicentre, controlled) with good comparators. The FDA and EMA outcome studies related to CVD would be included. The most effective method is to design and implement

international collaborative clinical trials in order to obtain results of value; the EPCRD will be exploited for this purpose (*see also* Milestone 4.1). The results need to reach significant statistical power when determining and validating the outcomes for treatment strategies. This cannot be obtained in small pilot trials. Safety and efficacy must be addressed during the follow-up because long-term consequences determine both advantages and disadvantages of the treatment. Primary and secondary outcomes of new treatment strategies need to be evaluated with respect to long-term vascular complications (atherosclerosis) manifested by coronary, cerebral and lower limb events. These would be the main endpoints of trials involving acute myocardial infarctions, stroke, lower limb amputations, as well as death from cardiovascular causes. Such events are signals of developed atherosclerosis, and their prevention by different strategies of treatment would benefit the patient. Surrogate markers for hard cardiovascular endpoints would be used in clinical trials. This is important to shorten and focus development of novel therapies (*see also* Milestone 3.1.10 and 3.2.16).

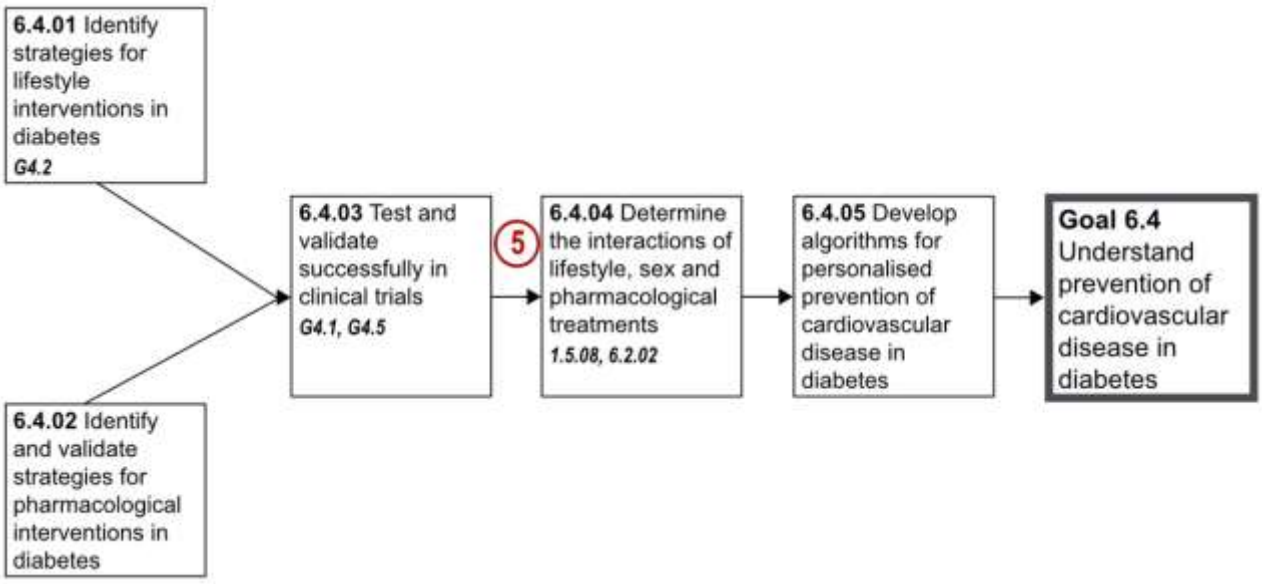
The outcomes and conclusions of such large clinical trials may influence the design of new treatment strategies, such as treatment algorithms (timing of pharmacological treatment, selection of drugs, non-pharmacological intervention such as physical activity or dietary regimen), new drug applications, intervention using new stents and by other newly developed techniques as well as their combinations. Research must determine how patients with increased risk of CVD should be treated or which strategies are most appropriate in patients with established vascular changes The resulting guidelines would provide the basis for new proposed standards of care, with a generally accepted recommendation of the treatment plan for type 1 or type 2 diabetes with or without vascular disease.

Milestone 6.3.08. Understand pharmacogenetic relationships
Individual patients respond in different ways to different drugs, and this response may be due to genetic background. Also, the optimal timing of drug administration must be ascertained to ensure successful treatment. It involves initiation of drugs at the correct time and order because currently such medication is usually performed late in the course of the disease. Identification of markers of responsiveness to treatment would aid characterisation of patients who respond best to a given treatment, and this should be considered before large-scale outcome trials are initiated (e.g. responsiveness to aspirin). The pharmacogenomic and pharmacogenetic studies would establish actual effects of the drugs, and such information would help with personalisation of treatment. Large-scale genetic studies are needed to provide the information necessary for this Milestone, which would make it possible to select the pharmacological treatment effective for the respective patient.

Milestone 6.3.09. Understand phenotype-specific relationships
Individual features of (tailored) patient-oriented therapy require evaluation, for example different phenotypes may be associated with different treatment responses. Detailed analysis would result in more reliable information on personalisation of treatment. This would require large cohorts to allow characterisation of specific profiles of different phenotypes (such as combinations of laboratory findings, body mass, arterial hypertension etc) and also ethnicity. The individual evaluation of all these parameters could provide information for selection of more reliable treatment to benefit the patient.

Milestone 6.3.10. Understand nutrigenetic relationships
Effects of nutrition, specifically meal composition, on individual responses to pharmacological treatment should be addressed by nutrigenetic studies. The gene polymorphisms may influence metabolic consequences of ingested meals. The gene-nutrition interaction will be estimated in independent studies, and the outcomes will be used for personalisation of complex treatment. The current lack of nutrigenetic data requires an exploration of the genetic contribution in nutrition-oriented studies. Such data would offer more practically oriented therapy because nutrition may significantly interfere with development of atherosclerosis. Understanding the potential for interference of nutrition-related factors with drug-specific conditions in such studies will be required. This line of research will lead to a better understanding of the most effective, tailored treatment.

Goal 6.4. Understand prevention of cardiovascular disease in diabetes



Roadblock 5. Patient and/or provider education campaigns

Introduction and background

Development of chronic vascular complications causes major problems both to people with diabetes and to health care professionals involved in their treatment and care. Complications worsen the clinical status of the patient, and therefore quality of life and life expectancy are impaired. In addition, the effect of treatment may be uncertain because of progressive development of the vascular disease. Progressive disturbance of the vessel wall ultimately leads to organ failure with increasing disability; even successful treatment fails to improve the situation over the long term. As an example, chronic heart failure causes repeated hospitalisations with worsening of breathing, fluid retention (oedema), loss of appetite and diminished interest in usual daily life activities. Therefore, prevention of atherosclerosis is the ultimate aim not only in patients with no current signs of macrovascular disease (secondary prevention) but also in patients with established atherosclerosis (tertiary prevention). Prevention may delay or diminish the development of vascular disease and also its progression.

Preventive procedures can be divided into changes to lifestyle and pharmacological intervention. These two research tracks in combination may be more effective than only one route alone; however, further research is required to provide the hard data necessary to validate effective prevention strategies for CVD in diabetes.

Milestone 6.4.01. Identify strategies for lifestyle interventions in diabetes

Lifestyle intervention is the most effective means to improve the prognosis for atherosclerosis. Sufficiently clear recommendations and guidelines already exist (American Diabetes Association and other national associations for type 1 and type 2 diabetes). Daily physical activity and reduced energy intake are known to be effective, but the majority of patients cannot achieve such goals and it is therefore necessary to develop a lifestyle intervention strategy. Sedentary lifestyle together with unbalanced hypercaloric intake is the main cause of obesity and diabetes development. In addition, they worsen insulin resistance together with hyperinsulinaemia, which are factors contributing to chronic vascular complications (atherosclerosis). The role of ethnic differences would need to be evaluated (*see also* Goal 4.2). Behavioural methods are very effective, and therefore should be developed and introduced in clinical practice, with careful research studies to validate the approach in terms of CVD outcome. The interaction between different clinical specialists (e.g. diabetologists, nutritionists, psychiatrics, angiologists) would generate new suggestions for improved quality of life in diabetes.

Milestone 6.4.02. Identify and validate strategies for pharmacological interventions in diabetes

Developing new drugs or intensifying the regimens of existing treatment is the basic tool of pharmacological intervention. It is essential that the risk factors (i.e. high blood pressure, obesity,

dyslipidaemia and others) be treated adequately. Tackling these with new drugs opens an area of research to elucidate mechanisms and intervention points leading to the prevention of atherosclerosis.

The effectiveness of combinations of different treatment strategies in reducing the risk and preventing diabetic macrovascular disease needs to be measured in animal experiments when direct investigation of the vascular wall is undertaken. Experimental studies to evaluate the influence of genetics on pharmacological intervention are needed to prevent development of initial vascular impairment. Studies of gene-drug interactions can be conducted to create new strategies for preventing macrovascular disease. Disclosure of genes with their polymorphisms may differentiate responders and non-responders to respective drugs and to estimate the reliability of the treatment. No such data are yet available. If this research is successful, the patient would then benefit from treatment to attenuate the risk factors of vascular disease before its development, representing a personalised approach to preventive medicine in this context.

Milestone 6.4.03. Test and validate successfully in clinical trials

Lifestyle changes and pharmacological intervention need to be tested in prospective follow-up studies. The effect of different approaches should be determined in large cohorts of people with diabetes. Studies of multiple drug treatments are needed to compare treatment combinations with a significant statistical power depending on sufficient numbers of patients in all arms of treatment. Therefore, patient registries and collaborations between national and international teams of investigators are needed (*see also* Goal 4.1). Validation of drug effects needs to be carried out in homogenous well-defined large groups of patients with known genetic characteristics. Selection is not useful when only a few collaborating centres participate, and therefore a wider team will be necessary. Successful results of current lifestyle and pharmacological interventions need to be examined (similar to Milestone 6.3.07). More effective treatment would improve the prognosis of patients and would be more helpful in preventing vascular disease. New data would further stimulate research in developing new strategies (e.g. drug combination, elucidation of new mechanisms of drug action).

Milestone 6.4.04. Determine the interactions of lifestyle, sex and pharmacological treatments

People with diabetes but with no vascular disease should be enrolled in clinical trials as the target population for determination of effective interventions. The goal of this investigation is to prevent vascular disease in diabetes, and therefore only patients free from any vascular changes and consequently with short diabetes duration should be selected. Specific biomarkers (*see* Milestone 6.2.02) can be used to evaluate initial vascular changes in long-term follow-up studies. The reason for analysing early changes is to confirm the effectiveness of treatment strategy in preventing vascular wall impairment. Such research would generate trials of 'secondary prevention' studying people with diabetes but without vascular complications. Those patients with existing vascular changes will be used to determine the intervention effects on prevention of organ failure. Such trials may show new potent ways/strategies to stabilise or slow-down existing vascular changes and how to prevent their further progression into organ failure (e.g. heart failure). This arm of research would thus involve studies of 'tertiary prevention'. Planned interactions with angiologists, cardiologists and large-vessel surgeons should be included in the research programme. Genetic predisposition to vascular changes (Goal 6.1) should be considered in clinical studies when the effects of intervention are determined. The experience and insight gained from the pharmacogenetic analyses can be used in follow-up studies to determine which genes increase the risk of vascular complications and thus when pharmacological intervention should be intensified. The results of this research may directly improve the patient's prognosis because such a tailored-treatment strategy should be more effective than usual, globally oriented treatment provided currently. Sex differences related to CVD prevention in males compared with (post)menopausal females should also be compared with the effectiveness of lifestyle and pharmacological intervention. Such preventive treatment would improve consequently the patient's wellbeing (*see also* Milestone 1.5.08).

Milestone 6.4.05. Develop algorithms for personalised prevention of cardiovascular disease in diabetes

Results from clinical studies of lifestyle implementation and pharmacological intervention (Milestone 6.4.04) would be used for research to pursue this final Milestone towards the Goal. Different types of intervention could be identified and their effectiveness evaluated. Large population-based studies would then be needed to elucidate which stratification of people with diabetes according to genetic and/or phenotypic data was most appropriate. Primary and secondary outcomes should be analysed by meta-analysis of large follow-up studies. Such analyses could support conclusions and development of prevention guidelines. Structured prevention planning would depend on the combination of genetic and

environmental risks being assessed. New recommendations for prevention would be based on individual characteristics used for determination of preventive treatment strategy. All necessary data (including genetic analysis, risk factors etc) would be first collected as a basis for decisions and suggestion of individual recommendations. National and ethnic specificities would be considered; however, more general recommendations from international trials would be important. Research in this area would help the patient with diabetes because treatment would be much more personalised and thus more effective than currently the case.

Roadblocks Chapter 6

Roadblock 1. Biobanks and biosample collections
No large biobanks at national or international level are available for extended genetic analyses, which are necessary to determine gene-related causes of cardiovascular disease in diabetes. This could be remedied by the proposed European Platform for Clinical Research in Diabetes (EPCRD – Chapter 4). It is supposed that multiple genes and their different combinations (as various gene mixtures) participate in development of macrovascular complications. Lack of data from large studies with adequate statistical power prevents clinicians from considering and using genetic information in clinical decisions for proper treatment.

Roadblock 2. Registries of people with diabetes
Large cross-sectional and follow-up clinical trials evaluating development of cardiovascular disease in people with diabetes need to have registries at national level. Identification of people with particular characteristics (such as genetic characteristics, risk factors) would allow for proper selection of individuals in such trials, thereby limiting heterogeneity in studied cohorts and increasing the significance of the results of these trials. Such registries would facilitate research and simplify the organisation of large cohorts with particular signs or properties (sub-groups). No such registries currently exist but they could be established in the context of the EPCRD.

Roadblock 3. Large-scale research networks
Although research networks do exist they are not sufficiently large to support national and international studies and clinical trials. Such networks would also support academic collaborations between experts and could best be set up under the auspices of the EPCRD.

Roadblock 4. Academic and industry collaboration
Scientific development needs to create focussed collaboration between academic investigators and industry that will help to apply research developments and improve the speed to which they can be put to use in the clinical environment. Independent (outside) evaluation of the results gained in academic-industry collaboration may bring more and earlier data on side effects of drugs. This includes collaboration of pharmaceutical companies in large and long-lasting clinical trials for cardiovascular endpoints, which would have to be evaluated especially if novel drugs were introduced.

Roadblock 5. Patient and/or provider education campaigns
Achieving the Goals of these road maps and transferring the knowledge to individuals may be hindered by the lack of education of people with diabetes and/or health care providers. This may slow further development in research activity. More information on the research Goals will be necessary in the diabetes community when creating groups for clinical trials. In addition, there is lack of knowledge on the importance of physical activity and dietary regimen, which may significantly modify results of treatment. The potential to improve the prognosis of the patient, including macrovascular disease, could be enhanced through education campaigns targeted at people with diabetes and providers.