INVITED REVIEW

# Glucocorticoids and Cardiovascular Disease

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## Abstract

Chronic excessive activation of glucocorticoid receptors induces obesity, insulin resistance, glucose intolerance, dyslipidaemia and hypertension. Subtle abnormalities of the hypothalamic–pituitary–adrenal axis and/or of tissue sensitivity to glucocorticoids are also associated with these cardiovascular risk factors in patients with the metabolic syndrome. Furthermore, glucocorticoids have direct effects on the heart and blood vessels, mediated by both glucocorticoid and mineralocorticoid receptors and modified by local metabolism of glucocorticoids by the 11β-hydroxysteroid dehydrogenase enzymes. These effects influence vascular function, atherogenesis and vascular remodelling following intravascular injury or ischaemia. This article reviews the systemic and cardiovascular effects of glucocorticoids, and the evidence that glucocorticoids not only promote the incidence and progression of atherogenesis but also modify the recovery from occlusive vascular events and intravascular injury. The conclusion is that manipulation of glucocorticoid action within metabolic and cardiovascular tissues may provide novel therapeutic avenues to combat cardiovascular disease.

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## Introduction

Atherosclerosis and its occlusive vascular consequences remain the most common cause of death in many parts of the world. Several risk factors for the development of atheroma are amenable to treatment, including hypercholesterolaemia, hypertension, hyperglycaemia and cigarette smoking. Secular trends show that cardiovascular disease is declining in prevalence in the developed world, and that the outcome from events such as myocardial infarction is improving, in part due to modern cardiological interventions (1). However, there is concern that the pandemic of obesity and associated metabolic syndrome threatens to reverse these secular trends. In order to make further improvements in the prevalence and outcome of occlusive vascular disease and avoid the threat posed by obesity, we will need to understand more about the complex mechanisms that promote atheromatous plaque formation and instability and determine recovery following occlusive vascular events. This review is focused on the role of glucocorticoids in atherogenesis, and highlights emerging data which suggest that manipulation of glucocorticoid action has important potential in improving the outcome of occlusive vascular disease.

## Glucocorticoid signalling and the cardiometabolic responses to stress

Glucocorticoids such as cortisol play a key role in the response to stress, including following sepsis, trauma, starvation and tissue ischaemia (2). Psychological stress can also activate the hypothalamic–pituitary–adrenal (HPA) axis, although in humans only selected psychological stimuli produce a robust increase in cortisol release. Cortisol induces a host of adaptive responses that may be homeostatic (adjusting systems to function normally in the face of a stressful environment) or allostatic (adjusting systems to function in a manner more appropriate to the stressful environment). Glucocorticoids provide a crucial 'brake' on innate inflammatory mechanisms, promoting resolution of inflammation (2). Many of these effects of glucocorticoids are relevant to cardiovascular and metabolic regulation, for example to maintain blood pressure in the face of septic shock or to promote efficient catabolism in the face of starvation.

Cortisol mediates its effects via activation of intracellular glucocorticoid receptors (GR: low affinity, type 2 corticosteroid receptors) and also mineralocorticoid receptors (MR: high affinity, type 1 corticosteroid receptors; Fig. 1A). GRs are ubiquitously expressed, but MRs are expressed only in selected tissues and at
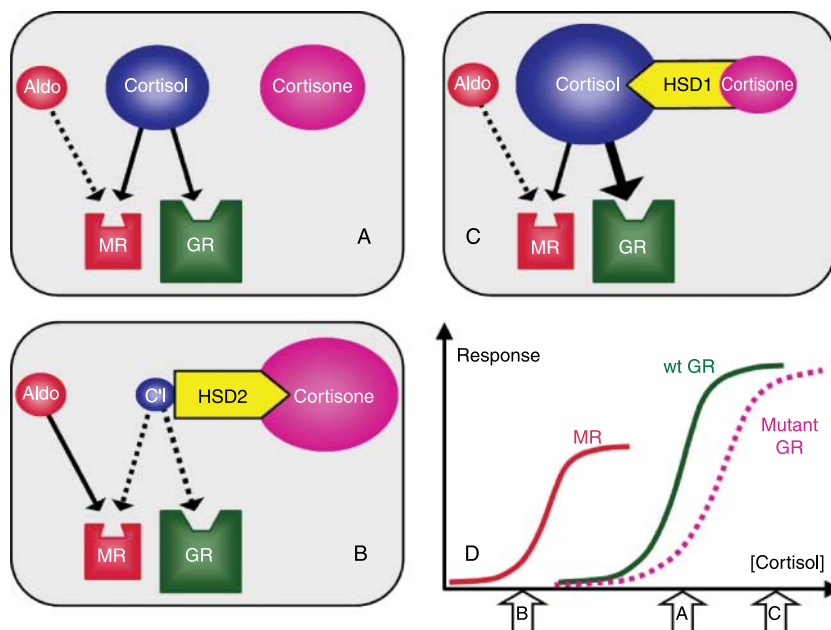
**Figure 1** A model for the influence of 11β-HSDs and GR mutants on receptor occupancy. (A) In the absence of 11β-HSDs, intracellular cortisol and cortisone concentrations reflect free concentrations in plasma, which are substantially higher than those of aldosterone (Aldo). Cortisol occupies both high-affinity low-capacity MR and low-affinity high-capacity GR. Examples include hippocampal neurones and probably myocardium. (B) In the presence of 11β-HSD2, intracellular cortisol concentrations are reduced, excluding cortisol from both MR and GR and allowing access of aldosterone to MR. Examples are in the distal nephron, colon and sweat glands and in vascular endothelial cells. (C) In the presence of 11β-HSD1, intracellular cortisol concentrations are increased. Occupancy of MR by cortisol may not increase, since capacity is limited, but occupancy of GR by cortisol is increased. Examples include vascular smooth muscle cells. 11β-HSD1 is also commonly expressed in cells which express GR but not MR, including hepatocytes, adipocytes, some areas of CNS and macrophages. (D) Tissue-specific differences in expression of 11β-HSDs may contribute to tissue-specific differences in glucocorticoid sensitivity in subjects with subtle alterations in GR (Table 1). In cells expressing 11β-HSD1 (C) or 11β-HSD2 (B), actions of GR may not be affected by a subtle shift in the dose–response curve because intracellular cortisol concentrations are at the extreme ends of the dose–response curve where the response induced by mutant GR is not markedly different from wild type.

lower levels. In some sites (such as distal nephron, colon, salivary and sweat glands and vascular endothelium), MRs bind aldosterone exclusively because cortisol is excluded by local 'pre-receptor' inactivation by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2, which converts cortisol to the inert 11-keto metabolite cortisone; Fig. 1B) (3). In other sites (classically in hippocampus and also probably in myocardium, vascular smooth muscle and adipose tissue), in the absence of 11β-HSD2, MRs are occupied by cortisol in competition with much lower prevailing concentrations of aldosterone (Fig. 1A and C). 11β-HSD1 is expressed in tissues that are important for metabolic (liver and adipose tissue), inflammatory (macrophage) and cardiovascular (vascular smooth muscle) function. 11β-HSD1 is predominantly a reductase, regenerating active cortisol from inert cortisone and thereby amplifying GR activation (Fig. 1C) (4, 5).

These classical intracellular MRs and GRs act as transcription factors on ∼30% of genes, with the pattern of response in individual cell types dictated by the enormous complexity of interactions with heterodimers, co-activators and co-repressors, and epigenetic factors including chromatin organisation. To add to this complexity, there may be a role for non-genomic

membrane receptor-mediated responses to glucocorticoids, but this remains of uncertain physiological relevance (6). Note that synthetic steroids vary in their susceptibility to metabolism by 11β-HSDs and in their binding affinities for GR and MR (7): 9α-fluorocortisol ('fludrocortisone') resists metabolism by 11β-HSD2 but retains activity at both GR and MR, prednisolone is susceptible to metabolism by 11β-HSDs but is relatively selective for GR over MR, and dexamethasone is relatively resistant to 11β-HSDs (8) and a potent selective GR agonist.

The metabolic effects of glucocorticoids in the liver, adipose tissue, pancreas and brain have been reviewed elsewhere (9–11): broadly, glucocorticoids oppose the effects of insulin and increase turnover between stored energy (in glycogen, triglycerides and protein) and freely available fuel for mitochondrial oxidation (glucose and free fatty acids). Glucocorticoids also raise blood pressure, only in part mediated by renal sodium retention and plasma volume expansion (12, 13). In addition, both GR and MR are expressed in cardiovascular tissues including the heart and arterial walls, where glucocorticoids act directly to maintain vascular tone and modify vascular inflammatory, proliferative and remodelling responses to injury (see below, reviewed in (14–16)).

# Glucocorticoids and risk factors for cardiovascular disease

During chronic activation of the HPA axis, the effects of glucocorticoids may become maladaptive (17, 18). The metabolic and cardiovascular consequences are apparent in Cushing's syndrome, which is characterised by central obesity, insulin resistance, hyperglycaemia, dyslipidaemia and hypertension. Given the similarities between Cushing's syndrome and the metabolic syndrome, subtle abnormalities of cortisol secretion and action have been sought in subjects with this constellation of risk factors for cardiovascular disease (19).

## The HPA axis

Activation of the HPA axis, with increased cortisol secretion rate and elevated morning plasma cortisol levels, has been associated with higher plasma glucose, triglycerides and blood pressure in several population-based cohort studies (20). Relationships of plasma cortisol with obesity, however, are more complex, since obesity is associated with increased metabolic clearance rate of cortisol, which tends to lower plasma cortisol levels despite enhanced cortisol production rate (20). As a result, elevated plasma cortisol and obesity have independent and additive effects in predicting cardiovascular risk factors (21, 22).

Since it was popularised by Per Bjorntorp (23), the concept has spread that central obesity and metabolic syndrome are consequences of psychosocial stress, mediated by neuroendocrine stress responses including activation of the HPA axis. However, empirical evidence is inconsistent concerning the role of psychosocial stress – and, in particular, its role as the basis for HPA axis activation – in metabolic syndrome (24, 25). An alternative hypothesis is that activation of the HPA axis is a phenomenon 'programmed' by adverse events during early life which retard fetal growth. This is supported by associations between low birth weight and elevated plasma cortisol in adulthood, both in the basal state (26–28) and in response to stress (29–31). The molecular basis for this HPA axis activation remains uncertain, although it may involve epigenetic modification affecting transcription of GR (32, 33).

## Tissue sensitivity to cortisol

In addition to control of cortisol action by the HPA axis, tissue sensitivity to cortisol may vary both between individuals and between tissues. Arguably, our understanding of the factors controlling tissue sensitivity to glucocorticoids (see above and Fig. 1) is simplistic, but we are at least beginning to understand the influence of variation in corticosteroid receptors and in pre-receptor steroid metabolism.

Simple bioassays, e.g. measuring the intensity of dermal vasoconstriction after overnight steroid application, suggest that tissue sensitivity to glucocorticoids is increased amongst subjects with cardiovascular risk factors (34–37). In part, this may be determined by variations in GR function (36). In metabolic syndrome, GR mRNA has been reported to be increased in skeletal muscle (38, 39) but not in adipose tissue (40). As detailed in Fig. 2 and Table 1, polymorphisms in the GR gene, which influence *in vitro* receptor function, have been associated with cardiovascular risk factors including - obesity (41). One might imagine that changes in GR function would not be cell-type specific, so that any change in sensitivity to cortisol in peripheral tissues would be compensated for by altered negative feedback control of the HPA axis and hence adjustment of circulating cortisol levels. Indeed, in very rare families with mutations in the GR gene causing autosomal dominant cortisol resistance, the resistance to cortisol does appear to be sufficiently uniform that the phenotype can be explained by increased ACTH secretion and hence excessive adrenal production of mineralocorticoids (11-deoxycorticosterone) and androgens (42, 43). However, the GR polymorphisms shown in Fig. 2 and Table 1 probably influence interactions between GR and other transcription factors, and may not induce uniform changes in receptor signalling; indeed, the effects may be not only tissue specific but potentially gene specific. This is exemplified in the case of the *Bcl1* polymorphism, which increases sensitivity of cortisol suppression by dexamethasone and of skin vasoconstriction by beclomethasone but paradoxically is associated with elevated plasma cortisol concentration (Table 2). Moreover, *in vitro* dose–response curves suggest that these polymorphisms are associated with subtle changes in sensitivity but not in maximum response to GR activation (44). The model in Fig. 1D illustrates that
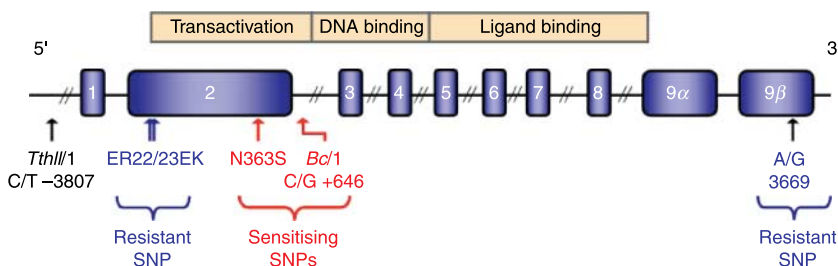


| Transactivation | DNA binding | Ligand binding |

*Tth*II/1 C/T −3807

ER22/23EK
N363S *Bc*/1 C/G +646

A/G 3669

Resistant SNP

Sensitising SNPs

Resistant SNP

**Figure 2** Common polymorphisms in the glucocorticoid receptor gene. Deleterious mutations causing autosomal dominant glucocorticoid resistance syndrome are clustered between exons 4 and 9 (not shown) and dramatically impact upon receptor binding to ligand or DNA. More common polymorphisms occur elsewhere as shown. Associated phenotypes are shown in Table 1.

**Table 1** Associations of genetic variation in the glucocorticoid receptor gene (see Fig. 2)[a] with cardiovascular risk and disease.

| | ER22/23EK | N363S | Bcl1 RFLP G allele | A/G 3669 |
|---|---|---|---|---|
| **Allele frequency in population** | ~5% | ~6% | ~35% | ~18% |
| *In vitro* glucocorticoid sensitivity | | Enhanced sensitivity to Dex in PMN cell proliferation assay (161) | No effect on GR binding or number of PMN cells (36, 161) | Impaired transrepression but normal transactivation in PMN (44) |
| *In vivo* glucocorticoid sensitivity | Resistance to Dex suppression (162) | Enhanced Dex suppression (161) | Enhanced Dex suppression (163); increased glucocorticoid-induced skin vasoconstriction (36); higher plasma cortisol (164) | Normal Dex suppression (44) |
| **Proposed molecular mechanism** | Increased GR-A:GR-B transcript ratio (165) | ? | ? | Stabilisation of dominant negative GRβ (166) |
| Phenotype | Higher lean body mass (167); insulin sensitisation (162); protective lipid profile (162); lower CRP (168); reduced mortality (168); cognitive protection (169) | Obesity in some (161, 170–173) cohorts; but not all (174, 175) dyslipidaemia (116); coronary artery disease (116) | Inconsistent with obesity (36, 163, 164, 176–180); hyperinsulinaemia in obese (181); familial hypertension (182) | No effect on CRP, obesity, hyperinsulinaemia or lipid profile (44); increase in rheumatoid arthritis (183); decrease in nasal *Staphylococcus aureus* (184) |

Dex, dexamethasone; PMN cell, peripheral blood mononuclear cell; RFLP, restriction fragment length polymorphism. ?, unknown.
[a] A TthIII/1 RFLP was also reported upstream of the promoter in association with elevated cortisol levels but no other phenotype has been found in other populations (174).

receptor occupancy and response depend upon intracellular cortisol concentrations, which, in turn, are influenced by intracellular glucocorticoid metabolism: thus, subtle variations in the GR dose–response curve may be more influential in some cells than in others, according to local expression of 11β-HSDs and whether the prevailing cortisol concentrations lie in a part of the dose–response curve which is markedly different between 'wild type' and 'mutant' GR. Since 11β-HSD1 is expressed in cells involved in negative feedback regulation of the HPA axis (45), it is conceivable that these are relatively unaffected by GR polymorphisms.

Variations in 11β-HSD activity have also been linked with risk factors for cardiovascular disease. 11β-HSD2 activity is deficient in a substantial minority of patients with essential hypertension (46, 47) and predicts salt sensitivity of blood pressure (48). 11β-HSD1 activity is increased in the adipose tissue of obese people (40, 49–58) and predicts the severity of associated metabolic complications of obesity (52, 59, 60). Inhibitors of 11β-HSD1 are in development for the treatment of type 2 diabetes and other features of metabolic syndrome, and have shown considerable promise in animal models (61–65) (see below).

The role of the HPA axis and variations in tissue sensitivity to cortisol in determining risk factors for cardiovascular disease in metabolic syndrome has been the subject of extensive research in the last decade and has been reviewed elsewhere (19, 20, 41). Less attention has been paid to the role of cortisol in determining the incidence, progression and complications of atheromatous cardiovascular disease. Although one might infer from the associations of abnormalities of the HPA axis, GR and 11β-HSD activity with cardiovascular risk factors that the same abnormalities would promote atherogenesis, this cannot be assumed since glucocorticoids also have effects within the blood vessel wall, which may modify effects mediated by systemic risk factors.

# Glucocorticoid signalling in cardio-vascular organs

Both GR and MR are expressed widely in the cardiovascular system, including in the vessel wall and myocardium (reviewed in (14–16)). GRs are also present in inflammatory cells, which invade vascular lesions, notably in macrophages (66). We have described 11β-HSD1 in vascular smooth muscle and 11β-HSD2 in the endothelium (67, 68), although this distribution may vary somewhat between species and between vascular sites ((69, 70), reviewed in (16)). Low levels of 11β-HSD1 and 11β-HSD2 have also been reported in rat and human heart (67, 71–75) and 11β-HSD1 is expressed in differentiated macrophages (76, 77). On the balance of the evidence, with reference to the model in Fig. 1, myocardial cells may follow Fig. 1A,

**Table 2** Cardiovascular effects of glucocorticoids.

| Site of action | Via glucocorticoid receptors | Via mineralocorticoid receptors |
|---|---|---|
| Vascular smooth muscle | ↑contractility e.g. to noradrenaline (185)<br>↓proliferation (138–140)<br>↓migration (141) | ↑perivascular inflammation (186)<br>↕vasoconstriction (153) |
| Endothelial cell | ↓endothelium-dependent vasodilatation (160)<br>↓angiogenesis (86, 134) | ↕vasodilatation (153) |
| Myocardium | | ↑fibrosis (133, 187) |
| Macrophage | ↕cytokines (188)<br>↑apoptosis (189)<br>↓phagocytosis of apoptotic neutrophils (66) | |
| Non-cardiovascular organs | Obesity<br>Hypertension<br>Dyslipidaemia<br>Insulin resistance<br>Glucose intolerance<br>Prothrombotic | Hypertension<br>Prothrombotic |

Published data show effects of corticosteroids to: ↑, increase; ↓, decrease; or ↕, either increase or decrease.

vascular endothelial cells may follow Fig. 1B, vascular smooth muscle cells may follow Fig. 1C, and macrophages may follow Fig. 1C (but with only GR and not MR present). There have also been sporadic reports that vascular tissue and myocardium express the enzymes necessary for *de novo* steroidogenesis from cholesterol (72, 78, 79), although the magnitude, if any, of this contribution appears to be very small.

The effects of glucocorticoids on cardiovascular tissues are summarised in Table 2, which shows diverse effects on vascular development, remodelling, tone and inflammation. There are substantial weaknesses in this field, however, since very few experiments have dissected systemic (e.g. actions in liver or kidney) from local (intravascular) effects of either glucocorticoids or mineralocorticoids, it has been difficult to recapitulate *in vivo* findings in experiments in isolated vessels *in vitro*, and the potential for occupancy of MR as well as GR by cortisol has not always been taken into account in interpretation of results.

The influence of 11β-HSDs on vascular function has been addressed using non-selective enzyme inhibitors (80–83), antisense knockdown (84) and in global 'knockout' mice (68, 85) but not yet by cell-specific manipulations of 11β-HSDs. While loss of 11β-HSD2 dehydrogenase inactivation of glucocorticoid in the endothelium was associated with enhanced vasoconstrictor responses, loss of 11β-HSD1 reductase regeneration of glucocorticoid in vascular smooth muscle did not influence vascular tone. More recent studies suggest that 11β-HSD1 influences remodelling responses in the vasculature (see below (63, 86)). In vascular cells and macrophages *in vitro*, pro-inflammatory cytokines up-regulate 11β-HSD1 expression (76, 77, 87), raising the intriguing possibility that local amplification of cortisol concentrations provides a counter-regulatory response which modifies remodelling during vascular

injury or inflammation. However, in *in vivo* studies we were unable to confirm this phenomenon (88).

Against this background, the responses to glucocorticoids within the blood vessel wall will reflect the balance between access of ligands to MR and GR, between systemic versus local effects, and between other complex determinants of receptor interaction with gene transcription and 'non-genomic' signalling alluded to above. The role of glucocorticoids in the incidence and progression of cardiovascular disease is therefore unpredictable.

# Glucocorticoids and incidence of occlusive vascular disease

## *Exogenous anti-inflammatory glucocorticoids*

Despite their effects to induce cardiovascular risk factors, studies in animals have suggested that medium-term GR-agonist therapy is atheroprotective in mice (89) and rabbits (90, 91), as judged by markers such as aortic cholesterol content or cellular proliferation indices. Conversely, aldosterone reportedly increases, and MR antagonists decrease, atherogenesis in mice (92, 93). Further, glucocorticoid excess may promote calcification within arteriosclerotic lesions (94). In humans, a major concern has been that anti-inflammatory glucocorticoid therapy induces atherogenesis in patients with inflammatory diseases (95, 96). Indeed, there appears to be a dose–response relationship between cumulative exposure to glucocorticoids and the prevalence of carotid artery atheroma visualised by ultrasound amongst patients with rheumatoid arthritis (97). It has been difficult, however, to confidently dissect effects of glucocorticoids from those of the underlying inflammatory disease, which may itself be pro-atherogenic.

Glucocorticoid therapy for inflammatory disease was adopted before the era of randomised controlled trials

(RCTs). Although some short-term RCTs have been conducted for example to assess efficacy of low-dose glucocorticoids as disease modifiers in early rheumatoid arthritis (98), it seems certain that RCTs will never be conducted which have sufficient statistical power and duration of exposure to detect effects of glucocorticoids on cardiovascular events. It would be considered unethical to withhold glucocorticoid therapy from patients with inflammatory disease, and unethical to expose patients who do not need anti-inflammatory therapy to the known adverse effects of glucocorticoids (fractures, hyperglycaemia, etc.) (98). In the absence of RCTs, the next best approach is by pharmacoepidemiology. Since glucocorticoids are one of the most commonly prescribed classes of drugs, they lend themselves to this approach. We have conducted two studies to examine the relationship between glucocorticoid therapy and cardiovascular events, making use of the data collected in the universal National Health Service in the UK (99, 100).

The first study was conducted using a case–control design comparing > 50 000 patients with cardiovascular disease and the same number of matched controls in the General Practice Research Database in England (99). In order for data to be collected, participants needed to be in contact with their primary care physician (general practitioner). For this reason, the study was conducted amongst patients who were all receiving glucocorticoid therapy of some kind, and the analysis compared doses of glucocorticoids received in the two groups. The odds ratio for use of oral glucocorticoid therapy (rather than topical or inhaled glucocorticoid therapy) in the group with cardiovascular disease was 1.31 (95% confidence intervals 1.21–1.29).

The second study was conducted using a population-based cohort design in > 150 000 residents of the Tayside region in Scotland (100) for whom data were collected in the Medicines Monitoring Unit for all drugs prescribed (which are identifiable because all pharmacy dispensing is recorded) and for morbidity and mortality from a variety of integrated databases. The rate of incident cardiovascular disease was ~17/1000 patient-years in subjects not exposed to glucocorticoids but rose to ~24/1000 patient-years in subjects treated with glucocorticoids by any route. Once adjusted for confounders (Fig. 3), the excess cardiovascular risk was entirely attributable to the relatively small group (~2% of the population) exposed to supraphysiological doses of glucocorticoids (>7.5 mg prednisolone or its equivalent each day), in whom the adjusted relative risk of cardiovascular events was 2.56 (2.18–2.99).

Although the primary end point of these studies was the occurrence of any cardiovascular event, we also examined rates of different events. Notably, glucocorticoids were most strongly associated with occurrence of heart failure and least strongly with cerebrovascular disease events (99, 100). This finding is consistent with the suggestion that glucocorticoids impair recovery from ischaemic
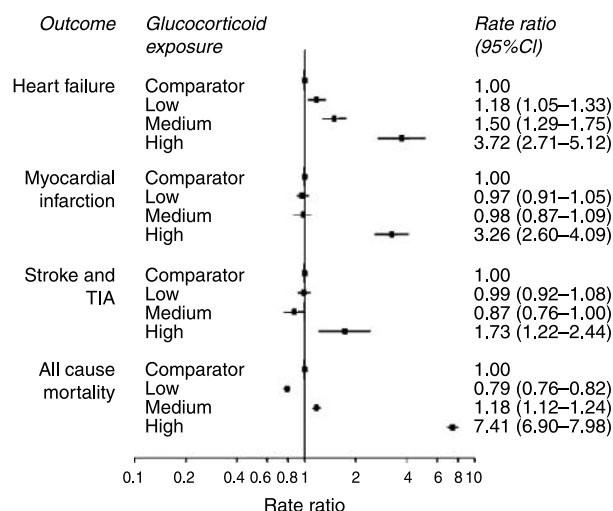


| Outcome | Glucocorticoid exposure | | Rate ratio (95%CI) |
|---|---|---|---|
| Heart failure | Comparator | | 1.00 |
| | Low | | 1.18 (1.05–1.33) |
| | Medium | | 1.50 (1.29–1.75) |
| | High | | 3.72 (2.71–5.12) |
| Myocardial infarction | Comparator | | 1.00 |
| | Low | | 0.97 (0.91–1.05) |
| | Medium | | 0.98 (0.87–1.09) |
| | High | | 3.26 (2.60–4.09) |
| Stroke and TIA | Comparator | | 1.00 |
| | Low | | 0.99 (0.92–1.08) |
| | Medium | | 0.87 (0.76–1.00) |
| | High | | 1.73 (1.22–2.44) |
| All cause mortality | Comparator | | 1.00 |
| | Low | | 0.79 (0.76–0.82) |
| | Medium | | 1.18 (1.12–1.24) |
| | High | | 7.41 (6.90–7.98) |

0.1  0.2  0.4 0.6 0.81  2  4  6 8 10
Rate ratio

**Figure 3** Cardiovascular disease risk in patients receiving anti-inflammatory glucocorticoid therapy. In a population-based cohort study, the incidence of cardiovascular events was recorded in 68 781 adults >40 years old receiving therapy with glucocorticoids and 82 202 adults not receiving glucocorticoids during a 4-year follow-up period. Daily glucocorticoid dose was quantified as low (inhaled, nasal and topical steroid only), medium (oral, rectal or parenteral doses <7.5 mg prednisolone equivalent per day) or high (≥7.5 mg prednisolone equivalent per day). The rate ratio is shown after adjustment for age, sex, social deprivation, diabetes mellitus, use of cardiovascular drugs, non-cardiovascular hospitalisation, cancer, renal disease and use of anti-rheumatic and bronchodilator therapy. Reproduced with permission from (100). TIA, transient ischaemic attack.

events, for example by inhibiting collateral angiogenesis and/or by increasing myocardial fibrosis (see below).

The greatest limitation of the pharmacoepidemiological approach is 'confounding by indication', i.e. the possibility that the risk is attributable to the underlying disease being treated rather than to the use of glucocorticoids. In both of our studies (99, 100), effects were consistent across different disease indications. Adjustment for smoking did not substantially attenuate the effect of glucocorticoids. However, in other studies involving cohorts of patients with rheumatoid arthritis, there is some evidence of interactions between effects of glucocorticoids and the underlying inflammatory disease on cardiovascular risk. In a Canadian cohort of > 40 000 subjects, no excess risk of heart failure with glucocorticoid exposure was identified (101). In a smaller US cohort, a dose-dependent risk of cardiovascular disease with glucocorticoid exposure was confirmed, but was only detectable amongst rheumatoid factor-positive patients (102). Studies in other disease groups have probably been too small to be confident of their findings. For example, in one cohort (*n* = 136) of polymyalgia/giant cell arteritis patients, glucocorticoid therapy predicted increased cardiovascular risk (103), but in another cohort (*n* = 364) this effect was not seen (104).

Intriguingly, adjustment for the presence of components of the metabolic syndrome (hypertension, diabetes mellitus and dyslipidaemia) did not eliminate

the effect of glucocorticoids (99, 100, 103), raising the possibility that the influence of glucocorticoids on cardiovascular outcome is not mediated exclusively by known cardiovascular risk factors and might be aggravated by actions in the blood vessel wall.

### Exogenous glucocorticoid replacement therapy

Although representing a small minority of patients being treated with glucocorticoids, in endocrinology practice we are concerned with patients with hypopituitarism or adrenocortical failure receiving replacement doses of glucocorticoids. The most commonly used steroids for replacement therapy are cortisol (hydrocortisone) or the pre-hormone cortisone (which is 'activated' to cortisol by 11β-HSD1 on first pass through the liver). Notably, replacement therapy usually involves non-selective GR/MR agonists (cortisol), by contrast with anti-inflammatory therapy, which usually involves selective GR agonists (prednisolone, etc). The pharmacokinetics of cortisol, which has high bioavailability and a short half-life (∼90 min), makes it impossible to replicate physiological circulating cortisol levels (105), especially since the normal peak of circulating cortisol occurs in advance of waking each morning. In order to achieve sufficiently prolonged effects after each dose, without excessively frequent daily dosing, most patients take doses that induce a supraphysiological level for the first hour or two after dosing. There is evidence from measurement of total cortisol metabolite excretion in urine that these 'standard' daily doses are supraphysiological (106), and indeed there is a dose-dependent risk of associated cardiovascular risk factors including obesity and dyslipidaemia (107). By comparison with 'reference' values in the population, cardiovascular event rates are reported to be higher in patients with hypopituitarism (108–111) and adrenocortical insufficiency (112). Although there may be several endocrine factors at play, it is plausible to attribute this excess to supraphysiological glucocorticoid therapy.

### Endogenous glucocorticoids

As described previously, many studies have reported associations between dysfunction of the HPA axis and risk factors for cardiovascular disease in the population. However, data are only now emerging concerning associations between the HPA axis and the occurrence of atheromatous disease. These studies are hampered by the lack of simple measures of HPA axis function which can be applied in large epidemiological studies. Most investigators have relied on fasting plasma cortisol levels, a crude index of HPA axis function. In the Caerphilly Heart Study, Davey-Smith *et al.* (113) reported a positive association between the plasma cortisol/testosterone ratio and incident vascular disease; cortisol alone was not an independent predictor. In smaller studies, higher plasma cortisol has also been

associated with the extent of atheromatous disease quantified by coronary angiography (114), and predicted mortality in patients with heart failure (115). Polymorphisms in the GR gene have recently been associated with cardiovascular event rate in population-based studies in Rotterdam (SWJ Lamberts, personal communication) and Sydney (116) (Table 1).

In spontaneous Cushing's syndrome, few investigators have accumulated sufficient numbers of patients to generate meaningful data on cardiovascular events. However, intermediate markers, such as carotid intima–media thickness, are abnormal in these patients (117) even after the removal of the tumour responsible for glucocorticoid excess (118).

### Reducing glucocorticoid action and atheroprotection

Given the association of elevated glucocorticoid action with obesity, cardiovascular risk factors and occlusive vascular disease events, it seems attractive to seek to reduce glucocorticoid action in order to prevent cardiovascular disease. It appears that simultaneous reduction of both GR and MR activation by glucocorticoids has most to offer (Table 2). With respect to reducing GR-dependent signalling, the challenge has been to reduce glucocorticoid action selectively in the blood vessel wall and/or in metabolically important tissues such as liver and adipose tissue, without: i) impairing negative feedback control of the HPA axis, producing compensatory hypercortisolaemia; ii) reducing glucocorticoid action in immune cells, producing a pro-inflammatory state; or iii) preventing an effective cortisol response during stress. Agents that inhibit cortisol biosynthesis or antagonise ligand binding to GR (119, 120) are likely to fall at one of these hurdles. However, inhibition of the cortisol-generating enzyme 11β-HSD1 may be safe and successful (4, 61). Since the enzyme is predominantly expressed in liver and adipose tissue and is also present in vascular smooth muscle, inhibitors may have disproportionately greater effects on metabolism and cardiovascular disease progression than on the HPA axis and the immune system. Moreover, during stress, although 11β-HSD1 inhibitors will reduce the component of intracellular cortisol derived from local regeneration, they should not prevent 'flooding' of the cell by cortisol from the circulation during significant hypercortisolaemia.

Selective 11β-HSD1 inhibitors have recently been developed and tested in rodents (62–65). In models of obesity and type 2 diabetes, they improve blood glucose, dyslipidaemia, hepatic steatosis, central obesity and insulin sensitivity. Most importantly, in ApoE-deficient mice 11β-HSD1 inhibition produces very striking protection from aortic cholesterol accumulation on Western high-fat diet, which was disproportionate to the improvement in serum lipid profile, suggesting a potent atheroprotective effect potentially mediated in the

blood vessel wall (63). 11β-HSD inhibitors are now being evaluated in early clinical trials.

## Glucocorticoids and outcomes from occlusive vascular disease

The role of glucocorticoids in occlusive cardiovascular disease may not be limited to promoting the development and progression of atheroma. Glucocorticoids may also influence the outcomes after plaque rupture, thrombotic occlusion and other vascular injury.

### Recovery from myocardial infarction

Given their anti-inflammatory effects, glucocorticoids have been proposed to be useful in reducing tissue damage after myocardial infarction (122). However, as noted above, the mechanisms of glucocorticoid action are complex. On one hand, acute induction of endothelial nitric oxide synthase, putatively through 'non-genomic' effects of GR, may be protective after both myocardial infarction (123) and cerebral ischaemia (124) in mice. Similarly, glucocorticoids may reduce tissue damage during cardiopulmonary bypass (125), coronary ischaemia (126) and renal ischaemia (127). On the other hand, glucocorticoids may limit tetrahydrobiopterin availability as cofactor for nitric oxide synthesis (128), potentially promoting synthesis of damaging reactive oxygen species rather than protective nitric oxide (129, 130). Glucocorticoids may also adversely influence longer term remodelling of the myocardium following infarction. MR-mediated fibrosis in the myocardium has received a great deal of attention since the randomised Aldactone evaluation study (RALES) and Eplerenone post acute myocardial infarction heart failure efficacy and survival study (EPHESUS) studies demonstrated the benefits of MR antagonists in patients with heart failure (131, 132). Although 11β-HSD2 has been described in human heart (72–75), its cellular distribution and magnitude of activity remain uncertain: it is likely to be insufficient to exclude cortisol from access to MR. Therefore, it may be cortisol rather than aldosterone which occupies MR in the myocardium (Fig. 1A) and influences fibrotic responses (133). In addition, GR activation prevents angiogenesis (86, 134, 135), a key process in the recovery from infarction which ensures collateral circulation and reperfusion. Administration of glucocorticoids beyond the first few days after infarction might be predicted to impair reperfusion.

A number of clinical trials have been undertaken to test the effects of glucocorticoids administered in the first few days after myocardial infarction. Most of these were conducted in the 1970s with suboptimal methodology, but a recent meta-analysis suggests a small beneficial effect on mortality (136). The increased incidence of heart failure amongst glucocorticoid users in the pharmacoepidemiology studies described above (99, 100, 137), however, raises the possibility that longer term glucocorticoid therapy has an adverse effect on vascular remodelling.

While anti-angiogenic therapy may have a role in oncology and in treating ischaemic retinopathies, pro-angiogenic therapy has been sought to improve collateral revascularisation following ischaemia and infarction. Since glucocorticoids inhibit angiogenesis and 11β-HSD1 regenerates glucocorticoids within blood vessels, we recently tested the hypothesis that loss of 11β-HSD1 would enhance angiogenesis (86). We found that 11β-HSD1 null mice exhibit enhanced angiogenesis in isolated aortic rings, in sponges inserted subcutaneously, in surgical wounds, and in the myocardium following coronary artery ligation and myocardial infarction. This was associated with improved recovery from infarction as judged by left ventricular ejection fraction (Fig. 4).

### Recovery from intravascular injury

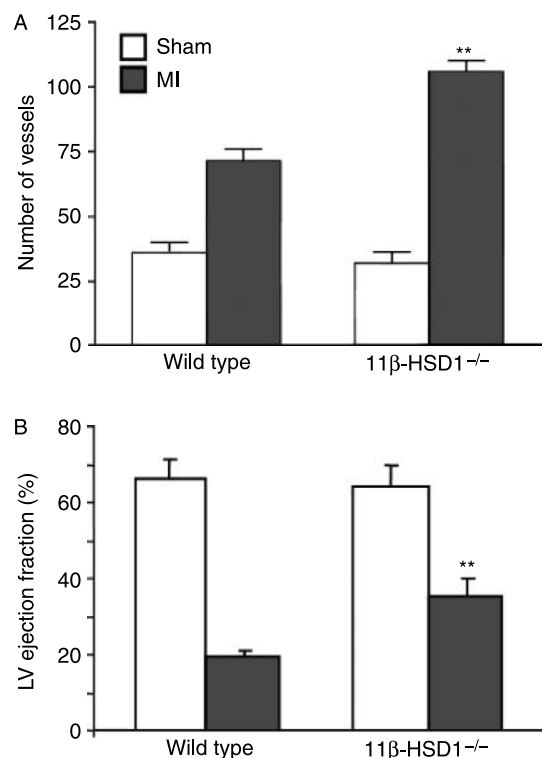One of the reasons for improved survival from cardiovascular disease is the advent of intravascular



**Figure 4** Amplification of myocardial angiogenesis and protection from left ventricular dysfunction in 11β-HSD1$^{-/-}$ null mice. Mice were studied 7 days after coronary artery ligation to induce a myocardial infarction (MI, shaded bars) or sham surgery (open bars). (A) Myocardial vessels were identified at light microscopy *in vitro* by von Willebrand factor immunohistochemistry. (B) Left ventricular ejection fraction was quantified by transthoracic echocardiography *in vivo*. 11β-HSD1$^{-/-}$ null mice had increased angiogenesis and were protected from left ventricular dysfunction induced by coronary artery ligation. **$P < 0.01$ versus wild type. Adapted from (86).

interventions, including balloon angioplasty (1). A major limiting factor following such procedures, however, is the occurrence of early restenosis in which vascular smooth muscle neo-intimal proliferation is prominent. Similar pathological processes may also be relevant in the spontaneous formation of occlusive plaques. On the basis that glucocorticoids are anti-inflammatory and have anti-proliferative (138–140) and anti-migratory (141) effects on smooth muscle cells, they have been employed to prevent restenosis (16, 142). Systemic administration was effective in many animal models (reviewed in (16)). However, in clinical trials, glucocorticoids have been successful in some (143–146) but not all (147–151) studies. A likely explanation for discrepant results is that the benefits of local anti-inflammatory effects in the injured blood vessel are offset by adverse systemic effects. Alternatively, the observation that MR antagonists also reduce neo-intimal lesion formation (152) suggests that the anti-inflammatory effects of GR activation may be offset by pro-inflammatory MR activation (153). To overcome these limitations, glucocorticoid-eluting stents have been proposed to deliver local anti-inflammatory therapy (154–156) using glucocorticoids devoid of affinity for MR, such as dexamethasone and prednisolone (7). However, there remains the risk that GR may induce changes within the vessel which offset any benefit of conventional anti-inflammatory effects, for example by increasing local angiotensin II (157, 158) or endothelin-1 (159) generation or by decreasing endothelial nitric oxide generation (160).

## Conclusions

The evidence reviewed above suggests that glucocorticoid excess not only induces cardiovascular risk factors, but also hastens the incidence and progression of atheromatous vascular disease. This probably reflects the combined effects of systemic and local vascular actions of glucocorticoids. Systemic effects are mediated through GR activation in liver, adipose tissue, pancreas and muscle; MR activation in kidney may also be involved in people with impaired 11β-HSD2 activity. Local effects in the blood vessel wall and myocardium are mediated by both GR and MR and modified in a cell-specific pattern by 11β-HSD1 and 11β-HSD2. These local effects may influence not only atherogenesis but also the outcomes of vascular occlusion and injury. They may be both protective (preventing neointimal proliferation via GR) and adverse (preventing angiogenesis via GR and promoting perivascular inflammation and myocardial fibrosis via MR). It is probable that cortisol is the principal ligand occupying MR in cardiovascular tissues, so that the focus on the renin–angiotensin–aldosterone axis in interpreting the clinical benefits of MR antagonists is arguably misplaced. In addition to MR antagonism, inhibition of 11β-HSD1 provides a route to prevent both

MR and GR activation in many tissues including liver, adipose tissue and vascular smooth muscle. The net effect of 11β-HSD1 inhibition appears to be atheroprotective and beneficial after myocardial infarction in mice. These findings offer the promise of therapeutic potential for tissue-specific manipulation of glucocorticoid action in the prevention and treatment of cardiovascular disease in humans.

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