Why is soluble intercellular adhesion molecule-1 related to cardiovascular mortality?

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Abstract

Background Increased plasma levels of soluble adhesion molecules are associated with an increased risk of atherothrombosis. The pathophysiological mechanisms responsible for these associations are not known. The aim of the present study was to investigate the association of soluble intercellular adhesion molecule-1 (sICAM-1) concentration and risk of cardiovascular and all-cause mortality among individuals with and without type 2 diabetes. In addition, we assessed potential pathophysiological mechanisms by which sICAM-1 may promote mortality.

Materials and methods Six hundred and thirty-one subjects taken from a general population of the middle-aged and elderly participated in this prospective cohort study. Baseline data collection was performed from 1989 to 1992; subjects were followed until 1 January 2000.

Results Subjects who died had higher levels of sICAM-1 than those who survived ($506(164)$ vs. $477(162)$ ng mL^{-1}, respectively). After adjustment for age, gender and glucose tolerance status, subjects with sICAM-1 levels in the upper quartile (≥ 550 ng mL^{-1}) had a relative risk of cardiovascular mortality of $2 \cdot 05$ (95% confidence interval, $1 \cdot 10$–$3 \cdot 81$) compared to subjects with sICAM-1 levels in the other quartiles. Further adjustment for classical cardiovascular risk factors or indicators of (sub)clinical atherosclerosis, endothelial dysfunction, inflammation and renal function did not materially alter this relative risk. A high sICAM-1 level was more frequent in subjects with type 2 diabetes than in subjects with a normal glucose tolerance ($33 \cdot 3$ vs. $17 \cdot 8\%$).

Conclusions Individuals with a plasma concentration of sICAM-1 higher than 550 ng mL^{-1} had a cardiovascular mortality risk that was twice that of individuals with a lower concentration. Classical cardiovascular risk factors (sub)clinical atherosclerosis, endothelial dysfunction and inflammation do not explain this excess risk.

Keywords Cardiovascular mortality, pathophysiological mechanisms, soluble intercellular adhesion molecule-1, type 2 diabetes

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Introduction

Interactions of endothelial cells and leucocytes play an important role in leucocyte recruitment and are mediated by adhesion molecules. Leucocyte recruitment and subsequent transmigration into the arterial intima are early features of atherosclerosis [1,2]. Besides selectins, membrane-bound intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) contribute to the adhesion of leucocytes to endothelium activated in response to inflammatory cytokines [3]. Soluble forms of some adhesion molecules are found in plasma; they are shedded cell membrane ligands and may therefore be used as a monitor of adhesion molecule expression [4,5]. Previous studies have shown an increased cellular adhesion molecule expression in several components of the athero-sclerotic plaque and a positive association of increased plasma levels of soluble (s) ICAM-1 with carotid intimal-medial thickness and cardiovascular mortality [6–8]. The pathophysiological mechanisms linking increased plasma sICAM-1 to atherothrombosis are unknown. Chronically increased levels may reflect progressive formation of atherosclerotic lesions [9]. In addition to its role in cell–cell adhesion, ICAM-1 also serves as a receptor for soluble fibrinogen, which suggests a role for ICAM-1 in throm-bosis [10]. High glucose levels enhance the expression of ICAM-1 on endothelial cells *in vitro* [11]. In a cross-sectional study, levels of sICAM-1 were shown to be higher among individuals with type 2 diabetes than among nondiabetic individuals [12]. ICAM-1 may therefore play a role in the accelerated macroangiopathy that is present in individuals with type 2 diabetes [12].

The aim of the present study was to investigate the association of sICAM-1 concentration and risk of cardi-ovascular and all-cause mortality among individuals without and with type 2 diabetes in a prospective population-based cohort study. In addition, we assessed potential pathophysiological mechanisms by which sICAM-1 may increase mortality. Specifically, we assessed whether sICAM-1 reflects (sub)clinical atherosclerosis (as assessed by the ankle-brachial pressure index and the presence of cardiovascular disease); endothelial dysfunc-tion [as reflected by the plasma concentration of von Willebrand factor and (micro)albuminuria]; chronic low-grade inflammation (as reflected by the plasma concen-tration of C-reactive protein and sVCAM-1) or a general increase in the expression of adhesion molecules (as reflected by the plasma concentration of sVCAM-1).

Methods

General study design

The study was performed in the Hoorn Study (the Netherlands), a population-based cohort study of glucose tolerance in a Caucasian population, conducted from October 1989 to February 1992, as described in detail before [13,14]. Briefly, a random sample of all men and women aged 50–75 was drawn from the municipal population registration office of Hoorn; 2484 individuals participated (response rate 71%). The present study population is an age-, sex- and glucose-tolerance-stratified random subsample ($n = 631$; response rate 89·1%), in whom an extensive cardiovascular investigation was performed.

Baseline investigations

SICAM-1

Concentrations of sICAM-1 were assessed in duplicate in deep frozen ($-70\,^{\circ}C$) heparin plasma samples. No plasma was available for 23 subjects. Concentrations of sICAM-1 were measured using enzyme-linked immuno-sorbent assay (ELISA) kits [Bender MedSystems, Wenen, Austria (Cat. no. BMS241)]. According to the manu-facturer, the intra- and interassay coefficients of variation for the assay were 5·6% and 7·8%, respectively.

Other measurements

We obtained an ankle-brachial blood pressure index ($n = 631$) and a resting electrocardiogram ($n = 625$) [13,14]. Subjects were classified as having cardiovascular disease when they had a history of myocardial infarction and/or had an electrocardiogram with a Minnesota code 1·1–1·3, 4·1–4·3, 5·1–5·3, or 7·1 and/or had undergone coronary bypass surgery or angioplasty, and/or had an ankle-brachial pressure index less than 0·9 in either leg and/or had undergone a peripheral arterial bypass or amputation. Furthermore, we obtained data on blood pressure, weight, height, body mass index, waist-to-hip ratio and smoking habits, glycated haemoglobin, use of diabetes medication and serum creatinine, homocysteine, total cholesterol, high-density lipoprotein cholesterol and triglyceride, and urinary albumin and creatinine levels [14–16]. Hypertension was defined as a blood pressure ≥ 160 mmHg systolic and/or ≥ 95 mmHg diastolic and/or the current use of antihypertensive medication. Subjects were classified as current cigarette smokers or nonsmokers. Creatinine clearance was calculated by the Cockroft–Gault formula [16], and the glomerular filtration rate was calculated according to Levey *et al.* [17] (Micro)albumi-nuria was defined as an albumin-to-creatinine ratio $> 2·0$ mg mmol^{-1} [14]. Concentrations of sVCAM-1, von Willebrand factor and C-reactive protein were assessed as previously described [18,19].

Follow-up

Data on the subjects' vital status on 1 January 2000 were collected from the mortality register of the municipality of Hoorn. Of 51 subjects who had moved out of town, information on vital status was obtained from the new local municipalities. For each subject, we determined

whether or not death had occurred during follow-up, and if so, the date at which death occurred. For all subjects who had died, the cause of death was extracted from the medical records of the general practitioner and the hospital of Hoorn and classified according to the ninth edition of the International Classification of Diseases [20]. Cardiovascular mortality was defined as codes 390–459 and cancer mortality as codes 140–240. Information on cause of death could not be obtained for 16 (15%) of the deceased subjects and one subject was lost to follow-up.

The Hoorn Study was approved by the Ethical Review Committee of the University Hospital Vrije Universiteit. Written informed consent was obtained from all participants.

Statistical analyses

The associations between sICAM-1 levels and classical cardiovascular risk factors (such as smoking and hypertension) and risk indicators [such as (micro)albuminuria and C-reactive protein and von Willebrand factor levels] were tested by linear regression analyses with sICAM-1 levels as dependent variable and risk factors or indicators as independent variables, all adjusted for age, sex and glucose tolerance status (unless this was the variable under consideration). To assess associations of cardiovascular risk factors and risk indicators with risks of cardiovascular and all-cause mortality, we performed Cox proportional hazards multiple regression analysis, in all cases – because of the stratification procedure – with adjustment for age, sex and glucose tolerance status. Results are described as relative risks (hazard ratios) with 95% confidence intervals. Survival over the follow-up duration was calculated by Kaplan–Meier curves for different groups and differences were tested by the logrank test.

Risk factors and indicators measured on a continuous scale were used as such in the regression models, except for levels of high-density lipoprotein cholesterol, C-reactive protein and von Willebrand factor, and body mass index and waist-to-hip ratio, because the association of these variables with mortality was nonlinear. Therefore, a low level of high-density lipoprotein cholesterol was defined as a level below $0 \cdot 9$ mmol L^{-1} [21], a high level of von Willebrand factor or C-reactive protein was defined as a level in the upper tertile ($> 1 \cdot 56$ IU mL^{-1} and $> 2 \cdot 84$ mg L^{-1}, respectively [19]), obesity as a body mass index above 27 kg m^{-2} for men and above 26 kg m^{-2} for women [22], and a high waist-to-hip ratio as a waist-to-hip ratio above $0 \cdot 95$ for men and above $0 \cdot 80$ for women [23]. Levels of triglyceride were log-transformed because of a better fit to the regression model.

To assess the associations of plasma sICAM-1 concentration with cardiovascular and all-cause mortality, we performed Cox proportional hazards multiple regression analyses. Because preliminary analyses and a previous study [8] suggested a nonlinear association between sICAM-1 and cardiovascular death, we divided the subjects into quartiles ($n = 152$) according to their sICAM-1 concentration. We calculated relative risks for subjects in the highest

quartile (above 550 ng mL^{-1}) with subjects in the lower three quartiles as the reference group. In the first model, we adjusted for the stratification variables age, sex and glucose tolerance. In subsequent models, we added one or more potentially confounding risk factors, such as hypertension, *or* risk indicators, specifically (micro)albuminuria and levels of sVCAM-1, von Willebrand factor and C-reactive protein. Two-sided P-values less than $0 \cdot 05$ were considered statistically significant.

Results

Table 1 (the two columns on the left) shows the baseline characteristics of the study population. Figure 1 shows the percentage of subjects with a sICAM-1 level in the highest quartile (> 550 ng mL^{-1}) by glucose tolerance status. A high sICAM-1 level was more frequent in subjects with type 2 diabetes than in subjects with a normal glucose tolerance ($33 \cdot 3$ vs. $17 \cdot 8\%$). The median (interquartile range) of sICAM-1 levels was 467 (376–550) ng mL^{-1} in the whole group, 443 (367–522) ng mL^{-1} in those with a normal glucose tolerance, 471 (363–570) ng mL^{-1} for those with an impaired glucose tolerance, and 492 (407–610) ng mL^{-1} in those with diabetes.

The mean duration of follow-up was $8 \cdot 2$ years (standard deviation: $2 \cdot 0$ years). During follow-up, 117 (54 with type 2 diabetes) of the 631 subjects died, of whom 45 (38%; 23 with type 2 diabetes) died of cardiovascular disease. Subjects who died had higher levels of sICAM-1 than those who survived (506(164) vs. 477(162) ng mL^{-1}, respectively). Table 1 (three columns on the right) shows relative risks of mortality associated with risk factors and risk indicators.

Associations of sICAM-1 level with cardiovascular risk factors and indicators

Table 2 shows which cardiovascular risk factors and indicators were significantly associated with sICAM-1 levels after adjustment for age, sex and glucose tolerance status (unless this was the variable under consideration).

SICAM-1 level and risk of mortality

Cardiovascular mortality was markedly higher among subjects with sICAM-1 levels in the upper quartile than among subjects with sICAM-1 levels in the lower quartiles (Fig. 2). This figure also shows that the relationship between sICAM-1 and cardiovascular mortality was non-linear. Table 3 shows that, after adjustment for age, sex and glucose tolerance status, subjects with sICAM-1 levels in the upper quartile (≥ 550 ng mL^{-1}) had a relative risk of cardiovascular mortality of $2 \cdot 05$ (95% confidence interval, $1 \cdot 10 - 3 \cdot 81$) compared to subjects with sICAM-1 levels in the three lower quartiles. Further adjustment for risk factors or risk indicators of cardiovascular disease did not materially

Table 1 Baseline characteristics and relative risk of cardiovascular and all-cause mortality associated with risk factors or risk indicators

Risk factor or indicator	All subjects ($n = 631$)	Contrasts for which relative risk is presented	Cardiovascular mortality RR (95% CI)*	All-cause mortality RR (95% CI)*
Male gender (%)	48	yes vs. no	1·49(0·82–2·71)	1·63(1·13–2·36)
Age (year)	64 ± 7	per 5 years increase	1·85(1·42–2·41)	1·63(1·40–1·90)
Type 2 diabetes (%)	27	yes vs. no	3·14(1·56–6·36)	2·56(1·67–3·93)
Hypertension (%)	39	yes vs. no	2·79(1·41–5·51)	1·74(1·18–2·56)
Current smokers (%)	28	yes vs. no	1·54(0·79–2·99)	1·67(1·12–2·49)
Body mass index (kg m^{-2})	27·2 ± 4·0	high vs. low‡	2·07(1·03–4·18)	1·43(0·95–2·17)
Waist-to-hip ratio	0·92 ± 0·09	high vs. low§	1·58(0·67–3·74)	2·04(1·17–3·55)
Total cholesterol (mmol L^{-1})	6·6 ± 1·2	per 1·0 mmol L^{-1} increase	1·15(0·90–1·46)	1·11(0·96–1·29)
HDL-cholesterol (mmol L^{-1})	1·3 ± 0·4	low vs. high¶	3·03(1·44–6·40)	1·85(1·14–3·00)
Triglycerides (mmol L^{-1})	1·6(1·2–2·2)	per 10% increase†	1·05(0·99–1·10)	1·04(1·01–1·08)
HbA1c (% of haemoglobin)	5·9 ± 1·3	per 1% of haemoglobin increase	1·04(0·83–1·30)	1·09(0·94–1·26)
Von Willebrand factor (IU mL^{-1})	1·22(0·86–1·74)	high vs. low**	2·22(1·21–4·09)	1·73(1·19–2·52)
C-reactive protein (mg L^{-1})	1·75(0·83–3·80)	high vs. low**	1·65(0·89–3·05)	1·39(0·95–2·04)
sVCAM-1 (ng mL^{-1})	1383 ± 454	per 100 ng mL^{-1} increase	1·08(1·03–1·13)	1·03(1·00–1·07)
sICAM-1 (ng mL^{-1})	482 ± 163	high vs. low‡‡	2·05(1·10–3·81)	1·43(0·96–2·13)
Homocysteine ((mol L^{-1})	11·4(9·3–14·1)	per 5 (mol/L increase	1·09(0·96–1·25)	1·07(0·96–1·19)
Microalbuminuria (%)	11	yes vs. no¶	2·57(1·31–5·06)	1·47(0·91–2·37)
Creatinine clearance (ml min^{-1}) §§	78·5(18·1)	per 5 mL min^{-1} increase	0·87(0·79–0·96)	0·99(0·89–1·01)
Glomerular filtration rate (ml min^{-1})¶¶	70·0(20·0)	Per 5 mL min^{-1} increase	0·79(0·70–0·88)	0·87(0·80–0·94)
Prior cardiovascular disease (%)	24	yes vs. no***	3·07(1·67–5·64)	2·06(1·41–2·99)
Ankle-brachial pressure index (% < 0·90)	10·6	high vs. low†††	3·89(2·07–7·29)	2·64(1·74–3·98)
Use of diabetes medication (%)	10·6	yes vs. no	1·31(0·30–5·78)	1·77(0·54–5·81)

Data are presented as mean ± standard deviation, percentage of the total or median (interquartile range).

HDL-cholesterol, high-density lipoprotein; HbA1c, haemogloblin-A1c; sVCAM-1, soluble vascular cell adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1.

*Relative risk (RR) with 95% confidence intervals (95% CI) obtained with Cox regression analyses of cardiovascular and all-cause mortality associated with continuous or dichotomous variables after adjustment for age, gender, glucose tolerance status (impaired glucose tolerance and type 2 diabetes), except when this was the variable under consideration.

†log-transformed.

‡ >> vs. ≤ 27 kg m^{-2} for males and > vs. ≤ 26 kg m^{-2} for females.

§≥ vs. < 0·95 for males and ≥ vs. < 0·80 for females.

¶ < vs. (0·9 mmol L^{-1}.

**Upper tertile vs. lower two tertiles (> 1·56 IU mL^{-1} for vWf and > 2·84 mg L^{-1} for CRP levels).

††Albumin-to-creatinine ratio ≤ vs. > 2·0 mg mmol^{-1}.

‡‡Upper quartile vs. lower three quartiles (> 550 ng mL^{-1}).

§§According to the Cockroft–Gault formula.

¶¶According to Levey *et al.* [26].

***A history of myocardial infarction and/or Minnesota code 1·1–1·3, 4·1–4·3, 5·1–5·3 or 7·1 on the electrocardiogram, coronary bypass operation and/or angioplasty and/or ankle-brachial pressure index < 0·90 and/or peripheral arterial bypass or amputation.

††† < vs. ≥ 0·90.

alter this relative risk. Adjustment for current smoking and the level of sVCAM-1 made the relative risk borderline significant. The relative risk of all-cause mortality associated with sICAM-1 levels was somewhat less than the relative risk of cardiovascular mortality (relative risk of the upper compared to the three lower quartiles of sICAM-1, 1·43; 95% confidence interval, 0·96–2·13; Table 3). Further adjustment for risk factors or indicators did not substantially affect the results (Table 3).

Additional analyses

The associations between sICAM-1 and cardiovascular and all-cause mortality were similar in diabetic and nondiabetic individuals. The relative risk of cardiovascular mortality associated with sICAM-1 levels did not substantially change during follow-up. After 2 years the relative risk was 2·37 (95% confidence interval, 0·48–11·75); after 4 years it was 1·65 (0·53–5·08); after 6 years it was 1·99 (0·88–4·5), and after 8·2 years it was 2·05 (1·10–3·81).

Discussion

Our data show that sICAM-1 levels are significantly associated with risk of cardiovascular mortality. Individuals with a plasma concentration of sICAM-1 higher
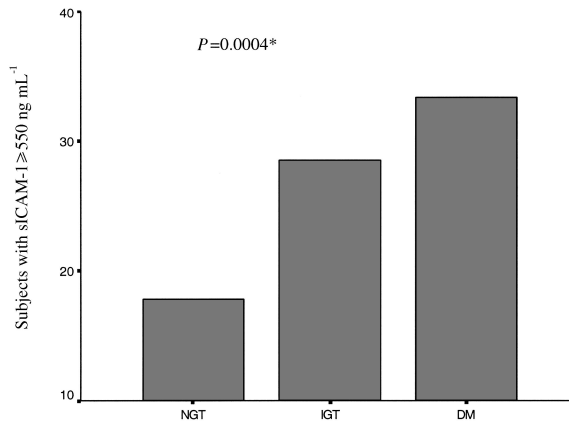
Figure 1 Percentage of subjects, with a normal glucose tolerance (NGT), an impaired glucose tolerance (IGT) and with type 2 diabetes (DM), with a soluble intercellular adhesion molecule-1 (sICAM-1) concentration above 550 ng mL^{-1}. *Trend tested by logistic regression analysis adjusted for age, sex and glucose status; NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = type 2 diabetes.

than 550 ng mL^{-1} had a cardiovascular mortality risk that was about twice that of individuals with a lower concentration. Moreover, the relative risk was largely independent of cardiovascular risk factors and indicators, and did not vary with time. After adjustment for smoking and sVCAM-1, the relative risks were borderline significant, but the point estimates remained similar, which suggests that the association between sICAM-1 and cardiovascular mortality could at most partly be explained by smoking or sVCAM-1. Our findings are consistent with prospective studies in healthy male physicians [8], in

healthy postmenopausal women [24], the Atherosclerosis Risk In Communities (ARIC) cohort [25], and selected patient groups with peripheral arterial disease [26] and stable angina pectoris [27].

The present study is the first to assess the association between a high plasma concentration of sICAM-1 and the risk of cardiovascular death with adjustment for clinical and subclinical cardiovascular disease, and to examine potential pathophysiological mechanisms by which sICAM-1 may promote mortality.

The pathophysiological pathway through which sICAM-1 is associated with risk of cardiovascular mortality is unclear. The current theory is that increased plasma concentrations of sICAM-1 reflect increased expression of ICAM-1 on endothelial cells, smooth muscle cells and monocytes, and thus may indicate progressive atherogenesis [1–4,9]. However, in our study high concentrations of sICAM-1 were associated with an increased cardiovascular mortality risk independent of (sub)clinical atherosclerosis, as reflected by the presence of prior cardiovascular disease and by the ankle-brachial pressure index. Therefore, it is unlikely that high sICAM-1 concentrations exclusively reflect progression of atherosclerosis.

Another hypothesis is that an increased concentration of sICAM-1 is a marker of endothelial stimulation and (or) of chronic, low-grade inflammation. Indeed, sICAM-1 levels were significantly associated with von Willebrand factor and (micro)albuminuria, i.e. potential markers of generalized endothelial stimulation that are associated with cardiovascular disease [14,19,28–30], and with C-reactive protein, a marker of inflammation [31,32]. However, our data show that sICAM-1 was associated with cardiovascular mortality independent of von Willebrand factor, (micro)albuminuria and C-reactive protein [8], which

Table 2 Soluble intercellular adhesion molecule-1 levels: associations with classical cardiovascular risk factors or indicators of (sub)clinical atherosclerosis, endothelial function and inflammation

	β*	SE(β)*	P-value
Gender (male vs. female)	$-8\cdot49$	$13\cdot15$	$0\cdot519$
Age (per 5-year increase)	$-6\cdot19$	$4\cdot635$	$0\cdot182$
Type 2 diabetes (yes vs. no)	$76\cdot69$	$15\cdot89$	$< 0\cdot001$
Hypertension (yes vs. no)	$41\cdot94$	$13\cdot93$	$0\cdot003$
Waist-to-hip ratio (per 0·01 increase)	$3\cdot05$	$0\cdot99$	$0\cdot002$
Current smoking (yes vs. no)	$61\cdot44$	$14\cdot51$	$< 0\cdot001$
HDL-cholesterol (per 0·1 mmol L^{-1} increase)	$-4\cdot20$	$2\cdot00$	$0\cdot036$
Triglycerides (per 10% increase) ‡	$4\cdot12$	$1\cdot27$	$0\cdot001$
Von Willebrand factor (per 0·1 IU/mL increase)	$2\cdot08$	$0\cdot97$	$0\cdot032$
C-reactive protein (per 10% increase) ‡	$2\cdot47$	$0\cdot51$	$< 0\cdot001$
sVCAM-1 (per 10% increase) ‡	$15\cdot05$	$2\cdot08$	$< 0\cdot001$
(Micro)albuminuria (yes vs. no)†	$48\cdot07$	$21\cdot62$	$0\cdot027$
Prior cardiovascular disease (yes vs. no) †	$47\cdot57$	$15\cdot72$	$0\cdot003$
Use of diabetes medication (yes vs. no)	$24\cdot65$	$54\cdot45$	$0\cdot66$

HDL, high-density lipoprotein; sVCAM-1,= soluble vascular cell adhesion molecule 1.

*Regression coefficient (β), standard error (SE[β]) and P-value obtained by linear regression analysis with sICAM-1 levels as dependent variable and risk factors or indicators as independent variables, all adjusted for age, sex and glucose tolerance status (unless this was the variable under consideration).

†Defined as described in legend to Table 1.

‡Log-transformed.
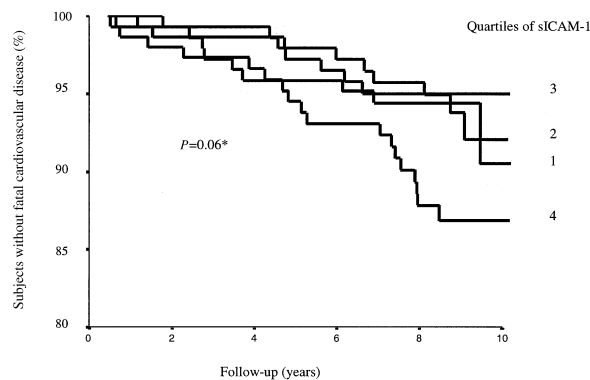
Figure 2 Cardiovascular survival (Kaplan–Meier curves) according to plasma soluble intercellular adhesion molecule-1 (sICAM-1) concentration in the lowest (1), two middle (2 and 3) and highest (4) quartile. *Logrank test for difference in survival for different quartiles.

argues against the hypothesis of sICAM-1 being a marker of endothelial stimulation or inflammatory activity.

An alternative hypothesis is that a high sICAM-1 level reflects a general increase in the expression of adhesion molecules. We tested this concept by adjusting for levels of sVCAM-1, which has also been found to be associated with cardiovascular mortality [18,33]. We found that sICAM-1 was indeed associated with sVCAM-1. However, the association between sICAM-1 and cardiovascular mortality was hardly altered by correction for

sVCAM-1. This suggests that sICAM-1 acts differently from sVCAM-1 in promoting atherothrombosis. ICAM-1 is expressed constitutively and has a broader expression than VCAM-1 [5]. In reaction to inflammatory cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), ICAM-1 is up-regulated on most tissues in acute and inflammatory diseases. In addition, ICAM-1 expression in human aortic smooth muscle cells peaks much more rapidly than VCAM-1 expression after stimulation by TNF-α or IL-1 [34]. ICAM-1 and VCAM-1 are both ligands for integrins on lymphocytes and monocytes, but only ICAM-1 is a ligand for neutrophils as well [5,35]. Therefore, sVCAM-1 and sICAM-1 may be related to cardiovascular disease through different pathways.

Finally, we examined whether renal dysfunction influenced the association between sICAM-1 and cardiovascular mortality, because levels of sICAM-1 were strongly associated with serum creatinine levels among subjects with chronic renal failure not receiving dialysis [36,37]. However, renal function was not associated with sICAM-1 in our study, nor did it influence the association between sICAM-1 and cardiovascular mortality.

In short, we examined several possible pathophysiological pathways that might explain the association between sICAM-1 and cardiovascular mortality. Our findings provide no evidence in favour of any of these hypotheses. We conclude from this that sICAM-1 is independently associated with cardiovascular mortality because it might reflect, or may be involved in, instability of atherosclerotic

Table 3 Relative risk of cardiovascular and all-cause mortality associated with plasma concentrations of soluble intracellular adhesion molecule-1 (sICAM-1)

Model	Added variables	Cardiovascular mortality ($n = 43$) RR (95% CI)*	All-cause mortality ($n = 117$) RR (95% CI)*
1	Age, sex, glucose tolerance status	2·05 (1·10–3·81)	1·43 (0·96–2·13)
2	Model 1 and hypertension	1·98 (1·06–3·70)	1·39 (0·93–2·08)
3	Model 1 and HDL †, total cholesterol and triglycerides†	2·04 (1·10–3·80)	1·37 (0·91–2·07)
4	Model 1 and creatinine clearance†	2·05 (1·10–3·81)	1·42 (0·96–2·12)
5	Model 1 and glomerular filtration rate†	2·16 (1·17–4·03)	1·52 (1·02–2·28)
6	Model 1 and body mass index †	1·96 (1·05–3·68)	1·42 (0·93–2·16)
7	Model 1 and waist-to-hip ratio†	1·96 (1·05–3·68)	1·41 (0·94–2·11)
8	Model 1 and prior cardiovascular disease†	2·13 (1·14–3·97)	1·41 (0·94–2·10)
9	Model 1 and ankle-brachial pressure index†	2·06 (1·11–3·82)	1·43 (0·96–2·13)
10	Model 1 and current smoking	1·86 (0·98–3·52)	1·29 (0·86–1·94)
11	Model 1 and glycated haemoglobin	2·03 (1·09–3·79)	1·40 (0·94–2·10)
12	Model 1 and microalbuminuria†	1·92 (1·03–3·59)	1·40 (0·93–2·11)
13	Model 1 and von Willebrand factor†	2·10 (1·13–3·90)	1·42 (0·95–2·12)
14	Model 1 and C-reactive protein†	1·95 (1·05–3·63)	1·34 (0·91–1·99)
15	Model 1 and sVCAM-1	1·75 (0·91–3·34)	1·38 (0·91–2·08)
16	Model 1 and use of diabetes medication	2·09 (1·12–3·90)	1·42 (0·95–2·13)

All subjects ($n = 608$).

HDL, high-density lipoprotein; sVCAM-1,= soluble vascular cell adhesion molecule 1.

*Relative risk (95% confidence interval) of mortality associated with the upper as compared to the lower quartiles of soluble intercellular adhesion molecule-1 (sICAM-1) concentration, as obtained with Cox multiple regression analyses. Model 1: adjusted for stratification variables; Model 2–15: as Model 1, plus adjusted for other potential risk factors or risk indicators associated with cardiovascular mortality.

†Defined as described in legend to Table 1

plaques and (or) a prothrombotic state [10]. These issues clearly need further investigation.

A high sICAM-1 level occurred significantly more often among subjects with type 2 diabetes than among subjects with a normal glucose tolerance [12,25,38]. We found that the association between sICAM-1 and cardiovascular mortality was similar in individuals without and with type 2 diabetes, but the latter more often had high sICAM-1 levels. These findings suggest that the pathophysiological mechanism(s) reflected by sICAM-1 levels operate frequently in individuals with type 2 diabetes and may thus be involved in their increased risk of atherothrombotic disease.

A limitation of the present study may be that concentrations of sICAM-1 were measured only once, although in duplicate, which might have led to nondifferential misclassification and consequently to underestimation of the relative risk of mortality.

In conclusion, a high plasma concentration of sICAM-1 doubles the risk of cardiovascular mortality. This association is largely independent of established cardiovascular risk factors and indicators. The prevalence of a high sICAM-1 concentration is significantly higher among individuals with type 2 diabetes than among individuals with a normal glucose tolerance. The present study suggests that sICAM-1 concentrations could be used as a tool in estimating the risk of future cardiovascular mortality. Therapeutic options to lower sICAM-1 and ICAM-1 already exist [10]. However, more work is necessary to establish whether lowering the levels of sICAM-1 decreases the risk of cardiovascular mortality.

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