Obesity Research & Clinical Practice 17 (2023) 40–46

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Visceral adipose tissue quantity and dysfunction and the occurrence of major bleeding in patients with established cardiovascular disease

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ARTICLE INFO

Keywords:
Visceral fat
Adipose tissue dysfunction
Metabolic syndrome
Bleeding
Cardiovascular disease

ABSTRACT

Objectives: To determine the association between both visceral fat quantity and adipose tissue dysfunction, and major bleeding in patients with established cardiovascular disease.
Methods: Patients from the Second Manifestations of ARTerial disease study with established cardiovascular disease were included. Visceral fat was measured using ultrasound and adipose tissue dysfunction was depicted using metabolic syndrome criteria (revised National Cholesterol Education Program). Cox regression models were fitted to study the relation with major bleeding defined as Bleeding Academic Research Consortium (BARC) type 3 or 5, or International Society on Thrombosis and Haemostasis (ISTH) major bleeding. Sensitivity analyses were performed using C-reactive protein levels to reflect adipose tissue dysfunction.
Results: In 6927 patients during a median follow up of 9.2 years, a total of 237 BARC type 3 or 5 bleedings and 224 ISTH major bleedings were observed. Visceral fat quantity was not related to major bleeding (HR 1.01, 95% CI 0.88–1.16 for BARC type 3 or 5 bleeding and HR 1.00, 95%CI 0.87–1.15 for ISTH major bleeding), nor was metabolic syndrome (HR 0.97, 95%CI 0.75–1.26 for BARC type 3 or 5 bleeding and HR 0.98, 95%CI 0.75–1.28 for ISTH major bleeding). Sensitivity analyses using C-reactive protein levels showed similar results. No effect modification was observed by sex, antithrombotic therapy, presence of metabolic syndrome or diabetes.
Conclusion: In patients with cardiovascular disease, no association was found between visceral fat quantity measured with ultrasound or measures of adipose tissue dysfunction and the risk of major bleeding, irrespective of antithrombotic agent use.

1. Introduction

Adiposity confers a higher risk of both cardiovascular disease and venous thromboembolism [1,2]. This might be explained by the influence of adipose tissue on primary and secondary hemostasis via the secretion of tissue factor, plasminogen activator inhibitor and pro-inflammatory cytokines, also resulting in hepatic synthesis of pro-thrombotic factors and inflammatory markers, and leptin and low adiponectin potentiating platelet activation [3]. Given these thrombogenic effects, visceral fat quantity and adipose tissue dysfunction may reduce the risk of bleeding, especially in patients using antithrombotic therapy [4,5].

Previous studies showed that patients with obesity have a lower major bleeding rate after coronary intervention, both directly and up to three years post-procedure. At the same time, no difference was seen in the risk of stent thrombosis between patients with and without obesity [6–9]. In the long run, adiposity confers a higher cardiovascular risk which, at least in part, may be caused by atherothrombosis [10]. Abdominal fat distribution has a stronger association with cardiovascular risks than excess adipose tissue or obesity itself. [11] The dysfunction of the adipose tissue compartment, as measured by metabolic dysfunction or adipocytokine levels, appears to be a strong driver

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https://doi.org/10.1016/j.orcp.2022.11.003

Available online 1 December 2022

of cardiovascular risk and is more directly linked with visceral fat than subcutaneous fat [11–13]. Even though waist circumference is closely linked to the size of the visceral adipose tissue compartment, it does not correlate as strongly with indicators of adipose tissue dysfunction [14]. Metabolic syndrome as a reflection of adipose tissue dysfunction is associated with a higher risk of cardiovascular disease [15,16]. One potential pathway is the impaired response to thienopyridines, irreversible platelet receptor inhibitors, in patients with metabolic syndrome. This may result in higher platelet reactivity and may therefore be a causal link between adiposity and adipose tissue dysfunction and atherothrombotic events [6]. In the effect on bleeding risk, body mass index (BMI) instead of adipose tissue was examined in previous studies [7–9], and metabolic syndrome has only been studied in the acute phase after coronary syndrome [6].

Based on current knowledge it might be argued that patients with obesity thus may benefit from intensifying antithrombotic treatment based on their higher long term cardiovascular risk without having a higher bleeding risk, at least in the short term [17,18]. Especially with the advent of more intensive antithrombotic treatment schedules, including dual pathway inhibition or dual platelet inhibition [19,20], it is essential to enhance the insight in the effect of adiposity on the bleeding risk in patients with cardiovascular disease.

The aim of the present study was to determine the relation between both visceral fat quantity as well as visceral fat dysfunction and the risk of major bleeding in patients with established cardiovascular disease.

2. Subjects

Patients originated from the Second Manifestations of ARTerial disease (SMART) study; an ongoing prospective cohort consisting of patients with established cardiovascular disease or severe risk factors referred to the University Medical Center Utrecht, the Netherlands [21]. Exclusion criteria for the SMART-study are age under 18 or over 79 years old, being unable to perform daily activities (Rankin scale $\geq$4), a terminal malignancy diagnosis at baseline or insufficient fluency in the Dutch language. The study complies with the Declaration of Helsinki, was approved by the ethics committee of the University Medical Center Utrecht and all participants gave their written informed consent. For the current study, patients enrolled between January 2000 and 2020 were included, because data on body fat measurements were collected from January 2000 onwards. For the current analyses, 7824 patients with a recent cardiovascular event (several weeks after hospitalization) or a history of established cardiovascular disease at baseline were selected, defined as cerebrovascular disease (transient ischemic attack, cerebral infarction, amaurosis fugax, retinal infarction or carotid surgery), abdominal aortic aneurysm, coronary artery (angina pectoris, myocardial infarction, cardiac arrest or coronary revascularization) or peripheral artery disease (symptomatic and documented obstruction of arteries of the lower limbs). Patients with C-reactive protein (CRP) levels above 10 mg/L (n = 897) at baseline were excluded, as these CRP levels more likely reflect an acute inflammatory response rather than the chronic low-grade inflammation associated with adipose tissue dysfunction which is normally seen [22].

3. Materials and methods

3.1. Baseline assessment

At inclusion in the SMART-cohort, information on patient characteristics, medical history, lifestyle and current treatment were acquired through a questionnaire. All physical examination measurements were obtained by trained staff according to a standardized protocol. Waist circumference was measured horizontally at the midpoint between the iliac crest and lower costal margin. The mean waist circumference of two measurements was calculated. If the two measurements differed by $>$ 2 cm, a third was taken and the mean of the closest two measurements was calculated. Venous blood samples were drawn at inclusion after a fasting period of at least eight hours to determine serum hemoglobin, lipids, glucose, creatinine and CRP levels. Visceral and subcutaneous adipose tissue were assessed by trained technicians at the diagnostic laboratory using an EPIQ-5 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands) according to a strict protocol on transducer position and pressure. Fat measurements were taken using a curved 4–2 MHz probe, at the end of quiet expiration on a frozen ultrasound frame at 3 points on the imaginary transversal line halfway between the iliac crest and lower costal margin: at the midsternal line and 10 cm to the left and right on the transversal line. The amount of subcutaneous fat was estimated by the distance between the linea alba and the skin with the probe transversely placed. Visceral adipose tissue thickness was measured in the longitudinal plane as the distance between the lumbar spine and the peritoneum. Each measurement was taken three times and then the mean of the measurements was calculated. Ultrasonography has been proven a suitable technique to measure intra-abdominal adipose tissue with good reproducibility [23].

Metabolic syndrome was defined as the presence of three or more out of five revised criteria from the National Cholesterol Education Program (NCEP): high waist circumference ($\geq$102 cm in men, $\geq$88 cm in women), hypertriglyceridemia ($\geq$1.7 mmol/L or treatment for elevated triglycerides), low high-density lipoprotein (HDL) cholesterol ($<$1.03 mmol/L in men, $<$1.29 mmol/L in women or treatment for reduced HDL-cholesterol), hypertension ($\geq$130/$\geq$85 mmHg or treatment with antihypertensive agents, or a history of hypertension) and high fasting glucose ($\geq$5.6 mmol/L or glucose-lowering treatment) [24]. In this definition, the waist circumference cut offs from the European Cardiovascular Societies were used because of the Dutch origin of the SMART cohort and compliance with the abdominal obesity definitions of the National Institutes of Health obesity guidelines.

3.2. Outcome assessment

All included patients were followed up through annual questionnaires, gathering information on hospitalization and outpatient clinic visits. If questionnaires indicated the possibility of the occurrence of a bleeding event, additional information was collected using hospital discharge letters and relevant laboratory and radiology examinations. Three independent physicians from the endpoint adjudication committee assessed the medical records to determine major bleeding events. If these three physicians all judged differently, the event was discussed with two other physicians from the committee to reach consensus. For this study, the outcome of interest was major bleeding defined using the Bleeding Academic Research Consortium (BARC) definition, with BARC bleeding types 3 and 5 being major bleeding events. [25] Bleeding events were also assessed according to the International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding. [26] These definitions of major bleeding events are shown in the Supplementary material (Table S1). The duration of follow-up is defined as the time period from study inclusion to first major bleeding, death from any cause, date of loss to follow-up or the latest date of endpoint ascertainment (January 1st of 2020).

3.3. Data analyses

Baseline characteristics are presented as means with standard deviations or medians with interquartile range, depending on their parametric distribution assessed by visual inspection of histograms, or frequencies with percentages, in strata of sex-pooled quartiles of amount of visceral fat. Cox proportional hazard models were fitted to estimate hazard ratios (HR) with 95 % confidence intervals (95%CI) describing the association between both visceral fat and metabolic syndrome and major bleeding, adjusted for confounders. Visceral fat was assessed as a percentage of total abdominal fat thickness (visceral adipose tissue thickness plus subcutaneous adipose tissue thickness) as well, to account

for the distribution of abdominal adipose tissue [27]. Sensitivity analyses were performed using a metabolic syndrome definition including elevated CRP (≥3 mg/L) instead of the high waist circumference criterion [28], and using CRP level alone, to further assess the relationship between the metabolic dysfunction of adipose tissue and bleeding risk. Additional sensitivity analyses were performed using the lower International Diabetes Federation thresholds for high waist circumference in the criteria for metabolic syndrome. [24] Models were adjusted for the predefined potential confounders sex, age, smoking status, alcohol intake, use of antiplatelet agents, use of oral anticoagulation, hypertension and renal function. In the analyses with metabolic syndrome as the determinant, hypertension was not adjusted for.

The role of antithrombotic agents is looked into further, because of the use of different antithrombotic agents in the high risk study population and the possible interaction between antithrombotic agents and metabolic syndrome [6]. This is done by testing for interaction and performing stratified analyses based on antithrombotic treatment. To assess whether the relation of visceral adipose tissue quantity and bleeding risk differs between patients with and without cardiometabolic dysfunction, effect modification by metabolic syndrome was evaluated, as well as diabetes and sex, because adipose tissue distribution and metabolic consequences differ between men and women [29].

Proportional hazard assumptions were tested by visual assessment of the plotted Schoenfeld's residuals against time. No violations were observed for visceral fat in cm, visceral fat as a percentage of total abdominal adipose tissue and metabolic syndrome. The linearity assumption, assessed by adding the continuous amount of visceral fat as a restricted cubic spline function to the model, was not violated.

As complete case analysis could lead to bias and loss of power, missing data was imputed by simple imputation using bootstrapping and predictive mean matching; subcutaneous adipose tissue (n = 247, 3.6 %), visceral fat (n = 201, 2.9 %), waist circumference (n = 211, 3.1 %), fasting glucose (n = 30, 0.4 %), triglycerides (n = 28, 0.4 %), HDL-cholesterol (n = 33, 4.7 %), systolic blood pressure (n = 11, 0.2 %), diastolic blood pressure (n = 40, 0.6 %), smoking status (n = 22, 0.3 %), alcohol consumption (n = 26, 0.4 %), creatinine (n = 23, 0.3 %) and clopidogrel use (n = 289, 4.2 %). Statistical analyses were performed using the open source statistical package R (version 1.3.1093). P-values ≤ 0.05 were considered statistically significant.

4. Results

4.1. Baseline characteristics

A total of 6 927 patients with established cardiovascular disease were studied, with a mean age of 60 ± 10 years and the vast majority being male (74 %). Baseline characteristics are presented stratified by sex-pooled quartiles of visceral fat thickness (Table 1). Within these strata, there was an uptrend across quartiles in the presence of metabolic syndrome and its components (waist circumference, blood pressure and antihypertensive treatment, triglycerides, fasting glucose, glucose-lowering treatment and inversely a lower HDL-cholesterol), level of CRP and presence of type 2 diabetes mellitus. There was no clinically relevant difference in the amount of subcutaneous fat was comparable across quartiles of visceral fat. The proportion of patients with cardiovascular disease increased across the quartiles.

4.2. Relation between visceral fat quantity and risk of major bleeding

During a median follow-up time of 9.1 years (interquartile range 5.0–13.1), with a total follow-up of 63 405 person-years, the endpoint of BARC type 3 or 5 bleeding occurred in 237 (3.4 %) of the 6 927 patients (incidence rate 3.7 major bleedings per 1000 person-years), and 224 patients experienced an ISTH major bleeding (incidence rate 3.5 major bleedings per 1000 person-years). There was no statistically significant difference in the risk of BARC type 3 or 5 bleeding or ISTH major

Table 1
Baseline characteristics by sex-pooled quartiles of visceral fat.

	Q1 (*N* = 1776)	Q2 (*N* = 1741)	Q3 (*N* = 1725)	Q4 (*N* = 1685)	p-value*
Visceral fat range (cm)					
Men (*n* = 5110)	3.2 – 7.8	7.9 – 9.3	9.4 – 11.0	11.1 – 22.3	
Women (*n* = 1817)	2.6 – 6.0	6.1 – 7.4	7.5 – 9.0	9.1 – 19.0	
Age (years), mean (SD)	59 ± 11	60 ± 10	61 ± 10	62 ± 9	< 0.001
Male, n (%)	1287 (72)	1305 (75)	1284 (74)	1234 (73)	0.325
Current smoking, n (%)	496 (28)	452 (26)	500 (29)	478 (28)	0.219
Current alcohol use, n (%)	1222 (69)	1174 (68)	1142 (66)	1040 (62)	< 0.001
Vascular disease, n (%)					
Cerebrovascular disease	580 (33)	508 (29)	495 (29)	412 (24)	< 0.001
Coronary artery disease	1054 (59)	1099 (63)	1125 (65)	1184 (70)	< 0.001
Abdominal aortic aneurysm	102 (6)	119 (7)	127 (7)	143 (8)	0.017
Lower extremity arterial disease	237 (13)	247 (14)	247 (14)	287 (17)	0.015
Polyvascular disease	181 (10)	211 (12)	243 (14)	294 (17)	< 0.001
Diabetes mellitus type 2, n (%)	153 (9)	209 (12)	326 (19)	487 (29)	< 0.001
eGFR (ml/min/1.73 m^2), mean (SD)	80 ± 17	78 ± 17	76 ± 18	76 ± 18	< 0.001
Adiposity measures					
Subcutaneous fat (cm), mean (SD)	2.3 ± 1.2	2.4 ± 1.1	2.4 ± 1.2	2.5 ± 1.5	< 0.001
Visceral fat (cm), mean (SD)	6.2 ± 1.1	8.2 ± 0.9	9.7 ± 1.0	12.3 ± 1.9	< 0.001
Visceral fat (% of abdominal fat), mean (SD)	74 ± 10	78 ± 8	80 ± 8	83 ± 8	< 0.001
Metabolic syndrome criteria					
Waist circumference (cm), mean (SD)	86 ± 10	93 ± 9	98 ± 9	106 ± 11	< 0.001
Systolic blood pressure (mmHg), mean (SD)	135 ± 21	137 ± 20	140 ± 20	142 ± 20	< 0.001
Diastolic blood pressure (mmHg), mean (SD)	80 ± 11	81 ± 11	82 ± 11	82 ± 12	< 0.001
Triglycerides (mmol/L), median (IQR)	1.1 (0.8–1.4)	1.2 (1.0–1.7)	1.5 (1.1–2.0)	1.7 (1.2–2.4)	< 0.001
HDL-cholesterol (mmol/L), mean (SD)	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	< 0.001
Fasting glucose (mmol/L), mean (SD)	5.8 ± 1.4	6.0 ± 1.3	6.3 ± 1.5	6.9 ± 2.0	< 0.001
Metabolic syndrome, n (%)	340 (19)	639 (37)	1015 (59)	1387 (82)	< 0.001
CRP (mg/L), median (IQR)	1.2 (0.6–2.5)	1.5 (0.8–3.0)	1.9 (1.0–3.5)	2.5 (1.4–4.4)	< 0.001
Medication					
Antihypertensive agent use, n (%)	1219 (69)	1309 (75)	1383 (80)	1451 (86)	< 0.001
	114 (6)	162 (9)	252 (15)	329 (23)	< 0.001

(*continued on next page*)

Table 1 (*continued*)

	Q1 (*N* = 1776)	Q2 (*N* = 1741)	Q3 (*N* = 1725)	Q4 (*N* = 1685)	p-value*
Glucose-lowering agent use, n (%)					
Lipid-lowering agent use, n (%)	1276 (72)	1326 (76)	1335 (77)	1316 (78)	< 0.001
Statins, n (%)	1232 (69)	1264 (73)	1279 (74)	1246 (74)	0.005
Fibrates, n (%)	5 (0)	15 (1)	17 (1)	28 (2)	< 0.001
Cholesterol absorption inhibitors, n (%)	73 (4)	77 (4)	86 (5)	107 (6)	0.013
Antithrombotic agent use, n (%)	1503 (85)	1484 (85)	1486 (86)	1456 (86)	0.415
Antiplatelet agents	1421 (80)	1381 (79)	1414 (82)	1339 (80)	0.182
Dual antiplatelet use	383 (22)	418 (24)	436 (25)	435 (26)	0.017
Anticoagulant agents	155 (9)	182 (10)	176 (10)	194 (12)	0.058
Antiplatelet plus anticoagulant	73 (4)	79 (5)	104 (6)	77 (6)	0.046

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; Q, quartile; SD, standard difference.
Polyvascular disease meaning two or more locations of vascular disease: cerebrovascular, coronary, lower extremity disease or abdominal aortic aneurysm. P-values were calculated using one-way ANOVA test for continuous variables with normal distribution, Kruskal-Wallis test for continuous variables with skewed distribution and χ^2-test for categorical variables.

bleeding across sex-pooled visceral fat quartiles (Fig. 1). Visceral fat quantity expressed in both cm and percentage of total abdominal fat was not significantly related to the risk of BARC type 3 or 5 bleeding in continuous analyses either (HR 1.01, 95%CI 0.88–1.16 resp. 1.08, 95% CI 0.94–1.26) (Fig. 2A). Results were similar for ISTH major bleeding (Fig. 2B).

4.3. Relation between metabolic dysfunction and risk of major bleeding

Metabolic syndrome as an indicator of visceral fat dysfunction was not statistically significant related to the risk of major bleeding (HR 0.97, 95%CI 0.75–1.26 for BARC type 3 or 5 bleeding and HR 0.98, 95% CI 0.75–1.28) for ISTH major bleeding) (Fig. 2). Replacing waist circumference with plasma CRP level of ≥ 3 mg/L in the metabolic syndrome definition revealed similar results and there was no statistically significant relation between plasma CRP levels and BARC type 3 or 5 or ISTH bleeding risks (Table 2). Lastly, using the lower International Diabetes Federation thresholds for high waist circumference in the criteria for metabolic syndrome did not alter the findings (Supplement Table S2).

4.4. Effect modification

There was no effect modification by metabolic syndrome in the relation between visceral fat quantity and the risk of major bleeding (p-values for interaction of 0.60 for the model including visceral fat in cm and 0.59 for the model including visceral fat as proportion of total abdominal fat). Diabetes mellitus did not modify the effect of visceral fat quantity on the occurrence of major bleeding either (p-values 0.49 and 0.24 for models including visceral fat in cm and as proportion of total abdominal fat, respectively).

In both men and women separately, no significant relation between visceral fat and the risk of major bleeding was seen (HR for men 0.93, 95%CI 0.79–1.10 and HR for women 1.28, 95 % CI 0.98– 1.68). The relation between metabolic syndrome and the risk of major bleeding did not differ between men and women either (p-value for interaction by sex 0.25).

No statistically significant effect modification was found by use of antiplatelet therapy in general, aspirin or clopidogrel specifically, or oral anticoagulation in the relation between visceral fat quantity and major bleeding (p-values for interaction 0.51, 0.91, 0.84 and 0.17 respectively), nor in the relation between metabolic syndrome and major bleeding (p-values for interaction 0.72, 0.85, 0.22 and 0.33 respectively). Hazard ratios stratified by antithrombotic treatment are listed in Supplement Table S3.

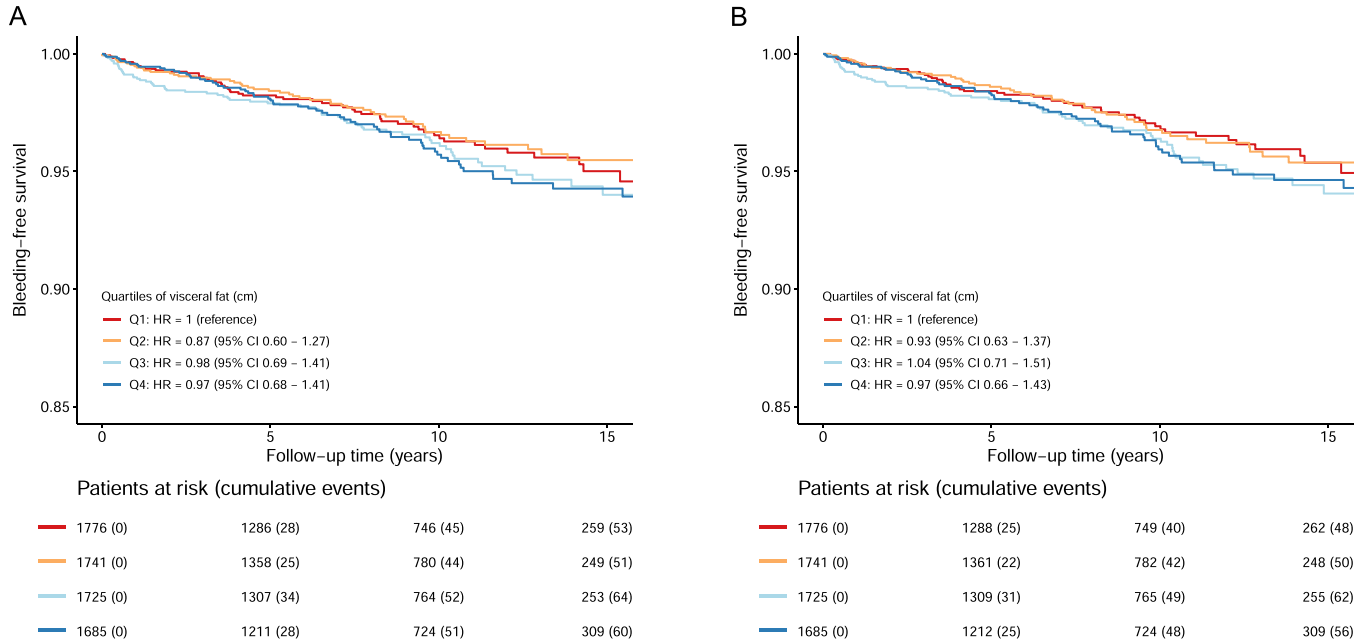

Fig. 1. Survival curves in sex-pooled quartiles of visceral fat for major bleeding A. BARC type 3 or 5 bleeding B. ISTH major bleeding Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile. Hazard ratios are adjusted for sex, age, smoking status, alcohol intake, hypertension, renal function and antithrombotic agent use. Corresponding quartile ranges of visceral fat are reported in Table 1.

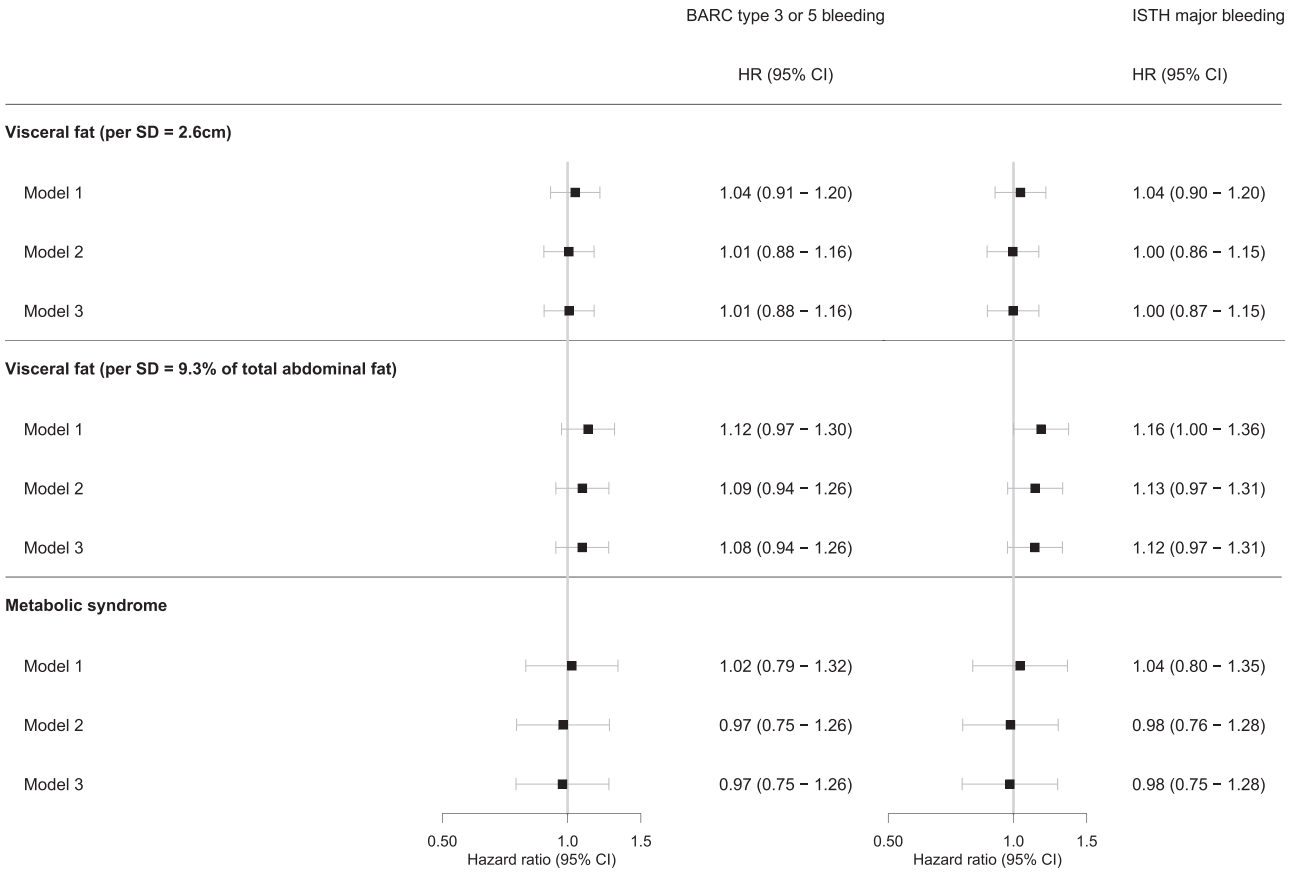

Fig. 2. Relation between adipose tissue quantity and metabolic syndrome and risk of major bleeding Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation. Model 1: adjustment for age and sex. Model 2: model 1 plus additional adjustment for current smoking, current alcohol use, hypertension and renal function. Model 3: model 2 plus additional adjustment for antiplatelet therapy and oral anticoagulant therapy (main model). Model 2 and 3 for metabolic syndrome are not adjusted for hypertension. Metabolic syndrome defined according to the revised criteria from the National Cholesterol Education Program.

Table 2
Relation between adipose tissue dysfunction and risk of major bleeding.

	HR (95% CI)	
	BARC type 3 or 5 bleeding	ISTH major bleeding
Metabolic syndrome including CRP ≥ 3 mg/L		
Model 1	1.04 (0.80 – 1.34)	1.04 (0.80 – 1.35)
Model 2	0.96 (0.74 – 1.24)	0.95 (0.73 – 1.24)
Model 3	0.95 (0.73 – 1.23)	0.95 (0.73 – 1.24)
CRP (per SD = 2.2 mg/L)		
Model 1	1.15 (1.02 – 1.30)	1.16 (1.03 – 1.31)
Model 2	1.10 (0.97 – 1.24)	1.10 (0.97 – 1.25)
Model 3	1.09 (0.96 – 1.23)	1.09 (0.96 – 1.24)

Abbreviations: CI, confidence interval; HR, hazard ratio; CRP, C-reactive protein; SD, standard deviation. Model 1: adjustment for age and sex. Model 2: model 1 plus additional adjustment for current smoking, current alcohol use, hypertension and renal function. Model 3: model 2 plus additional adjustment for antiplatelet therapy and oral anticoagulant therapy (main model). Model 2 and 3 for metabolic syndrome are not adjusted for hypertension. Metabolic syndrome defined according to the revised criteria from the National Cholesterol Education Program, using CRP ≥ 3 mg/L instead of the waist circumference criterion.

5. Discussion

In patients with established cardiovascular disease, no association was found between visceral fat quantity or dysfunction and the risk of major bleeding. Although visceral fat and its metabolic dysfunction have been found to confer an increased risk of cardiovascular events [12,15], these effects do not appear to translate into a reduced risk of bleeding in high risk patients with stable cardiovascular disease. Use of different antithrombotic agents did not seem to modify these findings.

Previously, in patients treated with either clopidogrel or prasugrel in addition to aspirin after an acute coronary syndrome, higher platelet reactivity (less response to thienopyridines) in patients with obesity was observed, translating into a lower 1-month bleeding rate in these patients [6]. This impact on platelet reactivity was only observed in patients with obesity and metabolic syndrome, underlining the potential role of metabolic dysfunction. In the present study, there was no relation between metabolic syndrome and major bleeding risk. If the impaired effect of thienopyridines in patients with metabolic syndrome is indeed causing a lower bleeding risk, potential explanations include the low percentage of patients with DAPT (24 %) in the present cohort and that patients included in the SMART cohort used a lower dose of clopidogrel. However, in the present study there was no statistically significant effect modification of the relation between metabolic syndrome and major bleeding by clopidogrel. Another explanation may be the inclusion of patients in the stable phase after a cardiovascular event in the current study, thus after the high bleeding risk period direct peri-procedural or after initiation of therapy.

The relation between BMI and the risk of severe bleeding was studied as primary safety endpoint in a prospective observational study in which clopidogrel in addition to aspirin was evaluated in patients with (multiple risk factors for) atherothrombotic disease [30]. In that study lower risks of severe bleeding were observed in patients with higher BMI compared to the lowest quartile, without a clear decline in bleeding risk when comparing the highest three quartiles. At the same time there was only a trend towards a lower bleeding risk among patients with a higher BMI when handling BMI as a continuous variable. The same was found

in a subgroup analysis of the GLOBAL LEADERS trial investigating patients undergoing PCI [7]. In that study, patients who underwent PCI for acute and chronic coronary syndrome were treated with dual antiplatelet therapy for either 1 month followed by 23 months of ticagrelor, or 12 months of dual antiplatelet therapy followed by 12 months of aspirin monotherapy. A reverse J-shaped curve was found indicating higher risk of BARC type 3 or 5 bleeding events for patients with lower BMI, compared to a BMI of 27 kg/m^2 as reference. Again, for patients with a BMI $\geq 30\ kg/m^2$, no statistically significant relation with bleeding was seen. Judging by the findings of the present study, there is no evidence that the higher risk of major bleeding found in low BMI patients is explained by the amount or dysfunction of visceral adipose tissue. Overdosing of antithrombotic agents could be a possible explanation for higher bleeding risk in patients with lower BMI, although high quality evidence is lacking on whether the dose of aspirin, clopidogrel and ticagrelor should be lowered in underweight patients [31]. Also, in a previous study in the SMART cohort combining patients with and without established cardiovascular disease, no association between BMI and bleeding (either fatal, intracranial or requiring hospitalization) was found [32]. The more the adiposity measurement reflects visceral adiposity [10], or even more its cardiometabolic dysfunction [15], the detrimental effects on cardiovascular risk become more clear. Regarding major bleeding however, no clear increased or reduced risk by visceral adiposity quantity or dysfunction appeared from the present study. The absence of a protective effect on bleeding in high risk patients with cardiovascular disease underlines that visceral fat is an important modifiable risk factor that should be addressed in the consulting room. When visceral fat does lead to more cardiovascular disease without inflicting a higher bleeding risk, it may identify a possible target population that could benefit from intensifying antithrombotic treatment such as dual platelet or dual pathway inhibition mentioned in guidelines for patients with high residual risk [33,34].

Strengths of this study are the large cohort of patients with cardiovascular disease, the prospective study design, the long follow-up and well documented bleeding endpoints. Potential study limitations that should be considered include the observational design in which the presence of unmeasured confounders cannot be ruled out, calling for caution in making firm conclusions on causality. Use of antithrombotic agents was assessed only at baseline, so the effect of antithrombotics on the relation between visceral fat and bleeding cannot fully be accounted for since antithrombotic use could have changed during follow up. Furthermore, adipose tissue measurements and presence of metabolic dysfunction could have changed during follow-up and thereby mitigating the differences. Because of smaller groups with limited number of events, the results of stratified analysis by antithrombotic treatment should be interpreted with caution. Besides, separate analyses in patients without antithrombotic agents could be biased because patients with cardiovascular disease have an indication for antithrombotic agents, so potentially a high estimated bleeding risk could be the reason for patients not using antithrombotic therapy. Lastly, there is no reference standard for estimating adipose tissue dysfunction. There is some evidence of a relation between metabolic syndrome and adipokines in patients with established cardiovascular disease [35]. Using different depictions of adipose tissue dysfunction based on metabolic syndrome criteria and CRP, depicting the adipose tissue-liver axis [3]. did however result in consistent results in their relation to the risk of major bleeding.

In conclusion, in patients with established cardiovascular disease, no association was found between either visceral fat quantity measured with ultrasound or measures of adipose tissue dysfunction and the risk of major bleeding. This can be of importance when informing patients and deciding on antithrombotic treatment, especially in patients with obesity at increased cardiovascular risk.

Ethical statement

The authors declare that the study was conducted in accordance with the Declaration of Helsinki and was carried out with the adequate understanding and written consent of participants. Formal approval to conduct the study has been obtained from the Medical Ethical Review Committee of the UMC Utrecht, which can be provided upon request.

CRediT authorship contribution statement

Maria Castelijns: Conceptualization, Methodology, Formal analysis, Writing – Original Draft. **Steven Hageman**: Methodology, Software, Validation, Writing – Review & Editing. **Ynte Ruigrok**: Validation, Investigation, Writing – Review & Editing. **Manon van der Meer**: Validation, Writing – Review & Editing. **Martin Teraa**: Validation, Writing – Review & Editing. **Jan Westerink**: Conceptualization, Methodology, Writing – Review & Editing. **Frank Visseren**: Conceptualization, Methodology, Writing – Review & Editing, Supervision.

Declaration of Competing Interest

All authors declare no conflict of interest. The UCC-SMART study was financially supported by a grant of the University Medical Center Utrecht, the Netherlands. The supporting sources had no involvement in study design, analysis, interpretation, writing of the results, or the decision to submit for publication.

Acknowledgments

We gratefully acknowledge the contribution of the research nurses; R. van Petersen (data-manager); A. Vandersteen (study manager) and the members of the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease-Studygroup (UCC-SMART-Studygroup): F.W. Asselbergs and H.M. Nathoe, Department of Cardiology; G.J. de Borst, Department of Vascular Surgery; M.L. Bots and M.I. Geerlings, Julius Center for Health Sciences and Primary Care; M.H. Emmelot-Vonk, Department of Geriatrics; P.A. de Jong and T. Leiner, Department of Radiology; A.T. Lely, Department of Gynecology and Obstetrics; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology & Hypertension; M.C. Verhaar, Department of Nephrology & Hypertension, F.L.J. Visseren (chair), Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2022.11.003.

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