Paradoxical effect of obesity on hemorrhagic transformation after acute ischemic stroke

Chi Kyung Kim1,2, Wi-Sun Ryu3, Beom Joon Kim4 and Seung-Hoon Lee1,2*

Abstract
Background: Among the patients with established coronary artery diseases, obese patients tend to have a more favorable prognosis, which is called as obesity paradox. Interestingly, mildly obese patients who underwent coronary revascularization had a lower risk of bleeding. In this context, we have investigated the association between obesity and hemorrhagic transformation (HTf) after acute ischemic stroke.

Methods: A total of 365 patients with first-ever acute ischemic stroke were included in this study. Demographic, clinical and radiological information was collected and HTf was evaluated through follow-up T2*-weighted gradient-recalled echo MRI performed usually within 1 week after occurrence of stroke. Body mass index was calculated, and obesity was defined using the World Health Organization Western Pacific Regional Office criteria.

Results: The HTf was identified in 59 patients (16.2%). As the severity of obesity increased, the occurrence of HTf decreased. Compared with the normal weight group and after controlling possible confounders including acute and previous treatment, stroke severity and subtype, the risk of HTf decreased significantly in the obese group (odds ratio, 0.39; 95% confidence interval, 0.17-0.87).

Conclusions: The better outcome for HTf seen in obese patients suggests the existence of a “bleeding-obesity paradox” in acute ischemic stroke.

Keywords: Obesity, Hemorrhagic transformation, Bleeding-obesity paradox, Ischemic stroke, Body mass index

Background
Hemorrhagic transformation (HTf) frequently occurs after ischemic stroke with or without thrombolytic treatment [1,2]. It was known that HTf after acute ischemic stroke was associated with poor outcome and delayed the initiation of proper anticoagulation treatment for stroke with cardioembolism [3]. Although certain studies have demonstrated the association between old age [4], high systolic pressure [5], or thrombolytic treatment [6] with HTf, the predictive factor for HTf after acute ischemic stroke is still elusive.

Obesity affects more than a billion adults worldwide, and is implicated as one of the major risk factors of cardiovascular diseases [7,8]. However, in patients with established coronary artery diseases, obese patients tend to have a more favorable prognosis, which is called as obesity paradox [8,9]. Interestingly, according to a recent study, mild obese patients who underwent coronary revascularization had a lower incidence of periprocedural bleeding, and the authors in that study called this phenomenon as “bleeding-obesity paradox” [10].

In ischemic stroke, HTf occurs after extravasation of blood over damaged cerebral vascular endothelium and is more directly associated with disease itself than bleeding after coronary revascularization [11]. However, few studies have investigated the effects of obesity on the bleeding after ischemic stroke. In this context, we sought to investigate the association between obesity and HTf, and assessed whether “bleeding-obesity paradox” exists in acute ischemic stroke.

Methods
A total of 744 first-ever acute ischemic stroke patients who had been admitted to Seoul National University Hospital within 7 days from disease onset between October 2002
and March 2006 were consecutively enrolled in this study. According to the classification of Trial of Org 10172 in Acute Stroke Treatment, amongst the chosen patients, subjects with the following conditions were excluded from this study: transient ischemic attack (n = 79; HTf = 0), strokes attributable to small vessel disease (n = 221; HTf = 0), or strokes of other determined etiology (n = 9; HTf = 1) [12].

Patients without complete workups (n = 70; 10 without initial MRI, 37 without follow-up MRI, 14 without checking height, and 9 without laboratory workups) were further excluded. The excluded 70 patients had more severe stroke than included patients, and in-hospital death rate of excluded patients was higher than that of included patients. However, other demographic and cardiovascular risk factors including the average and the distribution of body mass index (BMI) were not different between two groups (Additional file 1: Table S1). Therefore, our study population consisted of a total of 365 patients with first-ever acute ischemic stroke. The patient or the patient’s next of kin was provided informed consent, and the study was approved by the institutional review board at Seoul National University Hospital (H-0911-065-301).

Baseline demographic and clinical information collected at admission included age at onset, gender, body weight and height at the time of admission, hypertension (a high systolic blood pressure was defined as at least 140 mmHg at discharge, and a diastolic blood pressure as at least 90 mmHg at discharge. Hypertension was defined as a high systolic blood pressure or a high diastolic blood pressure or as the current use of antihypertensive medication), diabetes (previous use of antidiabetic medication, fasting blood glucose > 7.0 mmol/L), hyperlipidemia (previous use of lipid-lowering medication, total cholesterol > 6.0 mmol/L at admission), smoking, previous use of antiplatelet or anticoagulant medications, systolic and diastolic blood pressure levels at admission, the level of blood glucose and total cholesterol at admission, the initial National Institute of Health Stroke Scale (NIHSS) score, and thrombolytic or/and acute heparin treatment during acute stage. BMI was calculated as weight (in kilograms) divided by height (in meters squared), an obesity was defined using the criteria of the World Health Organization (WHO) Western Pacific Regional Office, which reflects a different risk factors and body fat distribution in the Asian Population [13].

All the participants underwent initial brain MRI before the initiation of thrombolytic or antithrombotic therapy (within 24 hours after admission) and follow-up brain T2*-weighted gradient-recalled echo (GRE) MRI usually within 1 week after occurrence of stroke (follow-up days: mean ± SD, 6.7 ± 1.4). The MRI studies were performed using 1.5-Tesla superconducting magnet (GE Healthcare, Chalfont St. Giles, UK). The standardized MRI protocol consisted of axial T2-weighted spin echo (repetition time/echo time, 2500 to 4500/80 to 112 ms; flip angle, 20°; slice thickness, 5 mm; gap width, 2 mm) and diffusion-weighted imaging (repetition time/echo time, 4000/73 ms; flip angle, 90°; slice thickness, 5 mm; gap width, 2 mm). The GRE images were obtained in the axial plane with the following parameters: repetition time/echo time, 500/15 ms; flip angle, 26°; matrix size, 256 × 192; slice thickness, 6 mm; and gap width, 2 mm. The HTf was identified when follow-up GRE images showed a low-signal area consistent with blood within the acute ischemic lesion, according to the pre-specified criteria [14]. White matter lesions (WMLs) and microbleeds were defined as being absent, or present as punctuate, early confluent or confluent abnormalities as seen on T2-weighted MR images, according to the previously proposed method [15]. Early confluent or confluent lesions were designated as advanced WMLs in this study. Microbleeds were defined as focal homogenous areas with a diameter of 2 to 5 mm as previously described [16,17].

The χ² test and the Student t test were used to compare categorical data and continuous data of the subjects, respectively. The distribution of demographic, clinical, and radiological variables were analyzed using χ² test for trends in proportion. The odds ratio (OR) and 95% confidence interval (CI) for the HTf in each obesity status were calculated using binary logic regression analyses. For multivariable analyses, potential confounders were adjusted such as age, gender, hypertension, diabetes, hyperlipidemia, current smoking, initial NIHSS, thrombolysis, acute heparin treatment, previous use of antiplatelet or anticoagulant, stroke subtype, and the presence of advanced WMLs and microbleeds. The adjusted OR and 95% CI for the HTf or cerebral microbleeds were calculated by multivariable analysis. Probability values were 2-tailed, and P values < 0.05 were considered significant. All statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL).

Results
Among 365 subjects, there were 246 men and 119 women. Subjects’ age ranged from 16 to 95 years, and their mean age was 64.7 years. Average BMI of subjects was 24.1 kg/m². According to the WHO obesity criteria for the Asian-Pacific Population, 94 patients (25.8%) were classified as overweight (BMI, 23.0-24.9 kg/m²) and 146 (40%) were classified as obese (BMI, ≥ 25.0 kg/m²).

The HTf was noted in 59 patients (16.2%). Table 1 shows that BMI was significantly lower in subjects with HTf (23.1 kg/m²) that in those without HTf (24.2 kg/m²). The average of initial NIHSS score and the proportions with cardioembolism and thrombolytic treatment were greater in subjects with HTf. However, the average age, glucose level, cholesterol level, and systolic and diastolic blood pressure at admission, and the proportions of
gender, hypertension, diabetes, hyperlipidemia, smoking, previous use of antiplatelet agents and anticoagulation, acute heparin treatment, and the presence of advanced WMLs and microbleeds were not different between those with and without HTf. As the severity of obesity increased, the incidence of HTf decreased, and the average of initial NIHSS score also decreased (Table 2). The proportion of subjects with hypertension increased according to the severity of obesity.

In the obese group, 15 (10.3%) subjects had HTf, and compared with the normal weight group, the crude OR for HTf in the obese group was 0.36 (95% CI, 0.18 to 0.71). After adjusting age, gender, hypertension, diabetes, hyperlipidemia, atrial fibrillation (reflecting stroke subtype), smoking, initial NIHSS score (reflecting stroke severity), thrombolytic and acute heparin treatment, and the presence of advanced WMLs and microbleeds, a 61% risk reduction of HTf in the obese group existed when

| Table 1 Baseline characteristics of patients with/without hemorrhagic transformation |
|---------------------------------|-----------------|-----------------|-----------------|
| Demographic                     | Hemorrhagic transformation | P value*         |
|                                | Absent (n = 306) | Present (n = 59) |
| Age, y                          | 64.4 ± 12.4      | 66.3 ± 9.1       | 0.28            |
| Gender, male                    | 209 (68.3%)      | 37 (62.7%)       | 0.45            |
| Body-mass index, kg/m²†         | 24.2 ± 3.2       | 23.1 ± 4.2       | 0.02            |
| Clinical                         |                  |                  |                 |
| Hypertension                    | 182 (59.3%)      | 37 (62.7%)       | 0.67            |
| Diabetes                        | 93 (30.4%)       | 17 (28.8%)       | 0.88            |
| Hyperlipidemia                  | 47 (15.4%)       | 5 (8.5%)         | 0.22            |
| Smoking                         |                  |                  | 0.95            |
| Never                           | 192 (62.7%)      | 37 (62.7%)       |                 |
| Past                            | 51 (16.7%)       | 9 (15.3%)        |                 |
| Current                         | 63 (20.6%)       | 13 (22%)         |                 |
| Previous use of antiplatelet agents | 9 (2.9%)   | 2 (3.4%)         | 0.69            |
| Previous use of anticoagulation | 9 (2.9%)         | 2 (3.4%)         | 0.69            |
| Initial NIHSS score, median (IQR)† | 8 (4–16)  | 3 (2–6)          | < 0.01          |
| Acute treatment                 |                  |                  |                 |
| Thrombolysis†                   | 10 (3.3%)        | 14 (23.7%)       | < 0.01          |
| Acute heparin treatment         | 98 (32%)         | 21 (35.6%)       | 0.65            |
| Stroke subtype†                 |                  |                  | < 0.01          |
| Large artery atherosclerosis    | 135 (44.1%)      | 11 (18.6%)       |                 |
| Cardioembolism                  | 81 (26.5%)       | 30 (50.8%)       |                 |
| Undetermined                    | 90 (29.4%)       | 18 (30.5%)       |                 |
| Laboratory                      |                  |                  |                 |
| Glucose, mmol/L                 | 6.5 ± 2.1        | 6.9 ± 2.3        | 0.14            |
| Total cholesterol, mmol/L       | 4.6 ± 1.0        | 4.6 ± 1.0        | 0.64            |
| Systolic blood pressure, mmHg   | 152 ± 25         | 153 ± 27         | 0.87            |
| Diastolic blood pressure, mmHg  | 88 ± 15          | 90 ± 17          | 0.39            |
| Prolonged PT/aPTT (%)           | 36 (11.8%)       | 8 (13.6%)        | 0.66            |
| Radiological                    |                  |                  |                 |
| Advanced WMLs                   | 76 (25.2%)       | 16 (28.1%)       | 0.63            |
| Presence of microbleeds         | 68 (22.7%)       | 15 (26.3%)       | 0.61            |

Values are mean ± SD or number of participants (percentage).
NIHSS indicates National Institute of Health Stroke Scale; WMLs, white matter lesion; and IQR, Interquartile range.
P values were obtained using the χ² test for categorical data, and the Student t test for continuous data.
P < 0.05.
compared with the normal weight group (Table 3). However, ORs for HTf or cerebral microbleeds did not decrease in the overweight or the obese groups compared with the normal group (Table 4).

Discussion and Conclusions
In the present study on patients with first-ever acute ischemic stroke, we found that the occurrence of HTf decreased according to the severity of obesity. In particular, obese subjects had a significantly decreased risk of HTf when compared with the normal weight group, after adjusting possible confounders including acute and previous treatment, and stroke severity and subtype.

Although our finding may seem controversial, the results are not surprising. Considering HTf as poor prognostic factor [3], the paradoxical effect of obesity on death after ischemic stroke, the most deleterious outcome, has been reported. In a Danish cohort of hospitalized acute stroke

Table 2 The proportions of clinical radiological variables by the severity of obesity

| Variables (n = 365) | Underweight (<18.5 kg/m²) | Normal weight (18.5-22.9 kg/m²) | Overweight (23.0-24.9 kg/m²) | Obesity I (25.0-29.9 kg/m²) | Obesity II (≥30 kg/m²) | P for trend* |
|-------------------|--------------------------|-------------------------------|-------------------------------|---------------------------|-----------------------|-------------|
| Demographic       | n = 18 (4.9%)            | n = 107 (29.3%)               | n = 94 (25.8%)                | n = 134 (36.7%)           | n = 12 (3.3%)         |             |
| Age, y            | 71.1 ± 11.2              | 65.3 ± 12.7                   | 65.2 ± 11.8                   | 63.4 ± 11.1               | 61.0 ± 12.8           | 0.08        |
| Gender, male      | 15 (83.3%)               | 73 (68.2%)                    | 62 (66.0%)                    | 88 (65.7%)                | 8 (66.7%)             | 0.67        |
| Clinical          |                          |                               |                               |                           |                       |             |
| Hypertension†     | 7 (38.9%)                | 50 (46.7%)                    | 58 (61.7%)                    | 96 (71.6%)                | 8 (66.7%)             | < 0.01      |
| Diabetes          | 3 (16.7%)                | 29 (27.1%)                    | 32 (34.0%)                    | 44 (32.8%)                | 2 (16.7%)             | 0.38        |
| Hyperlipidemia    | 1 (5.6%)                 | 13 (12.1%)                    | 17 (18.1%)                    | 20 (14.9%)                | 1 (8.3%)              | 0.55        |
| Current smoking   | 7 (38.9%)                | 21 (19.6%)                    | 23 (24.5%)                    | 23 (17.2%)                | 2 (16.7%)             | 0.23        |
| Initial NIHSS score† | 5 (3–12)               | 5 (2–11)                      | 4 (2–9)                       | 3 (2–5)                   | 3 (1–6)               | < 0.01      |
| Thrombolysis      | 0 (0%)                   | 9 (8.4%)                      | 6 (6.4%)                      | 9 (6.7%)                  | 0 (0%)                | 0.61        |
| Acute heparin treatment | 9 (50%)              | 37 (34.6%)                    | 31 (33%)                      | 39 (29.1%)                | 3 (25%)               | 0.44        |
| Antiplatelet Use  | 0                        | 5 (4.7%)                      | 4 (4.3%)                      | 2 (1.5%)                  | 0                     | 0.48        |
| Warfarin Use      | 0                        | 2 (1.9%)                      | 5 (5.3%)                      | 4 (3.0%)                  | 0                     | 0.54        |
| Radiological      |                          |                               |                               |                           |                       |             |
| Hemorrhagic transf.† | 4 (22.2%)              | 26 (24.3%)                    | 14 (14.9%)                    | 14 (10.4%)                | 1 (8.3%)              | 0.04        |
| Advanced WMLs     | 6 (35.3%)                | 26 (25%)                      | 24 (26.1%)                    | 35 (26.3%)                | 1 (8.3%)              | 0.6         |
| Presence of microbleeds | 2 (11.8%)            | 20 (19.4%)                    | 21 (22.8%)                    | 36 (27.1%)                | 4 (33.3%)             | 0.42        |

Values are mean ± SD, median (interquartile range), or number of participants (percentage).
NIHSS indicates National Institute of Health Stroke Scale; WMLs, white matter lesion.
*Based on χ² test of trend across the severity of obesity.
†P < 0.05.

Table 3 The risk of hemorrhagic transformation according to the severity of obesity

| OR for HTf | Unadjusted OR (95% CI) | Adjusted OR (95% CI)* |
|------------|------------------------|-----------------------|
| Underweight (<18.5 kg/m²) | 0.89 (0.27-2.94) | 1.05 (0.28-3.96) |
| Normal (18.5-22.9 kg/m²) | 1.00 (reference) | 1.00 (reference) |
| Overweight (23.0-24.9 kg/m²) | 0.55 (0.27-1.12) | 0.48 (0.21-1.11) |
| Obesity (≥22.5 kg/m²) | 0.36 (0.18-0.71)† | 0.39 (0.17-0.87)† |

HTf indicated hemorrhagic transformation; OR, odds ratio; and CI, confidence interval.
*ORs (95% CI) were adjusted by age, gender, hypertension, diabetes, hyperlipidemia, current smoking, initial NIHSS score, thrombolysis, acute heparin treatment, stroke subtype, previous aspirin use, and the presence of advanced WMLs and cerebral microbleeds.
†P < 0.05.

Table 4 The risk of hemorrhagic transformation or cerebral microbleeds according to the severity of obesity

| OR for HTf or cerebral microbleeds | Unadjusted OR (95% CI) | Adjusted OR (95% CI)* |
|-----------------------------------|------------------------|-----------------------|
| Underweight (<18.5 kg/m²) | 0.71 (0.23-2.18) | 0.65 (0.19-2.25) |
| Normal (18.5-22.9 kg/m²) | 1.00 (reference) | 1.00 (reference) |
| Overweight (23.0-24.9 kg/m²) | 0.87 (0.48-1.57) | 0.80 (0.42-1.52) |
| Obesity (≥25 kg/m²) | 0.93 (0.55-1.57) | 0.92 (0.51-1.69) |

HTf indicated hemorrhagic transformation; OR, odds ratio; and CI, confidence interval.
*ORs (95% CI) were adjusted by age, gender, hypertension, diabetes, hyperlipidemia, current smoking, initial NIHSS score, thrombolysis, acute heparin treatment, stroke subtype, previous aspirin use, previous warfarin use, and the presence of advanced WMLs.
patients, post-stroke mortality was inversely related to
obesity [18]. The phenomenon was also noted in an anal-
ysis of a health and nutrition status survey in US individ-
uals, which showed that in aged population, obese stroke
survivors tend to have a lower risk of mortality than pa-
tients with a normal weight [19]. However, the mechanism,
which states that obesity increases the longevity in obese
patient after ischemic stroke is not clear. Based on our
findings and a review of the previous studies, HTf might
be related to “obesity paradox” in acute ischemic stroke.

In the present study it was observed that as increasing
of obesity severity, the proportion of cardioembolic stroke and
severe stroke (reflected by initial NIHSS score) de-
creased, despite of the elevated prevalence of hypertension
[20]. The incidence of HTf may be influenced by the
differences in these baseline characteristics among BMI
groups [10]. To reduce these confounding effects, we con-
ducted a multivariable analysis after adjusting various
possible confounders including the nature of stroke (sever-
ity and subtype), acute and previous treatment. After
this adjustment, the presence of obesity independently
predicted the occurrence of HTf in our study. However,
the association between microbleeds and obesity was not
eclucidated in this study with first-ever acute ischemic
stroke patients. Although microbleeds were suggested as a
risk factor for cerebral hemorrhage [21], they are not a
confirmed mediator of hemorrhagic transformation after
ischemic stroke. Compared with HTf, the weak relationship
between obesity and microbleeds may reflect the different
pathophysiology of HTf and cerebral microbleeds. While
the abrupt reperfusion after ischemic tissues elicits HTf, the
spontaneous rupture of injured small arterioles in brain
leads cerebral microbleeds.

For the cause of bleeding-obesity paradox, biological
explanations exist. First, alterations in circulating coagula-
tion factors have been suggested. Obesity has been rela-
ted to higher levels of multiple coagulation factors such as
factor VII, VIII, fibrinogen, and plasminogen activator
inhibitor-1 [22,23]. Second, in studies investigating the
association between BMI and platelet aggregation, patients
with BMI ≥ 25 kg/m² were found to have suboptimal re-
response to antithrombotics than patients of normal weight
[24,25]. However, this phenomenon was evaluated in nor-
mal or coronary artery disease subjects, and not in acute
stroke patients. To clearly explain the “bleeding-obesity
paradox,” the assessment of the coagulability and drug
response in obese patient with acute ischemic stroke is
required.

In the present investigation, a number of points require
further clarification. First, due to the limitation of study
population, we focused on the relatively mild obese patients
and did not evaluate the phenomenon of “bleeding-obesity
paradox” in severely obese patients. To assess the effect of
BMI as a whole from underweight to severe obese, we
suggest that future studies on ischemic stroke patients
with widely-spread BMI should be undertaken. Second,
the long-term outcome of HTf, which is a major poor
prognostic factor in acute ischemic stroke, was not
evaluated in this study. Thus, we could not assess “obesity
paradox” per se in this study. Third, more severe stroke
patients were excluded because they could not undergo
brain MRI or did not have clinical information such as
height, and the effects of obesity on HTf in severe stroke
patients might not be evaluated completely.

The present study is unique because it documents the
better results about HTf in obese patients with acute
ischemic stroke, which persists after adjustment for acute
treatment and stroke severity and subtype. Thus, we
suggest the existence of a “bleeding-obesity paradox” in
ischemic stroke, and propose that the inverse association
between HTf and obesity in ischemic stroke may be
considered in the management of acute stroke patients.

Additional file

Additional file 1: Table S1. Baseline characteristics of excluded patients.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

CKK and S-HL devised the original study concept and design. BJK and W-SR
participated in the acquisition of data. CKK and S-HL performed statistical
analyses, interpreted the results and wrote the manuscript. All authors read
and approved the final manuscript.

Acknowledgements

This work was supported by grants of the Korean Health Technology R&D
Project, Ministry of Health and Welfare, Republic of Korea (A111014). The
analyses and interpretations of the data and the final content of the article
were produced independently of the financial sponsors.

Author details

1Department of Neurology, Seoul National University Hospital, 101 Daehak-ro,
Jongno-gu, Seoul 110-744, Republic of Korea. 2Clinical Research Center for
Stroke, Biomedical Research Institute, Seoul National University Hospital, Seoul,
Republic of Korea. 3Department of Neurology, Dongguk University Ilsan
Hospital, Goyang, Republic of Korea. 4Department of Neurology, Seoul National
University Bundang Hospital, Seongnam, Republic of Korea.

Received: 29 October 2012 Accepted: 18 September 2013
Published: 23 September 2013

References

1. Okada Y, Yamaguchi T, Minematsu K, Miyashita T, Sawada T, Sadoshima S,
Fujishima M, Omae T. Hemorrhagic transformation in cerebral embolism.
Stroke 1989, 20:598–603.

2. Larue V, von Kummer R, Muller A, Bluhmki E: Risk factors for severe
hemorrhagic transformation in ischemic stroke patients treated with
recombinant tissue plasminogen activator: a secondary analysis of the
European-Australasian Acute Stroke Study (ECASS II). Stroke 2001;
32:438–441.

3. Dziolowski I, Pevny JH, Barber PA, Demchuk AM, Buchan AM. Hill MD.
Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke
effectiveness study registry. Stroke 2007, 38:75–79.

4. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott
T, Franklin M, Grotta J, Haley EC Jr, et al: Association of outcome with
early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004, 363:768–774.
5. Castellanos M, Leira R, Serena J, Pumar JM, Lizasoain I, Castillo J, Davalos A: Plasma metalloproteinase-9 concentration predicts hemorrhagic transformation in acute ischemic stroke. Stroke 2003, 34:40–46.
6. Larue V, von Kummer R, del Zoppo G, Bluhmki E: Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. Stroke 1997, 28:957–960.
7. Haslam DW, James WP: Obesity. Lancet 2005, 366:1197–1209.
8. Lavie CJ, Milani RV, Ventura HO: Paradoxical effect of obesity on hemorrhagic transformation after acute ischemic stroke. BMC Neurology 2013, 13:212.

Cite this article as: Kim et al: Paradoxical effect of obesity on hemorrhagic transformation after acute ischemic stroke. BMC Neurology 2013, 13:212.