New Possibilities in Quantitative Assessment of Albuminuria in Patients with Atrial Fibrillation and Chronic Kidney Disease

Sokolova A.A.[1], Skripka A.I.[1]*, Ivanov I.I.[1], Kogay V.V.[2], Listratov A.I.[2], Gindis A.A.[1], Napalkov D.A.[1]

[1] I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

[2] Russian Medical Academy of Continuing Professional Education. Moscow, Russia

Aim. To evaluate the relationship between albumin to creatinine ratio (ACR) in a single and 24-hours urine spots and chronic kidney disease (CKD) progression pace in patients with atrial fibrillation, CKD and diabetes mellitus.

Material and methods. 60 patients with atrial fibrillation (AF) and CKD were enrolled, study duration was 15 months. The patients were divided into two groups depending on the presence of DM. Total number of ACR tests was 170, dynamics of CKD progression was estimated with CKD-EPI formula for first visit and 15th month's follow-up.

Results. The median score of CHA_2DS_2VASc scale was 4 [3;5]. The risk of hemorrhagic complications in both groups was low (median score 1 [1;1]. There is a strong statistically significant correlation between ACR in a single and 24-hours urine spots ($p<0.001$). No significant changes in kidney function within 15 months were found (GFR 53 [46;59] ml/min/1.73 m^2 vs 50.5 [45.63] ml/min/1.73 m^2 for patients with diabetes mellitus [DM] [p=0.94] and GFR 52.5 [46.58] ml/min/1.73 m^2 vs 50 [44.58] ml/min/1.73 m^2 for patients without DM [p=0.711]). When comparing the renal function of patients with and without DM after 15 months statistically significant differences were also not found ($p = 0.510$).

Conclusion. In respect that assessment of single sample ACR is much more practical and reliable, this method might replace traditional 24-hours urine assessment in future. However, due to the small sample size and the presence of wide discrepancies in individual cases, which can be associated with preanalytical errors in urine collection, large randomized clinical trials are needed to confirm the obtained data.

Keywords: albumin to creatinine ratio, chronic kidney disease, atrial fibrillation, diabetes mellitus, albuminuria.

For citation: Sokolova A.A., Skripka A.I., Ivanov I.I., Kogay V.V., Listratov A.I., Gindis A.A., Napalkov D.A. New Possibilities in Quantitative Assessment of Albuminuria in Patients with Atrial Fibrillation and Chronic Kidney Disease. *Rational Pharmacotherapy in Cardiology* 2021;17(3):423-428. DOI:10.20996/1819-6446-2021-06-09.

*Corresponding Author (Автор, ответственный за переписку): alenskripka@yandex.ru

Received: 18.05.2021
Accepted: 24.05.2021

Introduction

Atrial fibrillation (AF) is one of the most frequently encountered clinically significant arrhythmias, which leads to an increased risk of stroke [1]. AF and chronic kidney disease (CKD) combination is a serious problem due to its relatively high prevalence [2,3]. CKD increases the risk of thromboembolic complications and bleeding in patients on anticoagulant therapy, while AF itself leads to the progression of renal dysfunction [4,5]. In addition, diabetes mellitus (DM), which is the leading cause of CKD, makes a further significant negative contribution to renal function [6-8].

Currently, there are many different ways to assess renal function. The gold standard for measuring glomerular filtration rate (GFR) is clearance methods with the introduction of an exogenous glomerulotropic test agent, but they are laborious and expensive [4]. An indirect assessment of GFR can be performed using developed formulas such as CKD-EPI or MDRD, but they have several limitations, such as pregnancy, deviations in body weight, para- or tetraplegia [4]. An important indicator of renal function, which allows detecting disorders at the earliest stages, is the assessment of albuminuria [9-11]. Increased urinary albumin excretion reflects systemic endothelial dysfunction, glomerular barrier permeability and proximal tubule reabsorption capacity. Traditionally, albuminuria is assessed in a 24-hour urine sample, since the excretion of protein in the urine during the day can vary greatly, and this depends on the patient's diet and water balance. But this technique is also laborious and has several disadvantages. For example, incomplete collection due to missing sample of urine or incomplete emptying of the bladder will have a big impact on results. The greatest difficulties arise in older outpatients. The concentration of albumin in a single sample of urine was previously proposed to be used to simplify the assessment of albuminuria [4,12]. The level of creatinine excretion by the kidneys is practically constant [13], therefore, correction for its concentration allows obtaining an albumin-to-creatinine ratio (ACR), which will be the same for both a 24-hour urine and a single sample of urine, regardless of the time of urine collection or the level of hydration [14,15].

The aim of our prospective study was to assess the relationship between the albumin-to-creatinine ratio in a 24-hour and single samples of urine, as well as the rate of progression of renal dysfunction in patients with AF, CKD who receive anticoagulant therapy, depending on the presence of diabetes mellitus.

Materials and methods

From October 2018 to January 2020, 60 patients over 18 years of age with AF and CKD were included in the study (according to the KDIGO classification) who took dabigatran for the prevention of thromboembolic complications and were treated at the University Clinical Hospital №1 of the First Moscow State Medical University named after Sechenov I.M. The examination included the collection of anamnesis of life and disease (age, gender, body mass index, detection of concomitant diseases), physical examination, assessment of the risk of thromboembolic complications on the CHA2DS2-VASc scale and bleeding on the HAS-BLED scale. Criteria for excluding patients in the study: age <18 years, severe hepatic and renal failure (creatinine clearance according to the Cockcroft-Gault formula <30 ml/min), systemic connective tissue diseases, hematological and oncological diseases.

Patients included in the study (n=60) were divided into comparable groups depending on the presence of diabetes mellitus. The study duration was 15 months. The study was approved by the local ethics committee. All patients signed voluntary informed consent.

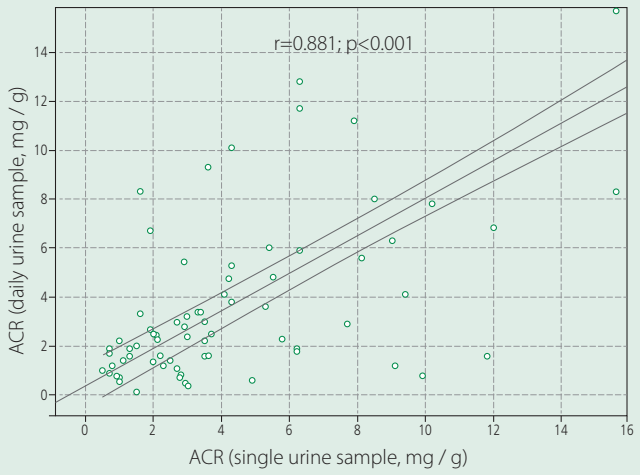
The calculation of the glomerular filtration rate (GFR) according to the CKD-EPI formula in accordance with the KDIGO recommendations was used as a method for assessing renal function. ACR was assessed by immunoturbidimetric analysis on a Synchron biochemical analyzer "Beckman Coulter", USA, using a commercially available Albumin kit (microalbuminuria, latex, BioSystems, Spain). This test system allows the quantitative determination of the amount of albumin in the range from 0.4 to 200 mg/L [16].

Statistical analysis of the results was performed using SPSS Statistics 26.0 software using a two-sided test with a significance level of 0.05. Categorical

variables were described in terms of frequencies and percentages and were assessed using Fisher's exact test or χ^2 test. Quantitative variables were described as means (M)± standard deviation (SD) for parameters with a normal distribution and as medians (Me) with an interquartile range [25%; 75%] for parameters with a distribution other than normal. Variables were compared using nonparametric Mann-Whitney U-test or Student t-test depending on distribution. The dynamics of GFR was assessed using the nonparametric Wilcoxon test for paired samples and the U test. The relationship between ACR was assessed using the linear regression method.

Results

The demographic and clinical characteristics of patients are presented in Table 1. Body mass index was statistically significantly higher in the group of patients with diabetes mellitus compared with the group without diabetes mellitus (p=0.02). The average score in both groups corresponded to the high risk of ischemic stroke and thromboembolic complications (CHA_2DS_2-VASc). The risk of hemorrhagic complications (HAS-BLED) in the examined patients was moderate.



ACR – albumin to creatinine ratio

Figure 1. Linear regression, the relationship between the albumin-creatinine ratio in the daily and single portions of urine

Estimation of albumin-to-creatinine ratio

The study was performed several times for each patient. The total number of studies was 170. The results of linear regression analysis are shown in Fig. 1. The correlation between ACR in a 24-hour and single urine samples is direct and high on the Chaddock scale (Pearson's correlation coeffi-

Table 1. Characterization and distribution of patients included in the study

Parametr	Patients with DM (n=30)	Patients without DM (n=30)	Total (n=60)
Male, n (%)	15 (50)	9 (30)	24 (40)
Age, years	71.3±8.28	74 [69;80]	72.4±7.3
BMI, kg/m^2	32 [26;36]	28.9±5.5*	29.9 [26;33]
CHA_2DS_2-VASc, score	4 [3;5]	4 [3;4]	4 [3;5]
HAS-BLED, score	1 [1;1]	1 [1;1]	1 [1;1]
Hypertension, n (%)	30 (100)	28 (93.3)	58 (96.6)
Coronary heart disease, n (%)	11 (36.7)	6 (20)	17 (28.3)
Congestive heart failure, n (%)	4 (13.3)	2 (6.7)	6 (10)
Dabigatran 110 mg, n (%)	10 (33.3)	11 (36.7)	21 (35)
Dabigatran 150 mg, n (%)	20 (66.7)	19 (63.3)	39 (65)
ACEi/ARBs, n (%)	28 (93.3)	22 (73.3)*	50 (83.3)
Beta-blockers, n (%)	24 (40)	19 (63.3)	43 (71.7)
Calcium channel blockers, n (%)	6 (20)	10 (33.3)	16 (26.7)
Statins, n (%)	27 (56.7)	22 (73.3)	49 (81.7)

Data are presented as M±SD or Me [25%; 75%], unless otherwise stated

* p <0.05 compared with patients with diabetes

DM – diabetes mellitus, BMI – body mass index, ACEi – angiotensin-converting enzyme inhibitors, ARBs – angiotensin II receptor blockers

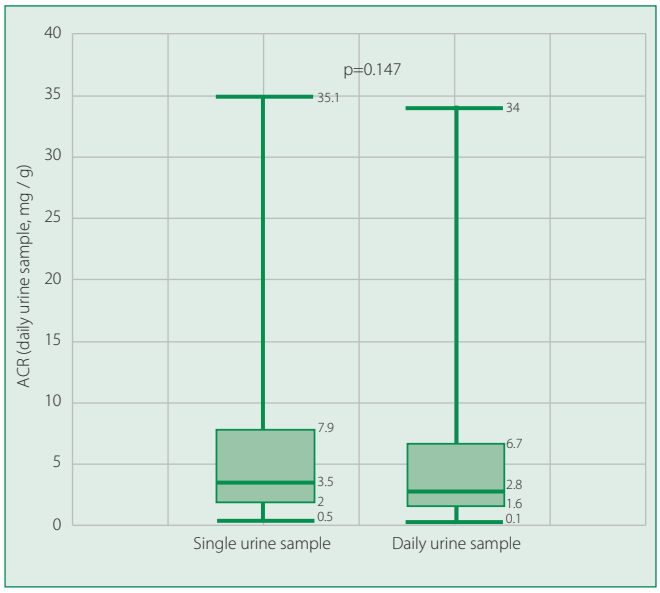


Figure 2. Comparison of albumin-to-creatinine ratios in single and daily urine portions

cient=0.881) and statistically significant (p <0.001). The resulting regression model took into account 77.6% of the factors determining ACR in a 24-hour urine sample. The observed dependence is described by the equation: y=0.4+0.77*x, where 0.4 is constant (95% CI: -0,15 – 1,284), x is the value of albumin-creatinine in a single urine sample (95% CI: 0,676 - 0,856). When the ACR increases by 1 unit in a single urine sample, an increase in this ratio in a 24-hour urine sample by 0.76 units should be expected. The influence of such factors as age, body mass index, blood albumin, total blood protein, GFR, and blood glucose on the model was found to be statistically insignificant. Differences between ACR in a single and a 24-hour urine samples were statistically insignificant when comparing samples using the nonparametric Mann-Whitney test (Fig. 2).

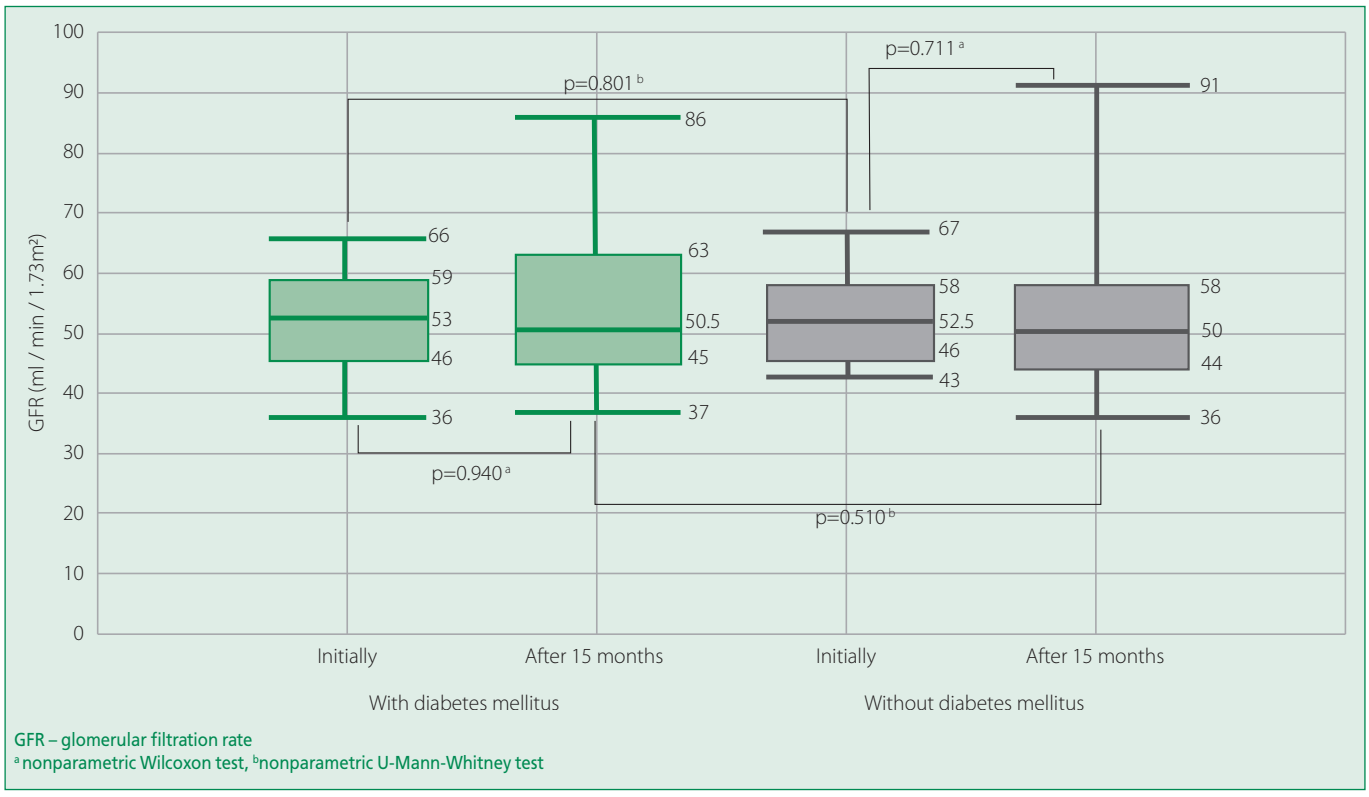
Assessment of the dynamics of renal function

No statistically significant changes were found when assessing the dynamics of GFR in patients with and without diabetes mellitus using the Wilcoxon nonparametric test for paired samples (Fig. 3).

There were also no statistically significant differences when comparing GFR values in patients at the first visit and after 15 months of follow-up, depending on the presence of diabetes mellitus (Fig. 3).

Discussion

There have been previous studies supporting the clinical relevance of assessing ACR in a single urine sample [14,15]. But many studies have included both patients with and without CKD. Our study in-



GFR – glomerular filtration rate
[a] nonparametric Wilcoxon test, [b]nonparametric U-Mann-Whitney test

Figure 3. Comparison of changes in glomerular filtration rate in patients with or without diabetes mellitus

cluded patients with documented stage 3A CKD. ACR was assessed for one patient several times during the study. Therefore, the presence of a high-strength direct correlation (according to the Chaddock scale) between the ACR values in a single and 24-hour urine samples and the absence of statistically significant differences between them may indicate the clinical equivalence and reproducibility of these methods. The presence of discrepancies in individual observations may be associated with preanalytical errors in the collection of a 24-hour urine sample (the material was collected by patients at home, the average age of patients was 72.43±7.3 years). It's possible that the assessment of renal function by ACR in a single urine sample will subsequently be able to replace the laborious and unreliable collection of a 24-hour urine sample, which can significantly improve the quality of diagnosis of CKD in the early stages.

Interesting data were obtained when assessing the dynamics of renal function. There were no statistically significant differences despite the presence of such comorbidities as diabetes mellitus and AF, which significantly accelerate the progression of CKD, in assessing the dynamics of GFR at the first visit and after 15 months. Moreover, significant differences were also not found when comparing GFR in patients depending on the presence of diabetes mellitus. Almost all patients were taking ACE inhibitors/angiotensin receptor blockers and statins, which have a positive pleiotropic effect on renal function. In addition to this all patients were taking dabigatran etexilate due to AF, which could also have a nephroprotective effect. According to previously published works, which found a close relationship between thrombin and inflammatory processes in the vascular wall with the involvement of the PAR217 thrombin receptor [8,17]. When modeling inflammatory atherosclerosis, the thrombin dabigatran inhibitors - etexilate [18] and melagatran [19] - reduced the phenomena of vasculitis, oxidative stress and the rate of progression of the growth of atherosclerotic plaques.

Study limitations

The main limitation of our study is the small sample size and relatively short follow-up period, which can affect the accuracy of the results obtained. It's possible that a statistically significant correlation between the presence of diabetes mellitus and the progression of CKD at follow-up visits will emerge as the number of patients increases.

Conclusion

During our study, we obtained data that indicate a close statistically significant relationship between the albumin-to-creatinine ratio in a single and a 24-hour urine sample. Significant advantages in the convenience and reliability of the analysis of a single urine sample showed that a one-time assessment of this indicator can subsequently replace the daily assessment in routine practice. However, due to the small sample size and wide discrepancies in individual cases, which may be associated with preanalytical errors in the collection of a 24-hour urine, large randomized clinical studies are needed to validate our findings.

Relationships and Activities: none.

Funding: The study was performed with the support of the Sechenov University.

References / Литература

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-e528. DOI:10.1161/CIR.0000000000000659.
2. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation. 2009;119(10):1363-9. DOI:10.1161/CIRCULATIONAHA.108.816082.
3. Bansal N, Zelnick LR, Alonso A, et al. eGFR and Albuminuria in Relation to Risk of Incident Atrial Fibrillation: A Meta-Analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. Clin J Am Soc Nephrol CJASN. 2017;12(9):1386-98. DOI:10.2215/CJN.01860217.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4S):S1-S115. DOI:10.1016/j.kint.2020.06.019.
5. Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol JASN. 2009;20(4):705-11. DOI:10.1681/ASN.2007111207.
6. Nasri H, Rafieian-Kopaei M. Diabetes mellitus and renal failure: Prevention and management. J Res Med Sci Off J Isfahan Univ Med Sci. 2015;20(11):1112-20. DOI:10.4103/1735-1995.172845.
7. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J. 2009;157(5):805-10. DOI:10.1016/j.ahj.2009.02.005.
8. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. J Am Coll Cardiol. 2015;65(23):2481-93. DOI:10.1016/j.jacc.2015.03.577.
9. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet Lond Engl. 2010;375(9731):2073-81. DOI:10.1016/S0140-6736(10)60674-5.
10. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011;79(12):1331-40. DOI:10.1038/ki.2010.550.
11. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79(12):1341-52. DOI:10.1038/ki.2010.536.
12. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? Ann Clin Biochem. 2009;46(Pt 3):205-17. DOI:10.1258/acb.2009.009007.
13. Koopman MG, Krediet RT, Koomen GC, et al. Circadian rhythm of proteinuria: consequences of the use of urinary protein:creatinine ratios. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1989;4(1):9-14.
14. Huan L, Yuezhong L, Chao W, HaiTao T. The urine albumin-to-creatinine ratio is a reliable indicator for evaluating complications of chronic kidney disease and progression in IgA nephropathy in China. Clin Sao Paulo Braz. 2016;71(5):243-250. DOI:10.6061/clinics/2016(05)01
15. Vart P, Scheven L, Lambers Heerspink HJ, et al. Urine Albumin-Creatinine Ratio Versus Albumin Excretion for Albuminuria Staging: A Prospective Longitudinal Cohort Study. Am J Kidney Dis Off J Natl Kidney Found. 2016;67(1):70-8. DOI:10.1053/j.ajkd.2015.05.025.
16. Medcalf EA, Newman DJ, Gorman EG, Price CP. Rapid, robust method for measuring low concentrations of albumin in urine. Clin Chem. 1990;36(3):446-9.
17. Sparkenbaugh EM, Chantrathammachart P, Mickelson J, et al. Differential contribution of FXa and thrombin to vascular inflammation in a mouse model of sickle cell disease. Blood. 2014;123(11):1747-56. DOI:10.1182/blood-2013-08-523936.
18. Lee I-O, Kratz MT, Schirmer SH, Baumhäkel M, Böhm M. The effects of direct thrombin inhibition with dabigatran on plaque formation and endothelial function in apolipoprotein E-deficient mice. J Pharmacol Exp Ther. 2012;343(2):253-7. DOI:10.1124/jpet.112.194837.
19. Bea F, Kreuzer J, Preusch M, et al. Melagatran reduces advanced atherosclerotic lesion size and may promote plaque stability in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2006;26(12):2787-92. DOI:10.1161/01.ATV.0000246797.05781.ad.

About the Authors

Anastasiya A. Sokolova
ORCID 0000-0001-5938-8917
Alena I. Skripka
ORCID 0000-0001-6753-1365
Ilya I. Ivanov
ORCID 0000-0003-3438-069X
Veronika V. Kogay
ORCID 0000-0002-7802-1843
Alexander I. Listratov
ORCID 0000-0002-0401-1132
Alla A. Gindis
ORCID 0000-0002-3959-94823
Dmitry A. Napalkov
eLibrary SPIN 2894-5010, ORCID 0000-0001-5938-8917