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Research Article

FEATURES OF COGNITIVE DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND THE EFFECT OF CYSTATIN C ON IT DEPENDING ON THE STAGE OF THE DISEASE

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ABSTRACT

Chronic kidney disease (CKD) is a global problem of modern medicine. The neurological complications arising from this disease are an integral part of this condition because the kidneys and the brain have a similar anatomical structure of the vessels and a similar physiological structure of the processes occurring in them. Cognitive disorders (CD) that occur in CKD accompany almost every patient, regardless of the stage of the disease, and affect the psychological and social quality of life of patients. According to the literature, there are a number of substances called biomarkers, by determining which we can identify emerging neurological complications in the early stages of CKD. In our work, we used a new biomarker of renal function, cystatin C, which is characterized by free glomerular filtration and is not subject to tubular secretion. Its level in the blood serum of patients does not depend on the age, gender, muscle mass, ethnicity, diet, physical activity and bad habits of the patient.

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KEYWORDS

Chronic kidney disease (CKD), cognitive impairment (CD), cystatin C.

INTRODUCTION

Chronic kidney disease (CKD) is damage to the kidneys or a decrease in their function, recorded for 3 months or more, regardless of the initial diagnosis [1] The term "Chronic kidney disease" was introduced into the International Classification of Diseases of the 10th revision in 2007 and replaced the term "Chronic renal failure". According to world data, the global prevalence of CKD in the general population averages 14.4% [2, 5], which is comparable to such socially significant diseases as hypertension, coronary heart disease, diabetes mellitus, and obesity [3, 5]. The neurological complications arising from this disease are an integral part of this condition, because the kidneys and the brain have a similar anatomical structure of the vessels and a similar physiological structure of the processes occurring in them. It is believed that cerebrovascular diseases among patients with CKD occur at least 2 times more often than in the general population and potentially determine the cardiovascular prognosis and the risk of developing cognitive impairment (CI) in patients with CKD, both in the pre-dialysis and dialysis period [4,6-8]. According to the National Kidney Foundation USA, the incidence of cerebrovascular complications in predialysis patients is 65% and reaches 90% in patients undergoing program hemodialysis. [9,10] According to a systematic review and meta-analysis by T. Etgen et al. in 2012, CKD is an independent somatic risk factor for the development of CI [11]. Cognitive disorders (CD) that occur in CKD accompany almost every patient, regardless of the stage of the disease, and affect the psychological and social quality of life of patients. Previously, the severity of CKD was defined by the level of decrease in glomerular filtration rate (GFR). Modern formulas for calculating GFR based on the level of serum creatinine give errors. In 2012, KDIGO (Kidney Disease Improving Outcomes) experts recommended the use of Cystatin C as an additional method for determining the filtration function of the kidneys in addition to creatinine to

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improve the accuracy of GFR estimates. Using the biomarker of kidney damage cystatin C, we can identify neurological complications in the early stages of CKD.

First isolated in 1961 and formally identified as a cysteine protease inhibitor in 1984, cystatin C (CysC) is a soluble, basic, non-glycosylated cysteine protease inhibitor found in nearly all mammalian tissues (27). CysC is found in seminal plasma (~3.7 μm) (28), cerebrospinal fluid (1–5 μm) (29, 30) and blood plasma (0.2–1 μm) (30) Detectable levels of the peptide are detected in saliva and urine [11–18].

The aim of our study was: To study the features of CR in patients with CKD depending on the stage of the disease and the effect of the biomarker of kidney damage cystatin C on it.

MATERIALS AND METHODS

Under our supervision, there were 100 patients

According to the ICD Classification 10 (N18), all patients are divided into 3 groups:

1. pre-dialysis patients (N18.1 N18.2 N18.3 N18.4) - 28 patients (28%). The mean age was 56.1±12.1
2. Patients on planned hemodialysis (N18.5) - 30 patients (30%). The mean age was 53.1±13.3
3. Patients after kidney transplantation (Z94.0) - 43 patients (43%). The mean age was 34.8±9.3

The criterion for exclusion from the study was the presence of thyroid diseases that can affect the level of serum cystatin C.

All patients underwent a standard neurological examination (collection of complaints, anamnesis of the disease, life, examination of neurostatus, and a scale for assessing cognitive functions according to the SAGE (Self-administered Gerocognitive Examination) scale was used, aimed at identifying mild and moderate impairments to memory and thinking. The choice of this test is due to the higher specificity and sensitivity of the study compared to the more popular MMSE questionnaire (SAGE specificity 95% versus 90% MMSE sensitivity 79% versus 71% MMSE), as well as the minimum possibility of a doctor's subjective influence on the test result from the patient, which made it possible to more objectively detect even the initial manifestations of CI in the examined patients [14]. a dimensional figure and a watch, an assessment of the patient's vocabulary, building a sequence, and a task for

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transforming phi gurus. The test result >20 points was assessed as normal; 17–19 points — mild CI; 15–16 points — the presence of moderate CI; less than 14 points - the presence of dementia. As well as the determination of the biomarker of kidney damage Cystatin C by enzyme immunoassay.

Patients did not statistically differ among themselves in terms of the level of education of patients but differed in age and professional employment due to younger patients after kidney transplantation. Table 1 shows the main statistics depending on the stage of the disease.

RESULTS

Table 1.

Index	Pre-dialysis period CKD C1, C2, C3a, C3b, C4 n=28	Hemodialysis program C5 n=30	Patients after transplantation n=43
Arithmetic mean	17,071	16,233	17,721
Standard deviation	1,215	1,569	1,221
Median	17	16	18
No CR	0	1 (3,33%)	3 (7%)
Simple CR	18 (64,2%)	9 (30%)	33 (76,7%)
Moderate CR	10 (35,7%)	18 (60%)	7 (16,2%)
Dementia	0	2 (6,6%)	0

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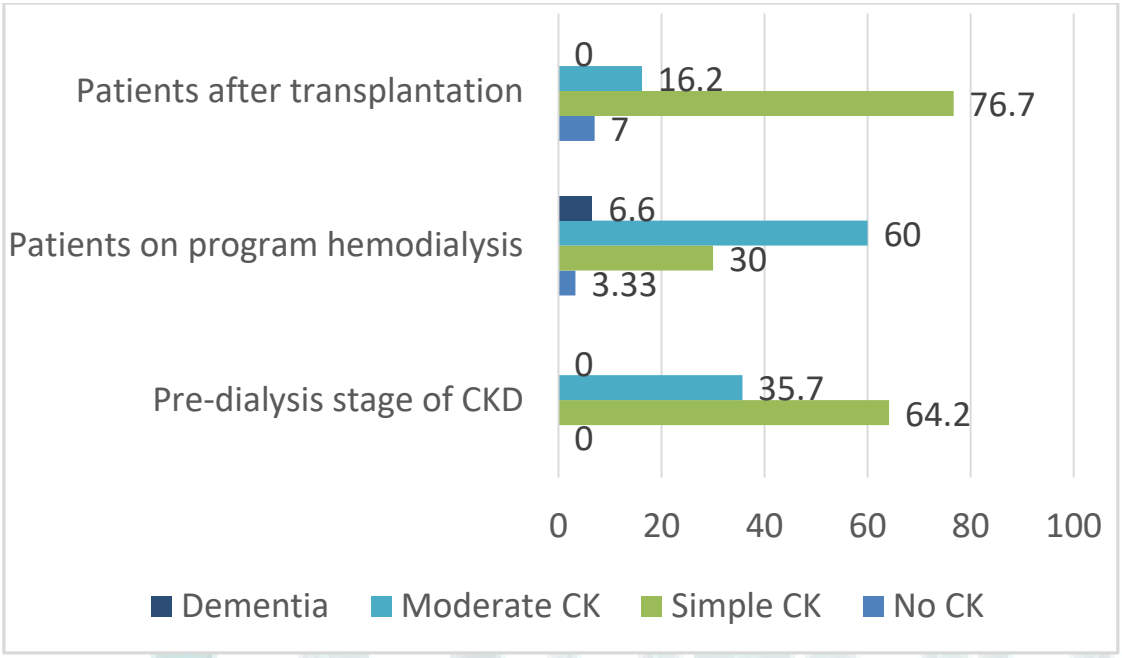

Figure 1 Frequency and severity of CR in patients with CKD depending on the stage

In the objective assessment of cognitive functions on the SAGE scale in the group of patients who do not receive hemodialysis (n=23), 18 patients (64.2%) had mild CI, 10 patients (35.7%) had moderate CI, none of them received scores corresponding to dementia. from patients. In the group of patients receiving program hemodialysis (n=30), 1 patient had no CR, his scores corresponded to the normative data, 9 (30%) patients had mild CR, 18 (60%) patients had moderate CR and 2 (6, 6%) of patients had signs of dementia. In the group of patients after kidney transplantation (n=43), the indicators of the cognitive scale were better, here 3 (7%) patients had no cognitive disorders, 33 (76.6%) patients had mild CR and 7 (16.2%) had moderate CR. The data obtained indicate that cognitive impairment is observed in all patients with CKD, regardless of the stage of the disease, but lower scores on the cognitive scale are observed in patients who are on hemodialysis, and according to our data, 64.2% of patients with CKD who do not receive hemodialysis have CR mild, which can be identified at an early stage and prevent further progression of cognitive dysfunction.

According to our data, none of the patients found it difficult to name the date and location, i.e.

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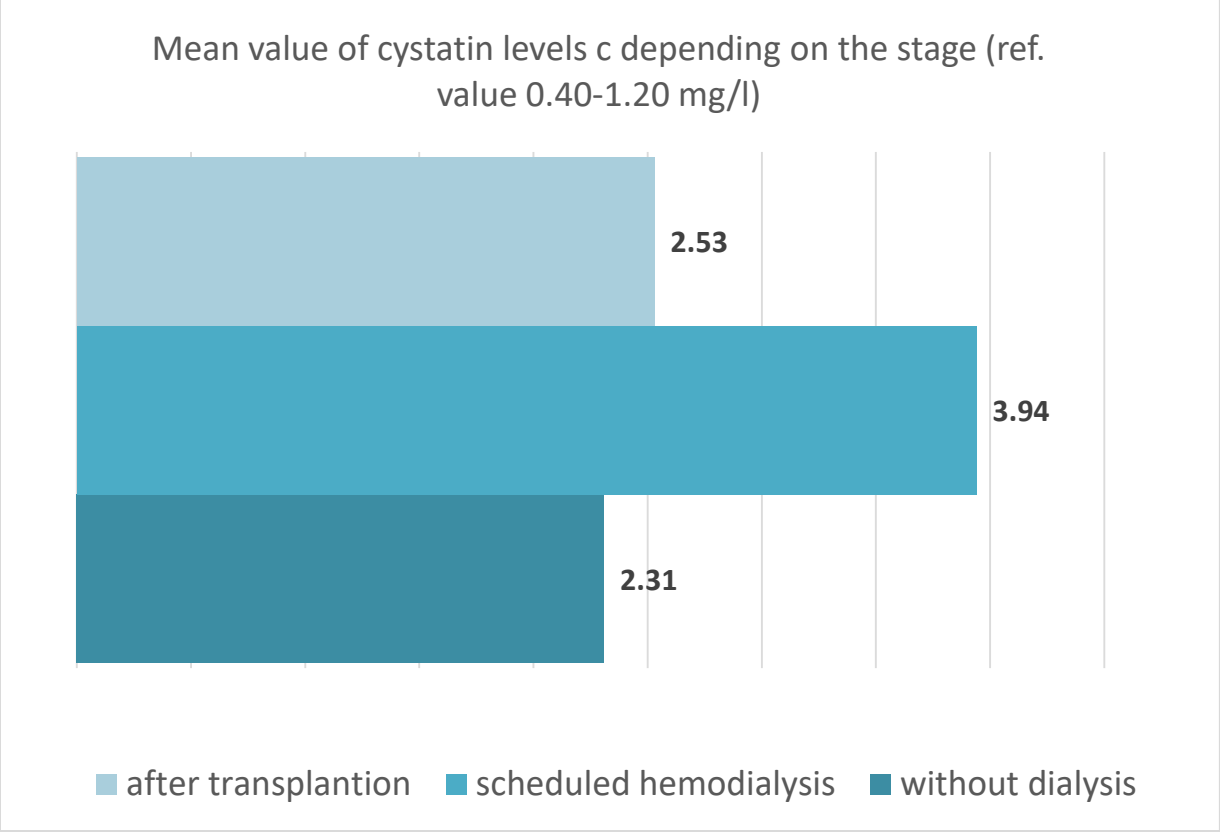
orientation in time and space is preserved in all patients. The greatest difficulties were caused by calculations, sequence building, and tests of drawing a clock and a three-dimensional figure. All patients under our supervision underwent determination of the level of cystatin C in the blood serum by enzyme immunoassay. Levels of cystatin C depending on the stage of the disease:

The average value of the level of cystatin C in the group of patients at the pre-dialysis stage of CKD was 2.31 ± 0.97, in the group of patients receiving program hemodialysis this value was higher, which indicates the progression of a decrease in renal function-3,94±1.97, in the group of patients who underwent kidney transplantation with an average value of Cystatin C was 2.53±1.45.



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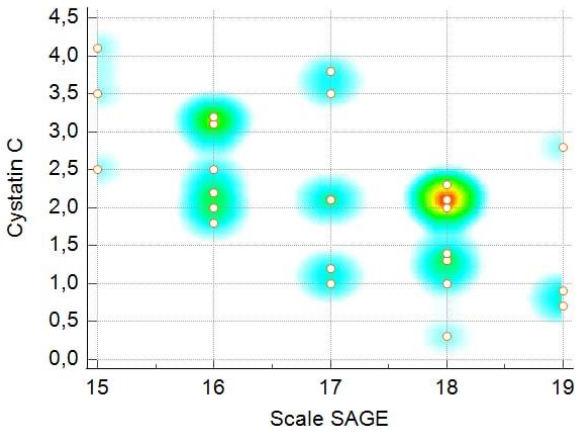
The relationship between two quantitative traits was carried out using the nonparametric Spearman correlation coefficient. The selected critical significance level was 5% (0.05), which is generally accepted in biomedical research.

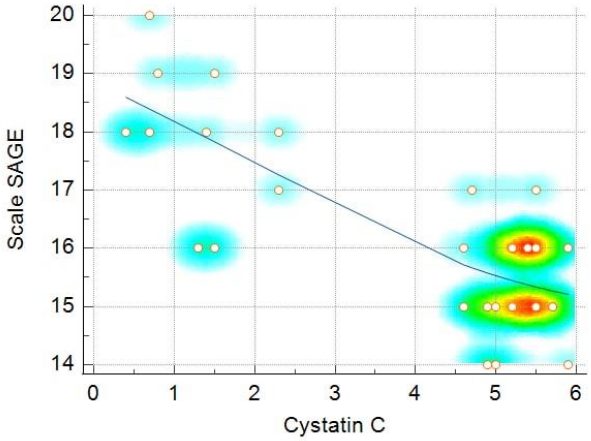
When analyzing indicators of cognitive function and the level of cystatin C in the serum of patients with CKD, statistically significant relationships were identified.

An inverse correlation relationship of moderate strength (r = -0.58**, P=0.0009) was found between the SAGE scores and the level of cystatin C in the group of patients who did not receive hemodialysis. A statistically significant relationship was also found between these indicators in the group of patients who are on planned hemodialysis (r = -0.77***, P<0.0001). In the group of patients who underwent kidney transplantation, the correlation was even (r = -0.47***, P=0.0014). These data indicate that the higher the level of cystatin C in the blood serum, the lower the score on the cognitive scale.

Predialysis stage of CKD



Programmed hemodialysis



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Patients after transplant

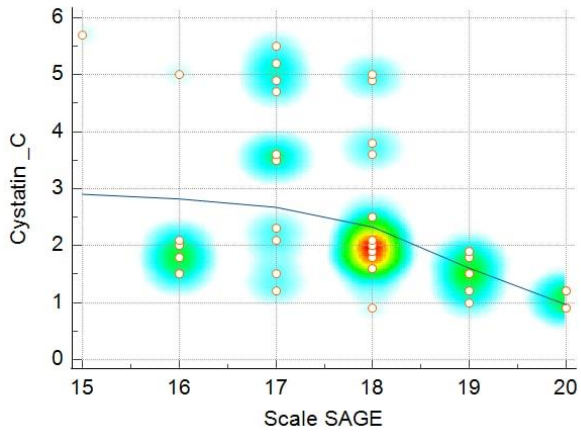

Figure 2 Variance chart. Correlation relationship between the level of cystatin C and the SAGE scale

DISCUSSION

As a result of using the SAGE scale, CRs were detected in almost all patients with CKD, regardless of the stage of the disease. Patients who are at the pre-dialysis stage of CKD in 64.2% of cases had mild CR; 35.7% moderate CR, signs of dementia were not detected in this group of patients. With the progression of renal pathology and the duration of the disease, the frequency of CR progressed so in the group of patients who are on planned hemodialysis, these figures are much higher (mild CR was detected in 30% of cases, 60% moderate, and 2 patients (6.6%) showed signs of dementia). Data on the high prevalence of CI in patients with CKD are also consistent with previously performed works by foreign authors. Thus, the first systematic review and meta-analysis by T. Etgen et al. (2012) suggested a relationship between the presence of CKD and the development of CI and confirmed the hypothesis that CKD is an independent somatic risk factor for the development of CI [12]. As a result of the meta-analysis carried out, the authors concluded that there was a decrease in cognitive functions in patients with CKD compared with patients without renal pathology (OR 1.65; 95% CI 1.32–2.05; $p<0.001$) [12]. These data indicate that timely early diagnosis of neurological disorders, namely cognitive impairment, will help to avoid further cerebrovascular complications. The role of cystatin C as a risk factor for cerebral

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complications was shown by N. Hashimoto et al. [30], in which researchers, having studied echocardiogram data in patients with stable and non-sustained atrial fibrillation, found that a calculated analysis using plasma cystatin C may predict cerebral disorders at the pre-dialysis stage of CKD. In an epidemiological study, higher cystatin C levels were associated with poorer performance on the Mini-Mental Status Assessment (MMSE) and the Digit Symbol Substitution Test [33]. According to the results of magnetic resonance imaging of the brain, an increase in the level of cystatin C is associated with an increased risk of lacunar infarcts and damage to the white matter of the brain [34, 35]. Our work also revealed statistically significant correlations between the level of cystatin C in the serum of patients and the scale of cognitive dysfunction, these data indicate that at elevated concentrations of cystatin C, the cognitive function of patients worsens.

Conclusions

1. The data obtained indicate that cognitive impairment is observed in all patients with CKD, regardless of the stage of the disease, but lower scores on the cognitive scale are observed in patients who are on hemodialysis (18 (60%))
2. Also, 64.2% of patients in the pre-dialysis stage of CKD have mild CR, which can be detected at an early stage and prevent further progression of cognitive dysfunction.
3. Kidney transplantation partially restores kidney function and alleviates many uremic symptoms, including cognitive functions of patients (mild CR in 33 (76.7%), moderate CR in 7 (16.2%)), at the same time, immunosuppressive therapy, as well as other psychological and social factors, can affect the cognitive functions of patients.
4. When analyzing cognitive function parameters and serum cystatin C levels in patients with CKD, statistically significant relationships were found in all three groups of patients. These data indicate that the higher the level of cystatin C in the blood serum, the more pronounced the pathological process in the kidneys and, accordingly, in the brain.

References

1. Etgen T, Chonchol M, Ferstl H, Sander D. Chronic kidney disease and cognitive

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impairment: a systematic review and meta-analysis. Am J Nephrol 2012; 35(5): 474-82.

2. Hill NR, st. Fatoba, Oke JL et al. Global prevalence of chronic kidney disease: a systematic review and meta-analysis. PLOS One 2016; 11(7): e0158765.
3. Khrulev A.E., Studyanikova S.F., Langraf S.V. Cognitive disorders in patients on hemodialysis. Bulletin of Neurology 2019; 51(2):36-40. Russian [Khrulov A. E., Studyanikova S. F., Langraf S. V. et al. Cognitive impairment in patients on program hemodialysis. Neurological Bulletin 2019; 51(2):36-40]
4. Khrulev A.E., Tolbuzova D.D., Plokhenko E.A. Cognitive status and risk factors for cognitive impairment in dialysis patients. General resuscitation 2020; 16(4):21-31. Russian [Khrulev A. E., Tolbuzova D. D., Plokhenko E. A. et al. Cognitive status and risk factors for cognitive impairment in dialysis patients. General resuscitation 2020; 16(4):21-31).]
5. Mark P.B. // Cardiovascular risk management strategies in chronic kidney disease // Transplant Nephrological Dialysis 2017; 33(1):23-5.
6. Nathan E., Penersen S. E. Dialysis encephalopathy // Acta.Pediatr. Scand. - 1980. - No. 69. - S. 793-796.
7. Nikitina A.A., Khrulev A.E. Cerebral circulation disorders in the pre-dialysis period of chronic kidney disease and mechanisms of their development. Medical Almanac 2018; 56(5):28-32. Russian [Nikitina A. A., Khrulev A. E. Cerebrovascular devices in the pre-dialysis period of chronic kidney disease and mechanisms of their development.Medical Almanac 2018; 56(5):28-32)]
8. Raskin Neil H. Neurological aspects of renal failure // Neurology and General Medicine / Ed. M.J. Aminoff. - 3rd ed. -2001. - S. 231-246.
9. Rogova I.V., Fomin V.V., Damulin I.V. Vascular cognitive impairment in chronic kidney disease. Neurology, neuropsychiatry, psychosomatics 2015; 7(1):11-8. Russian [Rogova I. V., Fomin V. V., Damulin I. V. et al. Vascular cognitive impairment in chronic kidney disease. Neurology, neuropsychiatry, psychosomatics 2015; 7(1):11-8].
10. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification // Amer. J. Dis. ... cand. honey. Sciences - 2007. - No. 39 (2). - P. 5-266.

FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
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11. Chronic kidney disease: Clinical guidelines / Russian Association of Nephrologists, 2019. [Chronic kidney disease: clinical guidelines / Russian Association of Nephrologists, 2019. URL: http://nonr.ru/wp-content/downloads/2020/01/Clin_guidlines_CKD_24 11_final-3–3. pdf (March 12, 2020)]
12. Charre D.W., Chang S.I., Merden R.A. et al. Brief Cognitive Assessment Tool for Mild Cognitive Impairment (MCI) and Early Dementia. Alzheimer's Disorder Association 2010;(24): 64-71.
13. Murkamilov I. T., Sabirov I. S., Fomin V. V., Murkamilova Zh. A., Aitbaev K. A., Raimzhanov Z. R. Assessment of nephrocerebral risk in the use of cystatin C in patients with chronic kidney disease. Journal of Neurology and Psychology named after S.S. Korsakova. 2018;118(9):10-16. https://doi.org/10.17116/jnevro201811809110
14. Hashimoto N., Nishiyama S., Watanabe T., Vanezaki M, Yamaura G, Arimoto T, Takahashi H, Shishido T, Miyamoto T, Kubota I. Abstract 13956: Estimated glomerular filtration rate based on Cystatin C is an Acceptable Parameter for Stroke in Patients with Atrial Fibrillation. Circulation.2015;132:A13956
15. Etgen T, Chonchol M, Ferstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. Am J Nephrol 2012; 35(5):474-82.
16. Estimated glomerular filtration rate based on Cystatin C is an acceptable Parameter for assessing stroke in Patients with Atrial Fibrillation. Circulation. 2015;132:A13956.