Title: Clinical significance of subclinical carotid atherosclerosis and its relationship with echocardiographic parameters in non-diabetic chronic kidney disease patients

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Version: 2 Date: 25 October 2013

Author’s response to reviews:

Dear editors and reviewers,

We greatly appreciate the opportunity to revise our paper in light of reviewers’ comments and resubmit it for publication on BMC Cardiovascular Disorders.

Enclosed is a revised version of our manuscript, previously submitted to your attention as MS: 1073766718106658 “Clinical significance of subclinical carotid atherosclerosis and its relationship with echocardiographic parameters in non-diabetic chronic kidney disease patients”.

We made our best efforts in order to make the requested revisions in light of the editor and reviewer’s comments. Below you can find an itemized, point-by-point detailed response to all the questions and comments of the reviewers.

We hope our paper is now suitable for publication on BMC Cardiovascular Disorders in its present form and we are now resubmitting it to your attention.

Referee 1:

Comments:

#1. The presence of carotid plaque and/or an increase in cIMT has indeed been shown to predict CV events in many previous studies, and the current paper is able to reproduce this. What restricts the clinical usefulness of cIMT measurements, however, is a demonstration that a change in cIMT with any kind of treatment correlates with a change in CV prognosis. This is the case for parameters such as Echo-LVH, ECG-LVH or proteinuria, where a change in the parameter does correlate with a change in prognosis. As a consequence, the enthusiasm for cIMT measurements has considerably declined over the last years (e.g. please see treatment guidelines of the European Society of Hypertension). I think this problem with cIMT measurements should be mentioned in this article.
The 2007 European guidelines on hypertension have emphasized that treatment-induced regression of asymptomatic organ damage could reduce the risk of fatal and nonfatal CV events. This has been shown with the treatment-induced regression of electrocardiographic LVH (JAMA 2004;292:2343–2349), the echocardiographic LVH (Hypertension 2004;44:459–464), LVM and left atrial size (JAMA 2004;292:2350–2356). Furthermore, the treatment-induced reduction in urinary protein excretion have also lowered adverse CV events (Hypertension 2005;45:198–202). However according to a recent analysis of the ELSA study, the treatment-induced cIMT changes in the carotid arteries failed to document a predictive value for CV events, possibly because the changes are minimal and their impact masked by large between-subject differences (Circulation 2009; 120:1084–1090). Therefore, the use and enthusiasm for cIMT as a marker of subclinical organ damage has considerably declined over the last years. We added this content in DISCUSSION section of revised manuscript (See “DISCUSSION” in revised manuscript)

Comments:

#2. However, what makes this paper interesting is the fact that carotid plaque and/or cIMT clearly and independently predicted CV prognosis in subjects with advanced, non-diabetic kidney disease. Patients with dialysis-dependent renal failure succumb to infections, cancer and course CV endpoints. However, the CV endpoints in patients on dialysis are not only coronary events but often sudden cardiac death, and atherosclerosis is considered not to play such an key role in the latter. In the latter, perhaps electrolyte disturbances are thought to be important contributors. This is perhaps why (antiatherosclerotic) statin treatment in the 4D and AURORA studies did not reduce CV events in hemodialysis patients. Less clear is the situation in patients with advanced, but not (yet) dialysis-dependent renal failure. Is their CV disease more of an atherosclerotic nature (and statins etc. maybe effective), or is their CV disease more like that in dialysis patients (and statins presumably ineffective). The SHARP trial was recently able to show that lipid lowering does reduces CV events in subjects with pre-dialysis dependent renal failure, suggesting that atherosclerosis does play an important role in these patients. The current study would support the findings of SHARP in that atherosclerosis predicts CV events in advanced, but not dialysis-dependent non-diabetic renal failure, keeping the weaknesses of cIMT measurements in mind. I think references to the 4D, AURORA and SHARP studies should be included in the manuscript.

Reply:

In our study, carotid plaque, a representative marker of atherosclerosis, was a main predictor of adverse CV events in non-diabetic CKD patients who were not yet on dialysis treatment. This finding would support the results of SHARP (Study of Heart And Renal Protection) study which evaluated the anti-atherogenic effect of statin in large cohort of patients with pre-dialysis CKD and patients undergoing dialysis. The study showed a significant reduction in major CV events (Lancet
377, 2181–2192, 2011) with statin treatment, suggesting that atherosclerosis does play an important role for adverse CV events. However, according to the results of another two large clinical trials conducted only in patients receiving hemodialysis, 4D (Deutsche Diabetes Dialyse Studie) and AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular e), statins showed little or no benefit as primary CV diseases prevention. With these, the pathophysiology of CV disease in non-dialysis CKD patients seems to be more strongly associated with atherosclerosis compared to that of patients receiving dialysis treatment. This may be why the carotid plaque predicted adverse CV events in our study.

Referee 2:

Comment 1:
Blood urea nitrogen in Table 1, looks not normal distribution data, if not it should be present as medians with ranges, and analysis methods should be carefully chose.

Reply:
As you pointed, serum BUN levels did not follow the normal distribution in our study. In revised manuscript, therefore, serum BUN levels were present as median with ranges and the differences between two groups were compared using Mann–Whitney U test.

Clinical characteristics Total (n=182) Carotid atherosclerosis + (n=99, 54.4%) - (n=83, 45.6%) p
Blood urea nitrogen (mg/dL)* 28.7 (10.8-118.3) 30.9 (10.8-118.3) 27.1 (12.2-99.0) 0.065
*median with ranges

Comment 2:
There is one thing I concerned that all the patients in this study just had one eGFR evaluation, while according to the CKD definition the eGFR< 60 mL/min/1.73 m2 should exist for 3 months. I suggest authors should recognize that in the limitation.

Reply:
CKD is defined as low eGFR (eGFR< 60 mL/min/1.73 m2) with abnormalities of kidney structure or function, present for > 3 months with implications for health. As mentioned in original manuscript, our hospital began an atherosclerosis surveillance program using carotid ultrasonography (US) with stable CKD patients since January 2008. To avoid the enrollment of ineligible patients, those taking any medications that may affect renal function, such as non-steroidal anti-inflammatory drugs, antibiotics, and herbal medications at the time of
evaluation were not included. However, the possibility of acute renal deterioration during study period or the frequency of renal function measures may be one of the limitations of our study (See “METHOD” and “DISCUSSION” section in revised manuscript).

Comment 3:
Obesity associated with CVD in several studies, authors did not offer waist circumference and analysis it’s impact on IMT and CVD. But I suggest BMI should be taken into univariate multivariate and survival analysis?

Reply:
In this study, we did not measure waist circumferences of the patients. Therefore, as you recommended, we analyzed the effect of BMI on carotid atherosclerosis and adverse CV events. As a result, the effect of BMI on atherosclerosis and adverse CV events was unclear in our study.

Table 3
Parameters Univariate analysis Multivariate analysis
Unstandardized coefficient β P Unstandardized coefficient β P
Age 0.02 (0.01, 0.02) <0.001 0.02 (0.01, 0.02) <0.001
Hypertension 0.29 (0.11, 0.48) 0.002 0.12 (-0.06, 0.30) 0.199
Systolic BP (mmHg) 0.01 (-0.01, 0.01) 0.103 - -
Diastolic BP (mmHg) -0.01 (-0.02, -0.01) 0.026 -0.01 (-0.06, 0.31) 0.177
Pulse pressure (mmHg) 0.01 (0.01, 0.02) <0.001 0.01 (-0.01, 0.01) 0.267
BMI (kg/m2) -0.01 (-0.04, 0.01) 0.176
Urine PCR (g/g)* -0.04 (-0.10, -0.01) 0.097 - -
hs-CRP* 0.09 (0.02, 0.15) 0.010 0.08 (0.02, 0.14) 0.013
Statins 0.11 (-1.10, 1.26) 0.215 - -
Echocardiographic data
LVH 0.13 (-0.02, 0.28) 0.095 - -
LVEF -0.01 (-0.01, 0.01) 0.161 - -
E/A ratio -0.28 (-0.56, 0.01) 0.052 - -
E' -0.05 (-0.08, -0.02) 0.003 - -
E/E' ratio 0.04 (0.02, 0.06) <0.001 0.02 (0.01, 0.04) 0.034

Table 4
Parameters Adverse CV events Univariate analysis Multivariate analysis
+ (n=23) - (n=159) P HR (95% CI) P
Age (years)† 72.5 ± 11.2 67.2 ± 15.1 0.098 1.05 (0.91-1.01) 0.087
Male, n (%) 13 (56.5) 83 (52.2) 0.740 - -
Smokers, n (%)† 13 (56.5) 57 (35.8) 0.012 3.13 (1.10-9.09) 0.036
Hypertension, n (%)† 20 (87.0) 109 (68.5) 0.043 1.61 (0.88-2.51) 0.101
SBP (mmHg) 138.9 ± 31.0 133.6 ± 19.2 0.181 - -
DBP (mmHg) 78.0 ± 14.0 75.1 ± 11.7 0.150 - -
Pulse pressure (mmHg) 60.9 ± 24.6 58.5 ± 15.8 0.552 - -
BMI (kg/m2) 24.1 ± 3.2 24.3 ± 3.7 0.746
Serum creatinine (mg/dL) 2.8 ± 3.1 2.7 ± 2.4 0.910 - -
LDL-cholesterol (mg/dL) 100.5 ± 34.1 96.2 ± 41.0 0.684 - -
Urine PCR* -0.97 ± 1.22 -1.2 ± 1.45 0.426 - -
hs-CRP (mg/L) *† 0.03 ± 1.27 -0.23 ± 1.10 0.220 1.22 (0.58-1.28) 0.486
Echocardiography
LVH† 13 (56.5) 56(35.2) 0.029 2.01 (0.81-5.34) 0.128
LVEF 58.3 ± 9.8 59.1 ± 9.7 0.778 - -
LVMI 112.0 ± 27.9 101.4 ±29.5 0.133 - -
E/A ratio† 0.64 ± 0.12 0.78 ± 0.30 0.013 0.02 (0.001-0.55) 0.022
E/E' ratio† 13.7 ± 5.21 11.3 ± 3.7 0.003 1.10 (1.01-1.21) 0.042
Carotid plaque, n (%)† 18 (78.3) 72(45.3) 0.001 7.80 (1.45-45.97) 0.017
Carotid IMT (mm) † 0.95 ± 0.13 0.84 ± 0.15 0.010 10.58 (0.43-26.87) 0.149

Comment 4:
CKD patients often present anemia and affects CVD. Authors should take anemia into analysis both in univariate, multivariate and survival analysis.

Reply:
As you pointed, anemia is a potential nontraditional risk factor for cardiovascular disease (CVD) in patients with CKD. As renal failure progresses, the incidence and severity of anemia increases. However, in our study, baseline hemoglobin levels were similar between patients with and without carotid atherosclerosis. The incidence of anemia (Hb less than 13.5 g/dL in men and 12.0 g/dL in women per KDOQI guidelines) was also similar between patients with and without carotid atherosclerosis (60.8% vs. 59.2%, p=0.266). Moreover, the effects of anemia on adverse CV events were statistically insignificant in this study (Hazard ratio 1.50, 95% CI 0.63-3.58, p=0.358). We think these results were due to the frequent injection of recombinant human erythropoietin in our CKD patients (In KOREA, recombinant human erythropoietin is under public insurance coverage when hemoglobin levels fall below 10.0 mg/dL in patients with eGFR<30 mL/min/1.73m2).

Comment 5:
Is E/E’ ratio predict CV outcomes in this cohort of CKD patients? Authors should analyze that.

Reply:
As shown in Table 4 of original article, E/E’ ratio predict CV outcomes in multivariate Cox proportional hazard model (Hazard ratio 1.10, 95% CI 1.01-1.21, p=0.042).

Comment (Minor Essential Revisions):
Are 23 adverse CV events occurred during the follow up all fetal or non-fetal?

Reply:
During the study periods, 23 cases of adverse CV events were observed: 20 non-fatal cases and 3 fatal CV events. Fatal events were occurred at 20.3, 30.3 and 31.5 months of follow-up (added in “RESULT” section of revised manuscript).

Editor’s Request:
(1) Authors’ Contribution
- Please place the Authors’ Contributions section after Competing interests. Please check the instructions for authors on the journal website for the correct format to use for Authors’ Contributions.

Reply:
We added the Authors’ Contributions section in revised manuscript. 1) Jwa-Kyung Kim: Data collection, analysis and writing up, 2) Young Rim Song: Data analysis and statistical advisory, 3) Min Gang Kim: Data analysis and statistical advisory, 4) Hyung Jik Kim: Study design Determination, 5) Sung Gyun Kim: Research initiative and study design determination

Thank you for your kind considerations and I am looking forward to hearing a positive reply from you soon.

Yours sincerely

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