Coronary Microvascular Function in Early Chronic Kidney Disease

David M. Charytan, MD, MSc; Heinrich R. Shelbert, MD; Marcelo F. Di Carli, MD

Background—Coronary microvascular dysfunction may underlie the high cardiovascular risk associated with chronic kidney disease (CKD), but the effects of CKD on coronary microvasculature function remain uncertain.

Methods and Results—We assessed myocardial blood flow changes in mild-to-moderate CKD and analyzed the association between creatinine clearance (CrCl) and peak myocardial blood flow and coronary flow reserve (CFR) measured as the ratio of stress to rest perfusion at baseline and at 1 year in 435 nondiabetic individuals who underwent quantitative rest and pharmacological stress positron emission tomography imaging. At baseline, CFR was significantly associated with CrCl (β per 10 mL/min increase, 0.07; P = 0.001). Factors such as age and blood pressure accounted for this association, and it was not significant in adjusted analyses (β = −0.02, P = 0.53). Peak flow was not associated with CrCl in either crude or adjusted analyses (β per 10 mL/min increase = −0.02 mL/min per g, P = 0.29). Although change in peak flow at 1 year was similar in patients with and without CKD, CrCl was a strong and independent predictor of a higher rate of change in CFR, with a loss of 0.11 CFR units/y (95% confidence interval, 0.01 to 0.20) for each 10 mL/min drop in CrCl (P = 0.03).

Conclusions—These findings demonstrate that mild-to-moderate CKD is not independently associated with a reduction in peak myocardial flow or CFR and suggests that microvascular changes are unlikely to explain the high cardiovascular mortality in mild to moderate CKD. Loss of CFR, however, may accelerate in mild to moderate CKD. Further studies are needed to determine whether these changes lead to more significant reductions that may reduce peak flows and CFR and contribute to cardiovascular risk in more severe CKD. (Circ Cardiovasc Imaging. 2010;3:663-671.)

Key Words: kidney ■ collateral circulation ■ vasculature

Chronic kidney disease (CKD) is associated with a high risk of development and dying of cardiovascular disease,1 a link that remains incompletely understood. Although traditional cardiovascular risk factors are common in CKD and may partly explain the increased risk,2 these factors fail to fully account for the increased incidence of myocardial infarction (MI) and cardiovascular death in this population.3 In fact, the association of several risk factors with cardiovascular outcomes is reversed in patients with advanced CKD,4 and the negative results of recent, large, randomized statin trials in patients with end-stage renal disease5,6 lend further support to the idea that nontraditional mechanisms may play a more important role in the pathophysiology of cardiovascular disease (CVD) in individuals with CKD than in those without CKD.

Clinical Perspective on p 671

Although a number of novel risk factors, in particular oxidative stress and inflammation,7 have received extensive attention in recent years as potential mechanisms underlying CVD in patients with CKD, other factors may also play a role. Coronary microvascular function is a particularly intriguing player that has not been well studied in CKD. Clinical studies in the general population have demonstrated that better collateral vascularization of the myocardium predicts better survival and fewer complications after an initial MI8,9, and experimental studies demonstrating increased infarct size and impaired ischemia-driven angiogenesis in uremic animals10,11 suggest that changes in microvascular supply or function could be partly explain the high cardiovascular mortality rate in the CKD population. Studies demonstrating a marked reduction in left ventricular (LV)capillary density12 in uremic animals and similar changes in a small cohort of patients with end-stage renal disease but without epicardial coronary artery disease13 lend further support to the concept that alterations in the coronary microvasculature may partly account for the increased risk of cardiovascular events in patients with CKD.

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From the Department of Medicine (D.M.C.), Renal Division, the Department of Radiology (M.F.D.C.), Division of Nuclear Medicine and Molecular Imaging, and the Noninvasive Departments of Medicine (Cardiology) and Radiology (M.F.D.C.), Cardiovascular Imaging Program, Brigham and Women’s Hospital, Boston, Mass; and the Department of Medical and Molecular Pharmacology (H.R.S.), David Geffen School of Medicine at UCLA, Los Angeles, Calif.

The trial was not registered because enrollment was completed in 2002.

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Correspondence to David Charytan, MD, Renal Division, Brigham and Women’s Hospital, 1620 Tremont St, 3rd Floor, Boston, MA 02120. E-mail dcharytan@partners.org

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Our objective was to investigate the relationship between peak myocardial blood flow (MBF), flow reserve, and CVR (as indices of coronary microvascular function) and renal function in humans without unstable coronary artery disease. We hypothesized that coronary vasodilator reserve would be reduced in patients with mild to moderate CKD. We used quantitative positron emission tomography (PET) imaging to measure regional MBF at rest and during maximal vasodilation by adenosine and to estimate CVR and vasodilator reserve.

Methods

Subjects

We analyzed data from patients screened for inclusion in the RAMPART trial, a multicenter, double-blind, randomized trial conducted between 1998 and 2002 that compared 2 doses of an acyl coenzyme A cholesterol acyltransferase inhibitor (avasimibe) in combination with a statin versus a statin alone.14 For inclusion in the screening phase, patients were required to be off lipid-lowering medications for at least 4 weeks and have 1 of the following: a history of coronary disease, an LDL cholesterol level ≥160 mg/dL, or 2 standard cardiovascular risk factors with an LDL ≥130 mg/dL. Women of child-bearing age, as well as patients with a history of diabetes, liver disease, uncontrolled hypertension, symptomatic heart failure, di- child-bearing age, as well as patients with a history of diabetes, liver disease, uncontrolled hypertension, symptomatic heart failure, and renal insufficiency, were excluded from participation. After the initial PET scan, the subset of individuals with a coronary flow reserve (CFR) <2.5 in at least 1 arterial territory or a stress defect occupying ≥15% of at least 1 coronary territory received a low-cholesterol diet for 4 weeks. Individuals with LDL ≥100 mg/dL after 4 weeks were randomly assigned to 1 year of therapy with avasimibe plus atorvastatin 10 mg/d or atorvastatin plus placebo. The study was approved by local institutional review boards at the participating centers, and all patients gave written informed consent.

Measurement of Myocardial Perfusion

Patients underwent PET imaging for assessment of MBF using whole-body PET tomographs (Siemens/CTI, Knoxville, Tenn) at 12 US sites. All subjects refrained from caffeine-containing beverages or theophylline-containing medication for 24 hours before the PET study. Patients using calcium channel blockers or β-blockers were instructed to withhold the medications for 24 hours before the PET study. All subjects were studied in the fasting state.

Using [13N]ammonia, MBF was measured at rest and during peak hyperemia, as described previously.15 A 10- to 15-minute transmission scan was acquired for correction of photon attenuation. Beginning with the intravenous bolus administration of [13N]ammonia (0.286 μCi/kg), serial images were acquired for 19 minutes. Thirty minutes later, intravenous adenosine (0.14 mg/kg/min) was infused for 6 minutes. Three minutes into the adenosine infusion, a second dose of [13N]ammonia was injected and images were recorded in the same acquisition sequence. Heart rate, arterial blood pressure, and 12-lead ECG were recorded at baseline and throughout the infusion of adenosine. Image acquisition protocols were standardized at each site, and measurements of MBF were performed at a core laboratory. For the purpose of this analysis, changes in hemodynamics represent the average of values during the 2 minutes after the injection of [13N] ammonia corresponding to minutes 4 and 5 of the adenosine infusion, during which most of the myocardial uptake of [13N] ammonia takes place and there is maximal hemodynamic effect of adenosine.16

Data Analysis

Serially acquired transaxial images were reoriented into short-axis slices of the LV myocardium and assembled into serial polar maps, as described previously.15 In brief, regions of interest were assigned to the territory of the left anterior descending coronary artery, left circumflex artery, right coronary artery, and the center of the LV blood pool. Regional myocardial and blood pool time-activity curves were then generated, and MBF was calculated by fitting the curves with a validated 2-compartment tracer kinetic model.17 Rest MBF was normalized by the rate-pressure product, an index of cardiac work. CFR (primary study end point) was defined as the ratio between hyperemic and basal MBF. An index of coronary vascular resistance (CVR) was calculated by dividing the mean aortic blood pressure by MBF. Unless otherwise noted, MBF, CFR, and CVR are presented as averages of the entire LV.

Physical Examination and Renal Function

Blood pressure, weight, and heart rate were recorded before each PET scan, and laboratories were drawn before the initial injection of radiotracer. Serum creatinine was analyzed at a central laboratory. Because information on race was missing in a large number of subjects, the Cockcroft-Gault18 equation was used to estimate creatinine clearance (CrCl). Renal function was categorized according to the stages advocated by the National Kidney Foundation:19 preserved renal function/stage 1 CKD, CrCl ≥90 mL/min; stage 2, CrCl 60 to 89 mL/min; and stage 3, 30 to 59 mL/min. Stage 3 CKD was subdivided into stage 3a (creatinine clearance 45 to 59 mL/min) and stage 3b to stage 5 (CrCl <45 mL/min) for secondary analyses.

Statistics

Data are presented as mean ± standard deviation or median (interquartile range, IQR) according to the baseline distribution. Differences in baseline characteristics and myocardial perfusion indices were compared across categories of renal function using ANOVA or nonparametric trend tests for continuous data and χ2 tests of trend for count data. Probability values for post hoc pairwise comparisons according to baseline renal function were adjusted using the Bonferroni correction for count and non-normally distributed variables or the Tukey-Kramer procedure for normally distributed variables. The relationship between CFR and renal function was assessed using multiple linear regression models that included CrCl as a continuous predictor and age, race, sex, smoking status, presence of a stress defect, body mass index, blood pressure, and LDL cholesterol levels as covariates. Among randomly assigned patients followed for 1 year, the change in CFR during randomized therapy was assessed using similar linear regression models that included randomized therapy as an additional covariate. Model fit was tested using graphical techniques, inspection of residual distribution, and tests of model specification. All analyses were performed in STATA 9.0 (Stata Corporation, College Station, Tex). A value of P <0.05 was considered significant for all analyses.

Results

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the study cohort. Among 435 patients evaluated, stage 3b to 5, stage 3a, stage 2, and stage 1 CKD were present in 5, 48, 224, and 158 patients, respectively. Mean CrCl was 53.1 ± 6.7 mL/min in stage 3 CKD, 75.4 ± 8.8 mL/min in stage 2, and 109.6 ± 19.4 mL/min in individuals with preserved renal function (P <0.001). Individuals with CKD were more likely to be female and were older than patients with preserved renal function. (mean age, 68.5 and 60.5 years in stage 3 and stage 2 CKD compared with 49.9 years in individuals with preserved renal function; P for trend <0.001). Individuals with CKD were also characterized by lower total body weights (70.4 and 82.8 kg versus 100.3 kg, P <0.001) and higher systolic blood pressures (137.2 and 134.5 mm Hg versus 126.0 mg Hg, P <0.001) than individuals without CKD.
Association of Renal Function With Baseline Myocardial Perfusion

As shown in Table 2 and Figure 1, resting MBF to the LV was highest in patients with stage 3 CKD (0.81±0.23 mL/min per g), intermediate in patients with stage 2 CKD (0.80±0.24), and lowest in patients with preserved renal function (0.74±0.24) (£0.03). Normalization for the rate-pressure product, an index of cardiac work, equalized the differences in resting blood flow across categories of renal function. Although, peak hyperemic blood flow after adeno-

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Class 3 CKD (n=53)</th>
<th>Class 2 CKD (n=224)</th>
<th>Preserved Renal Function (n=158)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>68.3±6.5†‡</td>
<td>60.5±7.9§</td>
<td>49.9±9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>27 (49.1)†‡</td>
<td>163 (72.8)§</td>
<td>133 (84.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (93.1)</td>
<td>148 (96.7)</td>
<td>84 (88.4)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0)</td>
<td>4 (2.6)</td>
<td>7 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (7.0)</td>
<td>1 (0.7)</td>
<td>4 (4.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.4±11.4†‡</td>
<td>82.8±11.2§</td>
<td>100.3±17.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, median(IQR)</td>
<td>26.0 (23.1–27.4)†‡</td>
<td>27.9 (25.9–29.8)§</td>
<td>31.7 (28.7–35.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>61.7±9.7</td>
<td>61.4±10.7</td>
<td>62.1±10.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>137.2±23.7†‡</td>
<td>134.5±20.83§</td>
<td>126.0±17.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>70.1±8.6</td>
<td>72.3±10.2</td>
<td>71.0±9.9</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Labs and imaging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>241.0±46.1</td>
<td>243.1±46.1</td>
<td>239±48.0</td>
<td>0.72</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>155.6±34.1</td>
<td>153.7±38.9</td>
<td>150.5±44.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Glucose</td>
<td>91.1±9.6†‡</td>
<td>98.2±20.0</td>
<td>101.1±23.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2±0.3†‡</td>
<td>1.2±0.2§</td>
<td>1.1±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CrCl, mL/min</td>
<td>53.1±6.7†‡</td>
<td>75.4±8.8§</td>
<td>109.6±19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stress defect present, n (%)</td>
<td>13 (24.5)</td>
<td>64 (28.6)§</td>
<td>28 (17.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Summed stress score, median(IQR)</td>
<td>0.0 (0.0–6.0)</td>
<td>0 (0.0–11.0)</td>
<td>0.0 (0.0–4.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Summed rest score, median(IQR)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Summed difference score, median(IQR)</td>
<td>0.0 (0.0–0.6.0)†‡</td>
<td>0.0 (0.0–5.5)§</td>
<td>0.0 (0.0–0.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*ANOVA for normally distributed continuous variables, nonparametric trend test for non–normally distributed continuous variables, and χ2 tests for count variables.
†Class 3 CKD significantly different from class 2 CKD; ‡class 3 CKD significantly different from preserved renal function; §class 2 CKD significantly different from preserved renal function using Tukey-Kramer correction for post hoc tests for normally distributed variables or Bonferroni correction for non–normally distributed and count variables.

### Table 2. Myocardial Flow Indices in the Left Ventricle at Baseline in the Full Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Class 3 CKD (n=53)</th>
<th>Class 2 CKD (n=224)</th>
<th>Preserved Renal Function (n=158)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting MBF, mL/min/g</td>
<td>0.81±0.23</td>
<td>0.80±0.24†</td>
<td>0.74±0.24</td>
<td>0.03</td>
</tr>
<tr>
<td>Normalized resting MBF, mL/min/g</td>
<td>0.98±0.22</td>
<td>0.97±0.22</td>
<td>0.95±0.25</td>
<td>0.44</td>
</tr>
<tr>
<td>Adenosine MBF, mL/min/g</td>
<td>1.81±0.61</td>
<td>1.88±0.66</td>
<td>1.95±0.79</td>
<td>0.39</td>
</tr>
<tr>
<td>Resting CVR, mm Hg/mL/min/g</td>
<td>118.82±27.69*</td>
<td>124.77±36.75</td>
<td>133.06±40.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Adenosine CVR, mm Hg/mL/min/g</td>
<td>54.01±23.75</td>
<td>56.11±26.23</td>
<td>53.46±23.02</td>
<td>0.57</td>
</tr>
<tr>
<td>Normalized flow reserve</td>
<td>1.88±0.63</td>
<td>1.99±0.70</td>
<td>2.17±0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>CFR</td>
<td>2.32±0.88*</td>
<td>2.48±0.94†</td>
<td>2.82±1.26</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Class 3 CKD significantly different from preserved renal function; and †class 2 CKD significantly different from preserved renal function using Tukey-Kramer procedure for post hoc pairwise comparisons.
sine infusion was lower in patients with more advanced CKD, differences in peak blood flow across categories of renal function were not significantly different (P for trend, 0.39). Peak flow at baseline was also not associated with CrCl in fully adjusted analyses, (β for each 10 mL/min = 0.02 mL/min per g; 95% confidence interval [CI], -0.06 to 0.19; P = 0.29). In unadjusted analyses, LV CFR was strongly associated with renal function and declined markedly across categories of decreasing renal function from 2.32±0.88 (stage 3 CKD) to 2.48±0.95 (stage 2 CKD) and 2.82±1.26 in patients with preserved renal function (P = 0.001) (Figure 1).

Similar trends were seen when the analysis was restricted to the subgroup without baseline stress defects: 2.35±0.90 (stage 3 CKD) to 2.63±0.88 (stage 2 CKD) and 2.89±1.19 in those with preserved renal function (P = 0.001) (Table 3). Renal function remained significantly associated with CFR after adjustment for sex, LDL cholesterol, and mean blood pressure (β = 0.04; 95% CI, 0.00 to 0.09; P = 0.04 in all patients and β = 0.05, 95% CI, 0.00 to 0.09; P = 0.03 in patients without baseline flow defects). However, with additional adjustment for factors such as age, body mass index, and race, the association was attenuated and lost statistical significance (Table 4).

In general, results were qualitatively similar after subdivision of class 3 into those with stage 3a CKD (n = 48) and those with stage 3b CKD (n = 5). However, using this categorization of renal function, both uncorrected and normalized baseline LV blood flow remained significantly higher in individuals with class 3b CKD. Normalized flow was 1.24±0.42 mL/min per g in individuals with stage 3b CKD, 0.96±0.17 mL/min per g in stage 3a, 0.97±0.22 mL/min per g in stage 2, and 0.95±0.25 mL/min per g in individuals with preserved renal function (P = 0.03).

**Renal Function and Change in Perfusion at 1 Year**

Changes in myocardial perfusion were evaluated in the subset of 244 randomly assigned patients who underwent repeat scanning after 1 year of combined therapy (avasimibe plus atorvastatin) or atorvastatin plus placebo (Table 5 and Figure 2). The change in peak MBF was not different across categories of renal function: stage 3, 0.17±0.60 mL/min per g; stage 2, 0.03±0.71 mL/min per g; and preserved renal function, 0.14±0.67 mL/min per g (P = 0.40). Multivariable adjustment for clinical and demographic factors did not alter this relationship: β for each 10 mL/min per g change in CrCl, 0.00; 95% CI, -0.07 to 0.06 (P = 0.96).

Neither low-dose therapy (β = 0.23; 95% CI, -0.09 to 0.55; P = 0.15) nor high-dose therapy (β = 0.15; 95% CI, -0.17 to 0.47; P = 0.36) was associated with change in CFR over time. In univariate analyses, the change in CFR did not differ significantly across categories of renal function (P = 0.34, Table 5). However, there were trends suggesting a greater percent increase in patients with normal or near-normal renal function than in patients with stage 3, as shown in Figure 2. With the alternative classification of CKD, we found that CFR decreased during follow-up (change in CFR,

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### Table 3. Myocardial Flow Indices in the Left Ventricle in Patients Without a Stress Defect on Baseline Imaging

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Class 3 CKD (n=40)</th>
<th>Class 2 CKD (n=160)</th>
<th>Preserved Renal Function (n=129)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting MBF, mL/min/g</td>
<td>0.83±0.25</td>
<td>0.80±0.25</td>
<td>0.73±0.24</td>
<td>0.04</td>
</tr>
<tr>
<td>Normalized resting MBF, mL/min/g</td>
<td>1.01±0.22</td>
<td>0.97±0.21</td>
<td>0.94±0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>Adenosine MBF, mL/min/g</td>
<td>1.85±0.63</td>
<td>1.99±0.60</td>
<td>1.99±0.75</td>
<td>0.48</td>
</tr>
<tr>
<td>Resting CVR, mm Hg/mL/min/g</td>
<td>116.71±28.06*</td>
<td>124.43±37.63†</td>
<td>133.44±39.82*</td>
<td>0.02</td>
</tr>
<tr>
<td>Adenosine CVR, mm Hg/mL/min/g</td>
<td>52.68±23.28</td>
<td>50.89±19.99</td>
<td>50.66±18.74</td>
<td>0.85</td>
</tr>
<tr>
<td>CFR</td>
<td>2.35±0.90*</td>
<td>2.63±0.88†</td>
<td>2.89±1.19</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Values presented are mean±SD.
*Class 3 CKD significantly different from preserved renal function; †class 2 CKD significantly different from preserved renal function using Tukey-Kramer procedure for post hoc pairwise comparisons.
−0.20±0.44) in patients with stage 3b CKD, increased slightly in individuals with stage 3a CKD (0.09±0.92), and increased more markedly in those with stage 2 CKD (0.24±1.02) or preserved renal function (0.37±1.07) (P=0.49). Adjusted models demonstrated an independent association of renal function with change in CFR over time in patients with and without stress defects at baseline, although the magnitude of the change was small. In models adjusting for baseline characteristics and randomized therapy, each 10 mL/min increase in creatinine clearance was independently associated with an increase of 0.11 (95% CI, 0.01 to 0.20; P=0.03) improvement in the CFR in all patients and 0.11 (95% CI, 0.00 to 0.22; P=0.05) in individuals without a flow defect at baseline (Tables 6 and 7).

**Discussion**

In this study, we analyzed the association of CKD with coronary microvascular function at baseline and its change

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### Table 4. Effects of Serial Adjustment for Baseline Risk Factors Models on the Association of Renal Function With Peak Perfusion or CFR in Individuals With and Without Flow Defects at Baseline

<table>
<thead>
<tr>
<th>Model</th>
<th>All Subjects</th>
<th></th>
<th>Subjects Without a Stress Defect at Baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted β for CrCl (95% CI)</td>
<td>P Value</td>
<td>Adjusted β for CrCl (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Peak perfusion</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CrCl only per 10 mL/min/1.73 m²</td>
<td>0.03 (−0.02−0.05)</td>
<td>0.07</td>
<td>0.03 (0.00−0.06)</td>
<td>0.05</td>
</tr>
<tr>
<td>Adjusted for sex, LDL cholesterol, and mean BP</td>
<td>0.03 (0.00−0.06)</td>
<td>0.04</td>
<td>0.04 (0.01−0.07)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for sex, LDL, mean BP, smoking, age, BMI, race, and presence of stress defect</td>
<td>0.02 (−0.06−0.02)</td>
<td>0.29</td>
<td>−0.02 (−0.08−0.03)</td>
<td>0.35</td>
</tr>
<tr>
<td>CFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl only per 10 mL/min/1.73 m²</td>
<td>0.07 (0.03−0.11)</td>
<td>0.001</td>
<td>0.08 (0.04−0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for sex, LDL cholesterol, and mean BP</td>
<td>0.04 (0.00−0.08)</td>
<td>0.05</td>
<td>0.05 (0.00−0.09)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for sex, LDL, mean BP, smoking, age, BMI, race, and presence of stress defect</td>
<td>−0.03 (−0.08−0.03)</td>
<td>0.31</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; BMI, body mass index.

---

### Table 5. Myocardial Flow in Left Ventricle at Baseline and at Follow-Up in Randomly Assigned Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Class 3 CKD (n=36)</th>
<th>Class 2 CKD (n=133)</th>
<th>Preserved Renal Function (n=75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting MBF, mL/min/g</td>
<td>0.80±0.24</td>
<td>0.85±0.25</td>
<td>0.80±0.25</td>
<td>0.33</td>
</tr>
<tr>
<td>Normalized resting MBF, mL/min/g</td>
<td>0.95±0.19</td>
<td>0.99±0.22</td>
<td>1.01±0.26</td>
<td>0.45</td>
</tr>
<tr>
<td>Adenosine MBF, mL/min/g</td>
<td>1.67±0.58</td>
<td>1.72±0.58</td>
<td>1.63±0.56</td>
<td>0.61</td>
</tr>
<tr>
<td>Resting CVR, mm Hg/mL/min/g</td>
<td>120.22±29.95</td>
<td>119.10±34.69</td>
<td>120.63±35.33</td>
<td>0.95</td>
</tr>
<tr>
<td>Adenosine CVR, mm Hg/mL/min/g</td>
<td>57.00±23.77</td>
<td>60.62±26.49</td>
<td>59.87±24.33</td>
<td>0.75</td>
</tr>
<tr>
<td>Normalized flow reserve</td>
<td>1.78±0.56</td>
<td>1.78±0.59</td>
<td>1.71±0.71</td>
<td>0.75</td>
</tr>
<tr>
<td>CFR</td>
<td>2.17±0.85</td>
<td>2.09±0.67</td>
<td>2.18±0.85</td>
<td>0.67</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting MBF, mL/min/g</td>
<td>0.86±0.22</td>
<td>0.79±0.26</td>
<td>0.76±0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Normalized resting MBF, mL/min/g</td>
<td>1.02±0.21</td>
<td>0.95±0.26</td>
<td>0.96±0.31</td>
<td>0.37</td>
</tr>
<tr>
<td>Adenosine MBF, mL/min/g</td>
<td>1.84±0.61</td>
<td>1.75±0.66</td>
<td>1.77±0.72</td>
<td>0.75</td>
</tr>
<tr>
<td>Resting CVR, mm Hg/mL/min/g</td>
<td>111.62±27.95</td>
<td>129.39±43.01</td>
<td>131.66±4.73</td>
<td>0.05</td>
</tr>
<tr>
<td>Adenosine CVR, mm Hg/mL/min/g</td>
<td>53.33±17.93</td>
<td>59.78±26.95</td>
<td>58.43±25.61</td>
<td>0.40</td>
</tr>
<tr>
<td>Normalized flow reserve</td>
<td>1.86±0.67</td>
<td>1.96±0.84</td>
<td>2.00±0.84</td>
<td>0.72</td>
</tr>
<tr>
<td>CFR</td>
<td>2.24±0.92</td>
<td>2.35±0.99</td>
<td>2.55±1.07</td>
<td>0.27</td>
</tr>
<tr>
<td>Change in normalized CFR at 1 y</td>
<td>0.08±0.70</td>
<td>0.15±0.84</td>
<td>0.30±0.85</td>
<td>0.36</td>
</tr>
<tr>
<td>Change in CFR at 1 y</td>
<td>0.06±0.89</td>
<td>0.24±1.02</td>
<td>0.37±1.07</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Values presented are mean±SD.
over time in patients with and without mild to moderate CKD. We did not find any significant differences at baseline or follow-up in peak myocardial perfusion after pharmacological stimulation in patients with and without mild to moderate CKD. Although there were differences in baseline CFR in individuals with and without mild to moderate CKD, renal function was not independently associated with CFR in analyses adjusting for other cardiovascular risk factors such as age and hypertension. In contrast, in the subset of patients followed for 1 year, lower CrCl was independently associated with a minimally accelerated loss of CFR at 12 months.

Only a few studies have compared coronary microvascular circulatory function in humans with CKD. Chade et al.20 used coronary flow wires to measure mid left anterior descending artery CFR in 605 patients without significant coronary disease and found that the odds of a low CFR were increased 2.03-fold in patients with stage 3 or higher CKD compared with individuals with estimated glomerular filtration rate >60 mL/min/1.73 m². However, they found that differences in age and sex were largely responsible for the observed differences in CFR. A similar study by Koivuvita et al.21 in 21 CKD patients and 10 control subjects without signs or symptoms of CVD who underwent myocardial PET imaging also did not find a significant association between CFR and CKD, although there was a trend toward low CFR with more significant CKD. In contrast, a study using transthoracic echocardiography in a cohort of 10 dialysis patients and 14 matched control subjects with normal coronaries, found that both peak flow and CFR were below normal in 50% of the dialysis patients compared with only 5% of control patients. These authors did not perform multivariable adjustment.

To our knowledge, the current study represents one of the largest cohorts evaluating the relationship between renal function and coronary microvascular function. In addition to the differences in the technical method used to measure myocardial perfusion, the characteristics of the current cohort also differ from prior analyses. Diabetics, those with uncontrolled hypertension, and individuals with advanced CKD were included in other studies but were excluded from the current analysis. The large number of patients in our study provides more reliable estimates of the independent effects of impaired glomerular filtration on myocardial perfusion that are unconfounded by the concurrent effects of diabetes or severe hypertension and, thus, a more robust understanding of the changes in myocardial perfusion that occur in the early stages of CKD.

Our findings extend on earlier investigations by confirming that the drop in CFR in early CKD is largely explained by factors such as age and elevated body mass index. Furthermore, we are the first to report that the decline in CFR that occurs in mild to moderate CKD is not accompanied by a concomitant decline in peak coronary vasodilator function. The similarity in the distribution of peak myocardial perfusion across categories of CKD suggests that the drop in CFR (the ratio of hyperemic to resting blood flow) in early CKD is caused largely by an increase in myocardial work and resting blood flow in CKD—a change probably driven by the rise in blood pressure and age as glomerular filtration rate declines.23,24—rather than by major changes in myocardial vascular function or supply, which would be expected to impair peak hyperemic blood flow.

To our knowledge, we are also the first group to examine the association of CKD with longitudinal changes in myocardial perfusion parameters. The (nonsignificant) trend toward lower peak myocardial perfusion with increasing severity of CKD as well as the independent association between declining CrCl and greater loss of CFR that we observed during 1 year of follow-up raise the question of whether small declines in CFR and peak MBF begin in early CKD but become more pronounced and potentially more important as the severity and duration of CKD increases. In this regard, a study with longer follow-up might have had increased power to detect changes in myocardial perfusion over time. This concept is supported by a recent angiographic study of patients with ≥80% stenosis of at least 1 coronary artery that found fewer collateral vessels in patients with a CrCl <80 mL/min than in patients with preserved renal function25 and by experimental studies demonstrating reduced myocardial capillary densi-
However, the absence of significant differences in peak flow in early CKD imply that differences in myocardial capillary rarefaction as a source of CFR loss in individuals with CKD. Regardless of the exact pathophysiology, the small magnitude of the observed differences in baseline CFR (and change in CFR over time) and the absence of significant changes in peak flow in early CKD imply that differences in myocardial perfusion and microvascular supply in individuals with versus without mild to moderate CKD are unlikely to play

### Table 6. Crude and Adjusted Associations With Change in CFR Over Time in All Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted β (95% CI)</th>
<th>P Value</th>
<th>Adjusted β (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl per 10/mL/min</td>
<td>0.06 (−0.01–0.11)</td>
<td>0.08</td>
<td>0.11 (0.01–0.20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nonwhite vs white race</td>
<td>0.23 (−0.33–0.80)</td>
<td>0.42</td>
<td>0.31 (−0.25–0.88)</td>
<td>0.28</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.16 (−0.45–0.12)</td>
<td>0.26</td>
<td>−0.26 (−0.58–0.06)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age &gt;60 y</td>
<td>−0.10 (−0.35–0.16)</td>
<td>0.45</td>
<td>0.01 (−0.34–0.36)</td>
<td>0.95</td>
</tr>
<tr>
<td>Randomized treatment vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>0.23 (−0.09–0.55)</td>
<td>0.15</td>
<td>0.19 (−0.13–0.51)</td>
<td>0.25</td>
</tr>
<tr>
<td>High dose</td>
<td>0.15 (−0.17–0.47)</td>
<td>0.36</td>
<td>0.17 (−0.16–0.49)</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL vs lowest quartile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd quartile</td>
<td>0.16 (−0.36–0.39)</td>
<td>0.08</td>
<td>−0.02 (−0.40–0.36)</td>
<td>0.91</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>−0.06 (−0.45–0.32)</td>
<td>0.075</td>
<td>−0.06 (−0.45–0.33)</td>
<td>0.76</td>
</tr>
<tr>
<td>Highest quartile</td>
<td>0.00 (−0.37–0.38)</td>
<td>0.98</td>
<td>−0.09 (−0.48–0.30)</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean BP per 10 mmol/L Hg</td>
<td>0.06 (−0.05–0.16)</td>
<td>0.27</td>
<td>0.06 (−0.05–0.17)</td>
<td>0.26</td>
</tr>
<tr>
<td>Stress defect</td>
<td>−0.07 (−0.36–0.21)</td>
<td>0.62</td>
<td>0.91 (−0.21–0.39)</td>
<td>0.55</td>
</tr>
<tr>
<td>Past or present smoking</td>
<td>−0.26 (−0.53–0.00)</td>
<td>0.05</td>
<td>−0.26 (−0.54–0.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI category vs &lt;25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>−0.07 (−0.44–0.30)</td>
<td>0.70</td>
<td>−0.21 (−0.59–0.17)</td>
<td>0.27</td>
</tr>
<tr>
<td>30–34.9</td>
<td>−0.19 (−0.61–0.23)</td>
<td>0.38</td>
<td>−0.40 (−0.85–0.58)</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>−0.10 (−0.41–0.61)</td>
<td>0.70</td>
<td>−0.32 (−0.62–0.27)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure.

grades in uremic animals and postmortem samples from individuals with end-stage renal disease.13

Without pathological data, we are unable to determine whether an analogous loss of myocardial capillaries underlies the accelerated loss of CFR that we observed at 1 year in individuals with mild to moderate CKD. We thus cannot exclude the possibility that changes in endothelial function and vasodilatory capacity of the coronary vessels account for the accelerated loss of CFR that we observed. However, the absence of significant differences in peak myocardial flow or indices of vascular resistance between individuals with and without CKD is more consistent with the presence of myocardial capillary rarefaction as a source of CFR loss in individuals with CKD. Regardless of the exact pathophysiology, the small magnitude of the observed differences in baseline CFR (and change in CFR over time) and the absence of significant changes in peak flow in early CKD imply that differences in myocardial perfusion and microvascular supply in individuals with versus without mild to moderate CKD are unlikely to play

### Table 7. Crude and Adjusted Associations With Change in CFR Over Time in Individuals Without a Stress Defect at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted β (95% CI)</th>
<th>P Value</th>
<th>Adjusted β (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl per 10/mL/min</td>
<td>0.06 (−0.02–0.13)</td>
<td>0.14</td>
<td>0.11 (0.00–0.22)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nonwhite vs white race</td>
<td>0.63 (−0.063–1.31)</td>
<td>0.07</td>
<td>0.72 (0.03–1.41)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.011 (−0.44–0.21)</td>
<td>0.50</td>
<td>−0.25 (−0.62–0.12)</td>
<td>0.18</td>
</tr>
<tr>
<td>Age &gt;60 y</td>
<td>−0.05 (−0.37–0.26)</td>
<td>0.75</td>
<td>0.06 (−0.37–0.49)</td>
<td>0.79</td>
</tr>
<tr>
<td>Randomized treatment vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>0.07 (−0.31–0.45)</td>
<td>0.72</td>
<td>0.01 (−0.38–0.40)</td>
<td>0.96</td>
</tr>
<tr>
<td>High dose</td>
<td>0.03 (−0.36–0.43)</td>
<td>0.87</td>
<td>0.06 (−0.33–0.45)</td>
<td>0.76</td>
</tr>
<tr>
<td>LDL vs lowest quartile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd quartile</td>
<td>−0.07 (−0.53–0.40)</td>
<td>0.78</td>
<td>−0.18 (−0.66–0.29)</td>
<td>0.45</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>−0.21 (−0.70–0.27)</td>
<td>0.39</td>
<td>−0.20 (−0.68–0.29)</td>
<td>0.42</td>
</tr>
<tr>
<td>Highest quartile</td>
<td>−0.17 (−0.63–0.28)</td>
<td>0.45</td>
<td>−0.24 (−0.70–0.23)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean BP per 10 mmol/L Hg</td>
<td>0.06 (−0.06–0.19)</td>
<td>0.33</td>
<td>0.06 (−0.08–0.19)</td>
<td>0.40</td>
</tr>
<tr>
<td>Past or present smoking</td>
<td>−0.34 (−0.65–0.03)</td>
<td>0.03</td>
<td>−0.33 (−0.65–0.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI category vs &lt;25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>−0.06 (−0.47–0.36)</td>
<td>0.79</td>
<td>−0.22 (−0.64–0.21)</td>
<td>0.31</td>
</tr>
<tr>
<td>30–34.9</td>
<td>−0.18 (−0.68–0.33)</td>
<td>0.49</td>
<td>−0.45 (−1.00–0.09)</td>
<td>0.10</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>0.10 (−0.03–0.68)</td>
<td>0.73</td>
<td>−0.37 (−1.08–0.33)</td>
<td>0.30</td>
</tr>
</tbody>
</table>
a major role in cardiovascular mortality until renal impairment progresses to advanced CKD.

Strengths of the present study include the assessment of coronary microvascular function in a large clinical trial cohort with uniform indications for assessment, the serial measurement of CFR and peak perfusion, and the use of myocardial PET imaging, which allows reliable, standardized measurements of MBF. Nonetheless, several limitations must also be acknowledged. The range of renal function was constrained by the trial’s inclusion criteria, and patients with diabetes, overt LV hypertrophy, recent coronary interventions, or recent MI were excluded altogether. Although these exclusions eliminated confounding by diabetes, ventricular hypertrophy, and active coronary disease, they limit the generalizability of our findings to the broader CKD population, especially those with advanced CKD, in whom these conditions are common. Our study also does not provide insight on the important question of how these conditions might interact with each other or the presence of CKD. An additional limitation is that the absence of direct measurements of glomerular filtration and incomplete information on race mandated that we use the Cockroft-Gault equation to estimate renal function instead of the more accurate MDRD equation.27

It should also be noted that angiographic data were not available. Although findings were similar in patients with and without baseline stress PET defects, we cannot definitively determine whether differences in the prevalence or progression of obstructive coronary lesions, coronary collateral supply, myocardial capillary density, or endothelial dysfunction in patients with and without CKD underlie the differences that we observed in CFR. Patients in the present study were clinically stable between baseline and follow-up, and significant progression of atherosclerotic epicardial disease during the observation period is unlikely to explain our findings. In contrast, factors such as blood pressure, heart rate, and cardiovascular medications may have varied. Differences in these factors, as well as technical aspects of the PET scanning procedure, may have contributed to the large variance in baseline CFR that we observed in this study. Additional longitudinal studies using PET scanning, coronary angiography, and pathological sampling of the myocardium are needed to clarify the underlying etiology responsible for differences in indices of myocardial perfusion in patients with normal renal function, moderate CKD, and those with advanced or dialysis-dependent CKD.

In conclusion, we studied coronary microvascular function at baseline and 1 year in patients with and without mild to moderate CKD and found that neither peak MBF nor flow reserve were independently associated with renal function at baseline. Although the loss of flow reserve at 1 year was accelerated in patients with worse renal function, changes in peak MBF did not differ significantly. These findings suggest that the primary change in myocardial perfusion that occurs early in CKD is an increase in baseline blood flow, probably reflecting increases in blood pressure and cardiac work. These data suggest that changes in coronary microvascular function are unlikely to explain the excess cardiovascular risk in mild to moderate CKD. Additional studies are needed to better define the relationship between these processes and the pathogenesis of cardiovascular disease in early CKD and to determine whether changes in perfusion become more pronounced at later stages of CKD.

Sources of Funding
Dr Charytan was supported by an American Heart Association Scientist Development Grant, a Norman S. Coplon Grant from Satellite Health Care, and the Paul Teschan Research Fund.

Disclosures
None.

References
CLINICAL PERSPECTIVE

Although the presence of even mild chronic kidney disease (CKD) is associated with an increase in the risk of myocardial infarction and cardiovascular death, the processes responsible for this association remain incompletely understood. Animal models of uremia suggest that microvascular disease is likely to play an important role in the cardiovascular sequelae of CKD. However, myocardial microvascular function has not been well studied in mild to moderate CKD. We used positron emission tomography scanning to assess myocardial microvascular function in individuals with and without mild to moderate CKD. Although lower creatinine clearances were independently associated with a modestly accelerated loss in coronary flow reserve during 1-year of follow-up, the presence of mild to moderate CKD was not independently associated with change in coronary flow reserve. Our results suggest that changes in myocardial microvascular structure and function are unlikely to explain the association of early CKD with an increased risk of cardiovascular death. These findings highlight a potential difference between advanced CKD and mild to moderate CKD and raise questions about efforts to target the myocardial microvasculature as a means of improving cardiovascular outcomes in early CKD.
Coronary Microvascular Function in Early Chronic Kidney Disease
David M. Charytan, Heinrich R. Shelbert and Marcelo F. Di Carli

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Résumés d’articles

Comparaison entre le ticagrelor et le clopidogrel chez les patients atteints d’un syndrome coronaire aigu avec sus-décalage du segment ST et relevant d’une reperfusion par intervention coronaire percutanée de première intention

Une analyse des sous-groupes de l’essai Platelet Inhibition and Patient Outcomes (PLATO)

Philippe Gabriel Steg, MD ; Stefan James, MD, PhD ; Robert A. Harrington, MD ; Diego Ardissino, MD ; Richard C. Becker, MD ; Christopher P. Cannon, MD ; Håkan Emanuelsson, MD, PhD ; Ariel Finkelstein, MD ; Steen Husted, MD, DSc ; Hugo Katus, MD ; Jan Kilhamn, MD, PhD ; Sylvia Olofsson, BSc ; Robert F. Storey, MD, DM ; W. Douglas Weaver, MD ; Lars Wallentin, MD, PhD ; pour les investigateurs de l’essai PLATO

Contexte—L’aspirine et le clopidogrel sont recommandés chez les patients atteints d’un syndrome coronaire aigu (SCA) ou relevant de la pose d’un stent coronaire. Le ticagrelor, un antagoniste oral réversible des récepteurs P2Y12, réalise une inhibition plaquettaire plus rapide, plus puissante et plus constante que le clopidogrel et pourrait être intéressant chez les patients présentant un SCA avec apparition aiguë d’un sus-décalage du segment ST (SST) etchez lesquels une intervention coronaire percutanée de première intention est programmée.

Méthodes et résultats—L’essai randomisé en double aveugle PLATO (Platelet Inhibition and Patient Outcomes [inhibition plaquettaire et événements cliniques] présenté par les patients) a comparé le ticagrelor au clopidogrel dans la prévention des événements vasculaires chez 18 624 patients pris en charge pour un SCA. La présente publication porte sur les 7 544 patients atteints de SCA s’accompagnant d’un SST ou d’un bloc de branche gauche qui ont été randomisés en vue de recevoir du ticagrelor ou du clopidogrel ou des médicaments supplémentaires administrés au moment de la réalisation de l’intervention coronaire percutanée) puis de 75 mg par jour, cela pendant 6 à 12 mois. La réduction de l’incidence du critère de jugement principal (infarctus du myocarde, accident vasculaire cérébral mal les effets exercés respectivement de 9,4 et 10,8 % ; risque relatif [RR] : 0,87 ; intervalle de confiance 95 % : 0,75 à 1,01 ; p = 0,07) a été constaté aux résultats globaux de PLATO. Il n’a pas été noté d’interaction entre la présence d’un SST ou d’un bloc de branche gauche et le traitement assigné par randomisation (p pour l’interaction = 0,29). Le ticagrelor a également diminué les taux de plusieurs critères de jugement secondaires, dont l’infarctus du myocarde considéré isolément (RR : 0,80 ; p = 0,03), la mortalité totale (RR : 0,82 ; p = 0,05) et la thrombose intra-stent avérée (RR : 0,66 ; p = 0,03). Le risque d’accident vasculaire cérébral a été faible dans les deux groupes, mais plus élevé dans ceux traités par le ticagrelor (1,7 % versus 1,0 % ; RR : 1,63 ; intervalle de confiance à 95% : 1,07 à 2,48 ; p = 0,02). Ce dernier n’a pas modifié le risque d’hémorragie grave (RR : 0,98 ; p = 0,76).

Conclusions—Chez les patients atteints d’un SCA avec SST pris en charge par réalisation d’une intervention coronaire percutanée première intention, les effets du ticagrelor ont été comparables à ceux observés dans l’essai PLATO global.


Mots clés : syndrome coronaire aigu ■ hémorragie ■ infarctus du myocarde ■ plaquettes ■ thrombose

La fonction microvasculaire coronaire dans l’insuffisance rénale chronique débutante

David M. Charytan, MD, MSc ; Heinrich R. Shelbert, MD ; Marcelo F. Di Carli, MD

Contexte—Le haut risque cardiovasculaire associé à l’insuffisance rénale chronique (IRC) pourrait découler d’une altération de la microvasculisation coronaire ; toutefois, on connaît mal les effets exercés par l’IRC sur la fonction microcirculatoire coronaire.

Méthodes et résultats—Chez 435 sujets non diabétiques ayant fait l’objet d’une exploration quantitative par tomographie à émission de positons dans les conditions basales et après induction d’un stress pharmacologique, nous avons évalué les modifications du flux sanguin myocardique causées par l’IRC. Il existait une corrélation significative entre l’IRC et la CICr (indice β pour chaque augmentation de 10 ml/min = 0,07 ; p = 0,001). Le lien entre l’IRC et la CICr était de nature sous-tendu par des facteurs tels que l’âge et la pression artérielle et a perdu sa significativité dans les analyses ajustées (β = -0,02 ; p = 0,53). Aucun lien n’a, en revanche, été objectivé entre le flux myocardique maximal et la CICr dans les analyses aussi bien brutes qu’ajustées (indice β par augmentation de 10 ml/min = -0,02 ml/min/g : p = 0,29). Bien que, à un an, les modifications du débit myocardique maximal aient été comparables chez les patients atteints d’IRC et chez ceux qui en étaient indemnes, la CICr s’est révélée être un puissant facteur indépendant prédictif de l’accélération du rythme de détérioration du FRC, celui-ci ayant diminué de 0,11 unité par an (intervalle de confiance à 95% : 0,01 à 0,20) pour chaque abaissement de 10 ml/min de la CICr (p = 0,03).

Conclusions—Ces données démontrent que l’IRC est présente dans l’IRM et tendent à indiquer que la forte mortalité cardiovasculaire observée chez les patients présentant une atteinte rénale n’est pas imputable à l’altération de la microcirculation coronaire. L’IRC est liée à modérée peut toutefois contribuer à accélérer la diminution du FRC. D’autres études sont nécessaires pour déterminer si ces modifications ont pour effet d’accentuer la détérioration du débit myocardique maximal et du FRC et si elles contribuent au risque cardiovasculaire dans l’IRC plus sévère. (Traduit de l’anglais : Coronary Microvascular Function in Early Chronic Kidney Disease. Circ Cardiovasc Imaging. 2010;3:663–671.)

Mots clés : rein ■ circulation collatérale ■ vascularisation

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