Despite a recent decrease,¹ the incidence of acute myocardial infarction (MI) remains elevated ² and is associated with a substantial mortality <6 months.³

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The long-term prognosis of MI is dependent on left ventricular (LV) remodeling (evaluated by LV dilatation), which is a well-documented surrogate indicating a high risk for heart failure (HF) onset and cardiovascular death.⁴ Although several risk factors have been identified (eg, anterior infarct location, infarct size, LV ejection fraction [LVEF] at discharge),⁵ the ability to predict LV remodeling remains difficult. Several studies have attempted to reduce LV remodeling by acting on different pathways, mostly aimed at decreasing LV overload, myocardial fibrosis, or inflammation during the acute phase of MI.⁶–⁸ We previously reported that cardiac extracellular matrix (ECM) turnover (assessed by circulating collagen peptides) is associated with clinical outcome in patients with HF and reduced EF after MI, independently from cardiac congestion (assessed by brain natriuretic peptide [BNP]), and may be targeted by mineralocorticoid receptor antagonists.⁶ Moreover, ECM turnover days and weeks after MI have been shown to contribute to the decline in cardiac function and eventual failure.⁹–¹² We also reported that a dual determination of BNP and collagen type I trimeric cross-linked peptide is predictive, in addition to brain natriuretic peptide and LV ejection fraction, of detrimental LV remodeling as well as cardiovascular deaths and hospitalizations for heart failure. (Circ Heart Fail. 2013;6:1199-1205.)

Key Words: collagen type I trimeric cross-linked peptide ■ myocardial fibrosis ■ myocardial infarction ■ procollagen type III-N-terminal peptide ■ ventricular remodeling

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Extracellular Matrix Turnover Biomarkers Predict Long-Term Left Ventricular Remodeling After Myocardial Infarction

Insights From the REVE-2 Study

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Background—Extracellular matrix turnover plays a key role in wound repair after myocardial infarction (MI). The aim of the study was to evaluate whether biomarkers of myocardial fibrosis measurements 1 month after MI may predict left ventricular (LV) remodeling.

Methods and Results—This prospective multicenter study included 246 patients with a first anterior Q-wave MI. Echocardiographic studies were performed at hospital discharge and 12 months after MI. Brain natriuretic peptide as well as biomarkers of myocardial fibrosis (type 1 collagen telopeptide, aminoterminal propeptide of type I procollagen, aminoterminal propeptide of type III procollagen) were measured 1 month after MI in 218 patients. In multivariate analysis, aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide ratio ≤1 (odds ratio [95% confidence interval], 1.86 [1.02–3.39]; P=0.043) 1 month after MI and brain natriuretic peptide >100 pg/mL (2.35 [1.28–4.31]; P=0.006) were associated with a pejorative LV remodeling, whereas LV ejection fraction at discharge (per 5% increment; 0.78 [0.65–0.94]; P=0.01) was independently associated with lower rates of detrimental LV remodeling at 12 months. Patients with high brain natriuretic peptide and aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide ratio ≤1, measured 1 month after MI, had the highest risk of developing a primary composite event (cardiovascular death or hospitalization for worsening heart failure; 14 events per 216 patients; P=0.0001) during a 3-year follow-up.

Conclusions—Myocardial fibrosis turnover after MI is associated with LV remodeling. Low aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide ratio (≤1) at 1 month is predictive, in addition to brain natriuretic peptide and LV ejection fraction, of detrimental LV remodeling as well as cardiovascular deaths and hospitalizations for heart failure. (Circ Heart Fail. 2013;6:1199-1205.)

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cardiac troponin I (cTnI) 1 month after MI (but importantly not at baseline) may help refine the prediction of LV remodeling; indeed, BNP is increased in response to LV overload, whereas an increase in cTnI may indicate myocyte injury. In contrast, C-reactive protein, a marker of inflammation, was found not to be associated with LV remodeling.13 The aim of the present study was to assess whether myocardial fibrosis, evaluated by collagen peptide measurements 1 month after MI, could have additional predictive value of LV remodeling after Q-wave anterior MI.

Methods

Study Population

The design as well as the inclusion and exclusion criteria of the REModelage V’Entriculaire-2 (REVE-2) study have been published in detail elsewhere.15 The study consisted in a prospective, multicenter study designed to analyze the association of circulating biomarkers with LV remodeling in patients with a first anterior wall Q-wave MI.14 Patients were enrolled from February 2006 to September 2008. Inclusion criteria were hospitalization <24 hours after symptom onset and a predischarge echocardiogram showing ≥3 akinetic LV segments in the infarct zone. Exclusion criteria were inadequate quality of the echocardiographic image, life-limiting noncardiac disease, significant valvular disease, or a previous Q-wave MI. The institutional ethics committee (Centre Hospitalier Universitaire de Lille) approved the study, and written informed consent was obtained from all patients. No ClinicalTrials.gov number was assigned to this study because it started in 2006.

Clinical Follow-Up

Clinical follow-up was performed at outpatient visits or by contacting the general practitioner or cardiologist between February 2009 and June 2011. Collected data included hospitalization for HF (symptoms of dyspnea or edema associated with bilateral rales, elevated venous pressure, interstitial or alveolar edema on chest radiographs, or the addition of intravenous diuretics or inotropic medications) and death.

Echocardiographic Assessment

Serial echocardiographic studies were performed at hospital discharge (days 3 to 7) and 3 months and 12 months after initial MI. A standard echocardiographic imaging protocol was used, with apical 4- and 2-chamber views. Two-dimensional echocardiograms of the LV short axis were recorded from the left parasternal region at 3 levels: the mitral valve, the midpapillary muscle, and the apex. All echocardiograms were analyzed at the Lille Core Echo Laboratory (Lille, France) as previously described.15 LV end-diastolic volume, end-systolic volume, and EF were calculated with a modified monoplane Simpson rule. LV remodeling was defined as a >20% increase in LV end-diastolic volume 12 months after initial MI.13,16

Biological Parameters Assessment

Biomarkers were measured in plasma and serum samples obtained at 1 month after MI. Plasma and serum were collected in glass tubes and processed <2 hours. Samples were stored at −80°C. Samples underwent no more than 2 freeze/thaw cycles before analysis in a core laboratory (Lille, France, for BNP; Nancy, France, for collagen peptides). BNP was measured with a fully automated 2-site sandwich immunoassay on an Advia Centaur analyzer (Siemens Diagnostic, Zurich, Switzerland). The lowest measurable concentration with this assay was 0.007 ng/mL, with a 10% coefficient of variation. cTnI was measured in plasma samples using a 3-site sandwich immunoassay on an Advia Centaur. The lowest concentration measurable with this assay was 22–87 and 19–83 ng/mL in men and women, respectively; aminoterminal propeptide of type III procollagen [PIIINP], biomarkers of collagen synthesis [reference range, 2.3–6.4 ng/mL]; type 1 collagen telopeptide [ICTP], biomarker of collagen degradation [reference range, 3.2–3.5 ng/mL]) as previously reported,6,17 with interassay variations <9.8%.

C-reactive protein was measured in serum samples using a sensitive latex-enhanced immunonephelometric method with the automated BN II nephelometer (Siemens Diagnostic). The minimum sensitivity for this assay is 0.15 mg/L. Estimated glomerular filtration rate was computed using the 4-variable Modification of Diet in Renal Disease (MDRD) study formula.16

Statistical Analysis

All analyses were performed using the SAS version 9.2 software (SAS Institute, Cary, NC). The 2-tailed significance level was set at P<0.05. Factors associated with LV remodeling, defined as an increase >20% of LV end-diastolic volume 12 months after MI, were first identified using univariate (after logarithmic transformation for collagen biomarkers), then by multivariate logistic regression. Significant covariables were identified among all patient characteristics listed in Table 1, that is, baseline characteristics and 1-month biomarker levels. Multivariate models retained only significant covariables. Validity assumptions of the multivariate models were thoroughly verified: BNP and PIIINP/ICTP ratio were dichotomized to meet the log-linearity condition. The cutoff values (>100 versus ≤100 ng/L for BNP and ≤1 versus >1 for PIIINP/ICTP ratio, roughly corresponding to the medians) were selected from receiver operating characteristic analysis as the best balance between sensitivity and specificity according to the Youden and the closest to (0,1) criteria.19 Results of logistic regressions were presented as odds ratios and their 95% confidence intervals. Event-free survival was illustrated using Kaplan–Meier curves for clinical outcome. Following these analyses, patient characteristics were presented according to PIIINP/ICTP ratio as mean±SD or percentages as appropriate. Between-group comparisons were performed using the Mann–Whitney and χ2 tests when appropriate.

Results

Patient Characteristics

A total of 246 patients were included in the REVE-2 study. One-year echocardiographic follow-up was achieved in 226 patients. Collagen peptide measurements were achieved in 218 patients. Therefore, our study population included 206 patients with both collagen peptide measurements 1 month after initial MI and 1-year echocardiographic follow-up. The characteristics of these 206 patients are summarized in Table 1. LV remodeling (>20% increase in LV end-diastolic volume 12 months after MI) was observed in 87 of 218 patients (40%). The median time of follow-up was 36 months, during which 14 of 216 patients presented clinical outcome (8 with hospitalization as only event, 4 with death as second event, 2 with death as first event).

Association of ECM Remodeling Biomarkers at 1 Month and LV Remodeling

In univariate analysis, the PIIINP/ICTP ratio (odds ratio [95% confidence interval], 2.09 [1.11–3.95] per decreasing loge; P=0.023) measured 1 month after MI, BNP measured...
## Table 1. Baseline Patient Characteristics

| Characteristics                              | All Patients (N=206) | ≤1 µg/µg (n=99) | >1 µg/µg (n=107) | P Value*  
|----------------------------------------------|----------------------|----------------|----------------|---------
| **General**                                  |                      |                |                |         
| Age, y                                       | 57±13                | 58±15          | 55±12          | 0.18    
| Men                                          | 166 (81%)            | 76 (77%)       | 90 (84%)       | 0.18    
| Body mass index, kg/m²                       | 27.3±4.7             | 27.4±4.8       | 27.3±4.7       | 0.98    
| Hypertension                                 | 75 (36%)             | 39 (39%)       | 36 (34%)       | 0.39    
| Diabetes mellitus                            | 37 (18%)             | 16 (16%)       | 21 (20%)       | 0.52    
| Hypercholesterolemia                         | 75 (36%)             | 33 (33%)       | 42 (39%)       | 0.38    
| Current smokers                              | 98 (48%)             | 43 (43%)       | 55 (51%)       | 0.25    
| **Myocardial infarction**                    |                      |                |                |         
| Killip class ≥2                              | 64 (31%)             | 30 (30%)       | 34 (32%)       | 0.82    
| CPK peak, UI/L                               | 2258 (1450–3984)     | 2678 (1369–4256) | 2133 (1531–3262) | 0.19    
| Multivessel disease                          | 81 (41%)             | 38 (40%)       | 43 (41%)       | 0.85    
| **Initial reperfusion**                      |                      |                |                |         
| Primary PCI                                  | 158 (77%)            | 72 (73%)       | 86 (80%)       | 0.19    
| Thrombolysis                                 | 23 (11%)             | 15 (15%)       | 8 (7%)         | 0.081   
| No reperfusion                               | 25 (12%)             | 12 (12%)       | 13 (12%)       | 1.00    
| PCI during hospitalization                   | 179 (88%)            | 82 (84%)       | 97 (92%)       | 0.088   
| eGFR, mL/min per 1.73 m²                     | 84±23                | 81±25          | 88±20          | 0.026   
| **Baseline hemodynamic**                     |                      |                |                |         
| Heart rate, bpm                              | 71±14                | 72±13          | 70±14          | 0.20    
| Systolic BP, mm Hg                           | 110±16               | 109±18         | 110±14         | 0.89    
| Diastolic BP, mm Hg                          | 63±11                | 61±12          | 64±10          | 0.036   
| Mean BP, mm Hg                               | 78±11                | 77±12          | 79±10          | 0.14    
| LVEDV, mL                                    | 100±29               | 98±30          | 102±29         | 0.29    
| LVESV, mL                                    | 51±22                | 51±24          | 51±19          | 0.52    
| LVEF, %                                      | 50±9                 | 49±9           | 50±8           | 0.59    
| LVEF ≤45%                                    | 61 (30%)             | 28 (28%)       | 33 (31%)       | 0.69    
| **Medications at discharge**                 |                      |                |                |         
| Aspirin                                      | 204 (99%)            | 98 (99%)       | 106 (99%)      | 0.96    
| Clopidogrel                                  | 199 (97%)            | 96 (97%)       | 103 (96%)      | 0.78    
| β-Blockers                                   | 202 (98%)            | 97 (98%)       | 105 (98%)      | 0.94    
| ACE inhibitors                               | 200 (97%)            | 96 (97%)       | 104 (97%)      | 0.92    
| Mineralocorticoid receptor antagonists       | 67 (33%)             | 35 (35%)       | 32 (30%)       | 0.40    
| Diuretics                                    | 48 (23%)             | 28 (28%)       | 20 (19%)       | 0.10    
| Statins                                      | 196 (95%)            | 93 (94%)       | 103 (96%)      | 0.44    
| **Biomarkers at 1 mo**                       |                      |                |                |         
| Cardiac troponin I ≥0.05 µg/L                | 36 (19%)             | 24 (25%)       | 12 (13%)       | 0.034   
| BNP, ng/L                                    | 86 (51–181)          | 99 (56–219)    | 79 (44–145)    | 0.036   
| CRP, mg/L                                    | 1.4 (0.7–3.4)        | 1.5 (0.7–4.4)  | 1.3 (0.6–2.8)  | 0.13    
| PINP, µg/L                                   | 36.9 (30.8–45.1)     | 35.5 (29.9–49.7) | 37.9 (31.8–44.1) | 0.57    
| PIIINP, µg/L                                 | 5.21 (3.88–6.78)     | 4.03 (3.45–4.98) | 6.28 (5.23–7.70) | <0.0001  
| ICTP, µg/L                                   | 4.76 (4.07–6.08)     | 5.29 (4.51–7.11) | 4.45 (3.69–5.16) | <0.0001  
| PIIINP/ICTP ratio                            | 1.02 (0.80–1.34)     | 0.79 (0.64–0.91) | 1.34 (1.13–1.70) | …      

ACE indicates angiotensin-converting enzyme; BNP, brain natriuretic peptide; BP, blood pressure; CPK, creatine phosphokinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICTP, type 1 collagen telopeptide; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; mean BP, mean arterial pressure (Lian formula); PINP, aminoterminal propeptide of type I procollagen; PIIINP, aminoterminal propeptide of type III procollagen; and PCI, primary percutaneous intervention.

*P values are from the Mann–Whitney test or the χ² test as appropriate.
at 1 month (1.72 [1.24–2.37] per log; \( P = 0.001 \)), and cTnI \( \geq 0.05 \) µg/L at 1 month (2.19 [1.08–4.44]; \( P = 0.030 \)) were associated with a pejorative LV remodeling, whereas higher LVEF at discharge (0.75 [0.62–0.89] per 5% increment; \( P = 0.001 \)) was independently associated with lower rates of detrimental LV remodeling 12 months after initial Q-wave anterior MI (Table 2).

Similarly, in multivariate analysis, PIIINP/ICTP ratio \( \leq 1 \) month after MI (1.86 [1.02–3.39]; \( P = 0.043 \)) and BNP >100 pg/mL at 1 month (2.35 [1.28–4.31]; \( P = 0.006 \)) were associated with a pejorative LV remodeling, whereas higher LVEF at discharge (per 5% increment; 0.78 [0.65–0.94]; \( P = 0.010 \)) was independently associated with lower rates of detrimental LV remodeling 12 months after initial Q-wave anterior MI. The discriminant power of the model (Harrell C statistic) was 0.698.

Accordingly, patients with reduced EF (LVEF <50%; cut-off value determined using receiver operating characteristic analysis) and BNP >100 pg/mL were more likely to develop LV remodeling 12 months after initial MI. Interestingly, PIIINP/ICTP ratio \( \leq 1 \) month after initial MI was able to identify twice (17%–40%) more patients with BNP \( \leq 100 \) ng/L and twice (21%–42%) more patients with LVEF >50% in whom LV remodeling ultimately developed at 12 months (Figures 1 and 2). Adding PIIINP/ICTP ratio (\( \leq 1 \)) to LVEF and BNP (\( \leq 100 \) ng/L) improved the sensitivity and the specificity of the model by 1.4% and 0.5%, respectively, for an integrated discrimination improvement of 1.9% (\( P = 0.051 \)).

### Table 2. Association of Echocardiographic and Biomarker Features With Left Venticle Remodeling >20% at 12 Months as Dependent Variable, Using Univariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Covariate</th>
<th>n/N C OR (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td></td>
</tr>
<tr>
<td>LVEF, per 5%</td>
<td>79/206 0.642 0.75 (0.62–0.89) 0.001</td>
</tr>
<tr>
<td>eGFR, per 10 units</td>
<td>79/205 0.497 0.99 (0.88–1.12) 0.89</td>
</tr>
<tr>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td>BNP, per logi</td>
<td>78/204 0.649 1.72 (1.24–2.37) 0.001</td>
</tr>
<tr>
<td>Cardiac troponin I, ( \geq 0.05 ) µg/L</td>
<td>78/203 0.563 2.19 (1.08–4.44) 0.030</td>
</tr>
<tr>
<td>CRP, per logi ( i )</td>
<td>79/205 0.537 1.12 (0.91–1.39) 0.29</td>
</tr>
<tr>
<td>PINP, per logi ( i )</td>
<td>78/205 0.527 1.16 (0.52–2.58) 0.73</td>
</tr>
<tr>
<td>PIIINP, per logi ( i )</td>
<td>79/206 0.542 0.69 (0.33–1.46) 0.33</td>
</tr>
<tr>
<td>ICTP, per logi ( i )</td>
<td>79/206 0.588 2.10 (0.98–4.53) 0.058</td>
</tr>
<tr>
<td>PIIINP/ICTP ratio, per decreasing logi ( i )</td>
<td>79/206 0.587 2.09 (1.11–3.95) 0.023</td>
</tr>
<tr>
<td>PIIINP/ICTP ratio, per increasing logi ( i )</td>
<td>78/205 0.538 0.66 (0.36–1.20) 0.17</td>
</tr>
</tbody>
</table>

BNP indicates brain natriuretic peptide (ng/L); C, Harrell C statistic (probability to rightly predict LV remodeling >20%); CRP, C-reactive protein (mg/L); eGFR, estimated glomerular filtration rate (4-variable Modification of Diet in Renal Disease study formula; mL/min per 1.73 m²); ICTP, type I collagen telopeptide (µg/L); LVEF, left ventricular ejection fraction; n/N, number of patients with LV remodeling >20%/total number; OR (95% CI), odds ratio (95% confidence interval); PINP, aminoterminal propeptide of type I procollagen (µg/L); PIIINP, aminoterminal propeptide of type III procollagen (µg/L); and \( r^2 \), determination coefficient (part of variance explained).

### Figure 1. Three-dimensional histograms according to receiver operating characteristic (ROC)–determined cutoffs for brain natriuretic peptide (BNP) and aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide (PIIINP/ICTP) ratio. M12 remodeling: left ventricle (LV) end-diastolic volume increase >20% at 12 months. Cutoff values determined from ROC curve (almost equal to medians): BNP \( \leq 100 \) vs >100 ng/L; PIIINP/ICTP ratio \( \leq 1 \) vs >1. Events/patients: 78/204.

### Figure 2. Three-dimensional histograms according to receiver operating characteristic (ROC)–determined cutoffs for left ventricular ejection fraction (LVEF) and aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide (PIIINP/ICTP) ratio. M12 remodeling: left ventricle end-diastolic volume increase >20% at 12 months. Cutoff values determined from ROC curve (almost equal to medians): LVEF <50% vs \( \geq 50 \% \); PIIINP/ICTP ratio \( \leq 1 \) vs >1 µg/µg. Events/patients: 79/206.

### Association of ECM Remodeling Biomarkers at 1 Month and Clinical Outcome

Ten of the 14 clinical outcomes (70%) were observed in patients with BNP \( \geq 100 \) ng/L and PIIINP/ICTP ratio \( \geq 1 \) at 1 month. The additional predictive values of the combination of BNP and PIIINP/ICTP levels for the risk of composite outcome are presented in Figure 3.

### Baseline Features of Patients According to Their PIIINP/ICTP Ratio at 1 Month

Clinical characteristics of patients with PIIINP/ICTP ratio \( \leq 1 \) and >1 at 1 month (Table 1) were similar except for diastolic blood pressure (61±12 versus 64±10 mmHg; \( P = 0.036 \)) and estimated glomerular filtration rate (81±25 versus 88±20 mL/min per 1.73 m²; \( P = 0.026 \)). Patients with a PIIINP/ICTP ratio \( \leq 1 \) had higher BNP (99 [56–219] versus 79 [44–145] ng/L; \( P = 0.036 \)) as well as a proportion of patients with cTnI \( \geq 1 \) had higher BNP (99 [56–219] versus 79 [44–145] ng/L; \( P = 0.036 \)) as well as a proportion of patients with cTnI \( \geq 1 \) had higher BNP (99 [56–219] versus 79 [44–145] ng/L; \( P = 0.036 \)). They also had higher ICTP (5.29 [4.51–7.11] versus 4.45 [3.69–5.16] µg/L; \( P = 0.036 \)) as well as a proportion of patients with cTnI \( \geq 1 \) had higher BNP (99 [56–219] versus 79 [44–145] ng/L; \( P = 0.036 \)). They also had higher ICTP (5.29 [4.51–7.11] versus 4.45 [3.69–5.16] µg/L; \( P = 0.036 \)).
Discussion

The results of the present study confirm that myocardial fibrosis turnover (as assessed herein by the PIIINP/ICTP ratio) is critical after a first anterior wall MI and probably plays a key role in LV remodeling despite optimal management (initial reperfusion therapy and use of optimal medical treatment at hospital discharge). LV remodeling was observed in 40% of our study patients despite this optimal management. Myocardial fibrosis turnover measured 1 month after MI was associated with LV remodeling at 12 months independently from other classical pathways such as pressure overload (BNP), inflammation (C-reactive protein), or initial myocardial injury (LVEF and cTnI). Of note, cTnI measurements 1 month after initial MI were significantly associated with LV remodeling at 12 months (P=0.03) but were no longer significant in multivariate models including BNP at 1 month, LVEF at discharge, and PIIINP/ICTP ratio at 1 month. This may suggest that, after an initial myocardial injury, ECM turnover and LV pressure overload could be the main factors leading to LV remodeling at 12 months after an anterior MI. Furthermore, in addition to LVEF at discharge and BNP measurements at month 1, PIIINP/ICTP ratio measured 1 month after MI may help to improve risk prediction of LV remodeling at 12 months and of a primary event at 3 years (cardiovascular death or hospitalization for worsening HF) after a first anterior wall MI.

In the post-MI heart, there is a time-dependent damage to myocytes and the ECM in the infarct zone, followed by gradual reparation with fibrosis. The noninfarct zone exhibits reactive hypertrophy, interstitial fibrosis, and increased collagen, leading to cardiac dysfunction and progressive dilatation. Therefore, in such pathological conditions, ECM remodeling may lead to myocardial fibrosis in addition to having deleterious effects on pumping capacity and diastolic function.17

In the present study, it was decided to measure myocardial fibrosis biomarkers 1 month after initial MI because we previously reported that, at this particular time, high BNP levels in REVE-2 patients were associated with adverse remodeling and that the highest levels of ECM turnover biomarkers were similarly observed at this time after MI in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study, but in which echo data were unfortunately not available.6 In this latter study, patients were enrolled post-MI HF and reduced EF (mean LVEF, 33±6%) and mostly with HF symptoms (90% of the overall population); however, HF symptoms were only present in 31% in REVE-2 study (30% with LVEF ≤45%). The combination of baseline BNP and ICTP values above the median was associated with a higher risk of cardiovascular death or HF hospitalization (hazard ratio, 3.03 [1.49–6.16]; P=0.002) in EPHESUS.5

We also decided to perform PIIINP measurements (a biomarker of collagen synthesis) because it seems to be the main component of reactive ischemic-related fibrosis and can be synthesized in a more rapid and reactive manner in addition to playing an important role in the development of new areas of myocardial fibrosis.20 Concomitantly, a higher ICTP level (a biomarker of collagen degradation) indicates an intensive and deleterious ECM turnover leading to LV remodeling and was previously found as a predictor of LV remodeling after MI,21,22 as it tended to be in the present study, in the univariate analysis of the LV remodeling–associated factors (Table 2). Furthermore, we previously reported that serum ICTP was associated with all-cause death23 and chronic HF symptoms onset23 after MI. Thus, ECM turnover by PIIINP/ICTP ratio was ultimately higher risk of cardiovascular death or HF hospitalization (hazard ratio, 3.03 [1.49–6.16]; P=0.002) in EPHESUS.5

![Figure 3. Kaplan–Meier curves depicting cardiovascular death or hospitalization for worsening heart failure. Event: cardiovascular death or hospitalization for worsening heart failure. Strata: combinations of brain natriuretic peptide (BNP) high (>100 ng/L) or low (≤100 ng/L) and aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide (PIIINP/ICTP) ratio high (>1) or low (≤1) at 1 month.](http://circheartfailure.ahajournals.org/)
(70% of patients with Killip class ≤2, mean creatine phosphokinase peak ≤3000 UI/L, mean LVEF = 50%, and only 30% of patients with LVEF ≤45%) in comparison with other studies, which highlighted this association in patients presenting with an MI and a low LVEF and HF symptoms.2,5

Several studies have attempted to develop risk scores in order to predict cardiovascular outcomes and LV remodeling in patients with MI.5,31 Such scores were solely based on the patients’ clinical and biological characteristics and type of MI. Unfortunately, these scores were not completely effective in suitably predicting and identifying patients at high risk of developing cardiac remodeling after MI, hence the reason for choosing to measure PIINP/ICTP ratio in addition to BNP and LVEF in the present study. Interestingly, low PIINP/ICTP ratio (≤1) could help to predict LV remodeling at 12 months more specifically in known low-risk patients (BNP ≤100 ng/L and LVEF >50%) than in high-risk patients (BNP >100 ng/L and LVEF ≤50%: Figures 1 and 2).

This risk prediction based on PIINP/ICTP ratio assessed at 1 month, in addition to LVEF at discharge or BNP at 1 month, may help clinicians to identify patients at high risk of developing LV remodeling. Patients with low PIINP/ICTP ratio (≤1) and high BNP 1 month after MI may thus be treated more aggressively with an optimization of the doses of the different drugs used. Indeed, we previously reported that mineralocorticoid receptor antagonists decrease ECM turnover and thus may decrease LV remodeling.5 Moreover, several studies (ie, ALBATROSS [Aldosterone Lethal effects Blocked in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six-months follow-up] and REMINDER [early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure] trials) are currently ongoing or recent to confirm the benefit of mineralocorticoid receptor antagonists in preventing LV remodeling in all cases of MI.7 In the present study, no significant difference in medical treatment at discharge with regard to PIINP/ICTP levels was observed although the observational design of REVE-2 precludes from inferring any causal relationship. Importantly, because of its stability, PIINP/ICTP ratio could be a good alternative to detect patients who are prone to develop LV remodeling after an initial Q-wave anterior MI compared with BNP and LVEF.

Study Limitations
Echocardiography was used herein to assess LV remodeling. Currently, cardiac MRI has been associated with lower variability and seems as the best technique for LV remodeling assessment.25 Echocardiography, however, because of its greater availability and technological advances, is also an appropriate option, especially when multicenter recruitment is considered. Because of the low number of events of composite clinical outcome (14 of 216; cardiovascular deaths or hospitalizations for worsening HF), we acknowledge a lack of robustness of life table result (Figure 3). Furthermore, our study population is to date the largest published prespecified biomarker analysis survey to evaluate LV remodeling after MI. Finally, our interpretation of PIINP concentrations is based on the current assumption shared by most authors that it depicts collagen type III synthesis, whereas earlier studies from Jensen et al26 proposed that serum PIINP may originate from ongoing synthesis or degradation of type III collagen fibrils with PIINP on their surface.

Conclusions
The ability to predict LV remodeling is difficult. Myocardial fibrosis turnover after MI is associated with LV remodeling. In the present study, low PIINP/ICTP ratio (≤1) at 1 month is predictive of detrimental LV remodeling at 12 months after Q-wave anterior MI and may also predict, along with BNP and LVEF, cardiovascular deaths and hospitalizations for worsening HF at 3 years. Additional studies are needed to evaluate early interventions on myocardial fibrosis turnover after MI to prevent LV remodeling.

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Disclosures
None.

References

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**CLINICAL PERSPECTIVE**

The long-term prognosis of myocardial infarction is dependent on left ventricular remodeling (evaluated by left ventricle dilatation), which is a well-documented surrogate indicating a high risk for heart failure onset and cardiovascular death. Although several risk factors have been identified (eg, anterior infarct location, infarct size, left ventricular ejection fraction at discharge), the ability to predict left ventricular remodeling remains difficult especially in patients with conserved left ventricular ejection fraction at discharge), the ability to predict left ventricular remodeling remains difficult especially in patients with conserved left ventricular ejection fraction at discharge. Myocardial fibrosis turnover after myocardial infarction is associated with left ventricular remodeling. Because of its stability, the ratio of aminoterminal propeptide of type III procollagen/type 1 collagen telopeptide, a marker of myocardial collagen turnover, could be a good alternative to detect patients who are prone to develop left ventricular remodeling after an initial Q-wave anterior myocardial infarction compared with brain natriuretic peptide and left ventricle ejection fraction. This ratio was found in this study of >200 patients 1 month after first anterior Q-wave myocardial infarction to be associated with remodeling at 1 year, as well as with longer-term outcomes. These data could help clinicians to better identify patients at high risk to develop left ventricular remodeling after a Q-wave anterior myocardial infarction and consequently treat them more aggressively.
Extracellular Matrix Turnover Biomarkers Predict Long-Term Left Ventricular Remodeling After Myocardial Infarction: Insights From the REVE-2 Study
Romain Eschalier, Marie Fertin, Renaud Fay, Christophe Bauters, Faiez Zannad, Florence Pinet and Patrick Rossignol

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