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Growth-differentiation factor 15 for long-term prognostication in patients with non-ST-elevation acute coronary syndrome: An Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) substudy☆,☆☆,★,★★

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ABSTRACT

Background: No five-year long-term follow-up data is available regarding the prognostic value of GDF-15. Our aim is to evaluate the long-term prognostic value of admission growth-differentiation factor 15 (GDF-15) regarding death or myocardial infarction (MI) in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).
Methods: This is a subanalysis from the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial, including troponin positive NSTE-ACS patients. The main outcome for the current analysis was 5-year death or spontaneous MI. GDF-15 samples were available in 1151 patients. The prognostic value of GDF-15, categorized into <1200 ng/L, 1200–1800 ng/L and >1800 ng/L, was assessed in unadjusted and adjusted Cox regression models. Adjustments were made for identified univariable risk factors. The additional discriminative and reclassification value of GDF-15 beyond the independent risk factors was assessed by the category-free net reclassification improvement (1/2 NRI(>0)) and the integrated discrimination improvement (IDI)
Results: Compared to GDF-15 < 1200 ng/L, a GDF-15 > 1800 ng/L was associated with an increased hazard ratio for death or spontaneous MI, mainly driven by mortality. GDF-15 levels were predictive after adjustments for other identified predictors. Additional discriminative value was shown with the IDI, not with the NRI.
Conclusion: In patients presenting with NSTE-ACS and elevated troponin T, GDF-15 provides prognostic information in addition to identified predictors for mortality and spontaneous MI and can be used to identify patients at high risk during long-term follow-up.

1. Introduction

Patients presenting with non-ST-elevation acute coronary syndrome (NSTE-ACS) constitute a broad and heterogeneous group in terms of risk of subsequent death and nonfatal ischemic events. Adequate risk stratification potentially assists in estimating prognosis and may guide the treating physician in clinical decision making [1]. Risk stratification is based on a combination of clinical history and characteristics, electrocardiography, biomarkers and imaging modalities.

Abbreviations: CABG, coronary artery bypass grafting; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; IDI, integrated discrimination improvement; MI, myocardial infarction; NRI, net reclassification improvement; NSTE-ACS, non-ST-elevation acute coronary syndrome; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

☆☆ Trial registration: www.controlled-trials.com/ISRCTN82153174.

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Growth-differentiation factor 15 (GDF-15) is a member of the transforming growth factor β cytokine family that is weakly expressed under healthy conditions, but produced in response to oxidative stress, inflammation and tissue injury. Its prominent anti-apoptotic, anti-hypertrophic, and anti-inflammatory actions in cardiovascular disease models suggest that GDF-15 may play a counter-regulatory role in the context of cardiovascular injury [2–4]. In patients, GDF-15 has been detected in the infarcted myocardium and in atherosclerotic plaques [2,5].

Elevated circulating levels of GDF-15 have been shown to be associated with the composite of mortality and myocardial infarction (MI) up to two years of follow-up in two large cohorts of patients with NSTE-ACS [6,7]. However, the association of GDF-15, measured on admission, with cardiovascular events during long-term follow-up has not been assessed. The ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial compared an early invasive strategy with a selectively invasive strategy in patients with NSTE-ACS and a positive cardiac troponin T test on admission [8]. No differences in clinical outcomes were observed up to 5-year follow-up [9,10]. In the present substudy of the ICTUS trial, we evaluated the prognostic value of GDF-15 regarding long-term outcomes.

2. Methods

2.1. Study design

The design of the Dutch multicenter ICTUS trial and the long-term follow-up have been published previously [8,10]. In short, 1200 patients with NSTE-ACS and elevated cardiac troponin T were randomized to an early invasive or a selective invasive strategy.

2.2. Patients

Patients (age 18 to 80 years) were eligible if the following criteria were met: symptoms of ischemia that were increasing or occurring at rest, with the last episode occurring <24 h before randomization; elevated cardiac troponin T level (≥0.03 μg/L); and either ischemic changes as assessed by electrocardiography or a documented history of coronary artery disease. Exclusion criteria were: ST-segment elevation MI <48 h; an indication for reperfusion therapy; hemodynamic instability or overt congestive heart failure; and an increased risk of bleeding. This study complied with the principles in the Declaration of Helsinki and was approved by all the local institutional review boards. All patients gave written informed consent. The author(s) of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.3. Randomization

Patients randomized to the early invasive strategy were scheduled to undergo coronary angiography within 24 to 48 h with revascularization if appropriate. Patients in the selective invasive group initially medically stabilized, with angiography and revascularization performed only in case of refractory angina, hemodynamic or rhythmic instability, or clinically significant ischemia on the pre-discharge exercise test. During initial hospitalization, 76% of the patients randomized to the early invasive strategy and 40% of the patients to the selective invasive strategy were revascularized. These percentages were 81% and 60% at 5-year follow-up. Pharmacological treatment consisted of aspirin, clopidogrel, enoxaparin, abciximab during all percutaneous coronary interventions (PCI), and intensive lipid-lowering therapy.

2.4. Follow-up

Patients were contacted by telephone after 5 years from randomization. All potential outcome events were recorded; hospitalizations were reviewed for potential outcome events unless there was an unequivocally non-cardiac reason for admission. If a patient could not be contacted, information was obtained from the patients' family, general practitioner, treating cardiologist and hospital records. Follow-up was censored at the date of last telephone contact, or at 5 years, whichever came first. If the patient was lost to follow-up, censoring was done at the date of last clinical follow-up. Information on vital status was obtained from the Dutch national population registry and was verified until September 12, 2008. Cause of death was obtained from the general practitioner and hospital records. Follow-up for mortality was censored at 5 years. If a patient could not be identified in the national registry, censoring was done at the date of last clinical follow-up.

2.5. GDF-15 laboratory analysis and other biomarkers

Baseline samples were obtained on admission and stored for central analyses of biomarkers. Blood samples were collected in tubes without anticoagulant, and the samples

Table 1
Baseline characteristics according to GDF-15.

	GDF-15			
	<1200 ng/L (n = 380)	1200–1800 ng/L (n = 423)	>1800 ng/L (n = 348)	P-value
Demographics				
Age (years)–mean (SD)	56 (9)	63 (10)	68 (9)	<0.001
Body-mass index–mean (SD)	27.2 (3.4)	27.1 (3.6)	27.1 (4.1)	0.81
Male sex–no. (%)	294 (77.4%)	304 (71.9%)	243 (69.8%)	0.02
Clinical history–no. (%)				
Myocardial infarction	78 (20.5%)	80 (18.9%)	109 (31.3%)	0.001
Percutaneous coronary intervention	47 (12.4%)	39 (9.2%)	50 (14.4%)	0.44
Coronary artery bypass grafting	19 (5.0%)	35 (8.3%)	46 (13.2%)	<0.001
Risk factors–no. (%)				
Current cigarette smoking	156 (41.1%)	185 (43.7%)	134 (38.5%)	0.51
Hypertension	118 (31.1%)	157 (37.1%)	169 (48.6%)	<0.001
Hypercholesterolemia	122 (32.1%)	148 (35.0%)	130 (37.4%)	0.14
Diabetes	20 (5.3%)	44 (10.4%)	96 (27.6%)	<0.001
Family history of coronary artery disease	170 (44.7%)	186 (44.0%)	132 (37.9%)	0.07
Electrocardiographic abnormalities–no. (%)				
ST-segment deviation ≥0.1 mV	181 (48.9%)	193 (47.5%)	182 (55.5%)	0.06
Left bundle branch block	3 (0.8%)	2 (0.5%)	9 (2.7%)	0.03
Aspirin use on admission–no. (%)	108 (28.4%)	150 (35.5%)	178 (51.1%)	<0.001
Laboratory assessments–median (IQR)				
Troponin T (μg/L)	0.25 (0.11–0.61)	0.30 (0.13–0.76)	0.33 (0.13–0.82)	0.03
C-reactive protein (mg/L)	2.8 (1.4–6.8)	4.4 (1.8–10.6)	5.8 (2.5–18.0)	<0.001
Creatinin clearance* (mL/min/1.73 m^2)	114 (96–134)	94 (79–112)	75 (60–100)	<0.001
NT-proBNP (ng/L)	386 (163–747)	589 (263–1253)	1197 (462–2709)	<0.001

GDF-15: growth-differentiation factor 15, IQR: interquartile range, and SD: standard deviation.
CRP measurements were available in 1144 patients, and NT-proBNP in 1131 patients.
Electrocardiography data were available in 1149 patients.
* Creatinine clearance was calculated according to the Cockcroft and Gault formula.