International Journal of Cardiology 292 (2019) 241–245

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Growth differentiation factor-15 and all-cause mortality in patients with suspected myocardial infarction☆,☆☆

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ARTICLE INFO

Article history:
Received 29 January 2019
Received in revised form 27 March 2019
Accepted 28 April 2019
Available online 25 May 2019

Keywords:
Biomarkers
Acute coronary syndromes
Mortality/survival

ABSTRACT

Background: To assess the prognostic performance of Growth differentiation factor-15 (GDF-15) concentrations in unselected patients presenting with suspected acute myocardial infarction (AMI) and adjudication based on high-sensitivity cardiac troponin (hs-cTn).

Methods and results: In an ongoing prospective multicenter diagnostic study, consecutive patients presenting with suspected AMI to the emergency department and available GDF-15 and hs-cTnT concentrations were included. Adjudication of AMI was performed central by two independent cardiologists using all available clinical information including cardiac imaging and serial hs-cTn concentrations. Overall, 718 patients were included, with 23% (162/718) having an adjudicated diagnosis of AMI. The cumulative incidence of death within 2 years was 19% in patients with AMI (30 deaths in 162 patients) versus 5% in patients without AMI (25 deaths in 556 patients; $P < 0.001$). In AMI patients, GDF-15 provided an AUC of 0.89 (95% confidence interval [CI] 0.83–0.94) for 2-year death versus 0.55 (95% CI 0.44–0.66) for hs-cTnT ($P < 0.001$). A GDF-15 cutoff of ≤1560 ng/L predicted 2-year survival in 47% (76/162) of AMI patients and had 100% sensitivity (95% CI 88–100%) for 2-year death. In patients without AMI, GDF-15 provided an AUC of 0.83 (95% CI 0.76–0.89) versus 0.76 (95% CI 0.67–0.85) for hs-cTnT ($P = 0.096$). A GDF-15 cutoff of ≤886 ng/L predicted 2-year survival in 37% (203/556) of non-AMI patients and had 100% sensitivity (95% CI 86–100%) for 2-year death.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
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https://doi.org/10.1016/j.ijcard.2019.04.088
0167-5273/

Conclusions: GDF-15 concentrations at emergency department presentation have a high predictive accuracy for all-cause death in patients with suspected AMI and allow the identification of a large proportion of AMI patients with very low mortality risk.

1. Introduction

Acute myocardial infarction (AMI) is a major cause of death worldwide [1,2]. While the clinical introduction of high-sensitivity cardiac troponin (hs-cTn) assays has substantially improved the early diagnosis of AMI, hs-cTn concentrations at presentation have only modest accuracy in prediction of short- and long-term complications from AMI including death [3,4]. Accordingly, uncertainty remains regarding the intensity of care including the length of ECG-rhythm monitoring necessary for many patients with AMI [1]. Therefore, accurate identification of event-risk in AMI patients could have substantial clinical implications. Growth differentiation factor-15 (GDF-15) seems to be a biomarker of both cardiac dysfunction as well as non-cardiac comorbidity representing a measure of systemic inflammation and oxidative stress [5–11]. As such, GDF-15 concentrations have been suggested as tool in risk-stratification [5–8]. However, until now GDF-15 was mainly evaluated in rather selected clinical trial cohorts [5,9–13], in which both cardiac and non-cardiac comorbidities typically are underrepresented or even excluded. We hypothesized that the true clinical utility of GDF-15 in patients with suspected AMI may still have not been appropriately characterized. In addition, these previous studies, including our own [14], did not use adjudication of AMI using serial hs-cTn measurements as recommended in current guidelines [1,7,15]. Consequently, smaller AMIs were potentially missed and not included in previous analyses.

Therefore, the aim of this study was to assess the potential clinical use of GDF-15 concentrations to accurately estimate the risk of death in unselected patients with suspected AMI, particularly to reliably identify hs-cTn-adjudicated AMI patients at extremely low-risk of death and therefore appropriate candidates for rapid discharge from a monitored unit after revascularization.

2. Methods

2.1. Population

This secondary analysis was part of an ongoing prospective international multicenter study (**A**dvantageous **P**redictors of **A**cute **C**oronary syndromes **E**valuation; ClinicalTrials.gov: NCT00470587) [3]. The study was carried out according to the Declaration of Helsinki, required written informed consent. While recruitment was independent from renal function at presentation, patients with end-stage renal failure on chronic dialysis were excluded.

2.2. AMI adjudication and prognostic endpoint

The final diagnosis was performed centrally in a core lab for all patients twice: Once based on conventional cTn levels used onsite (this method was used in initial analyses to determine the performance of hs-cTn assays as well as first GDF-15 analyses) [3,14,16] and once, as used in this analysis, including hs-cTn concentrations in order to also take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays [1,3,16].

As described previously [16], AMI was defined and (hs-)cTn levels interpreted as recommended in current guidelines [1,2]. Summarized, AMI was adjudicated when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Two independent cardiologists reviewed all available medical records pertaining to the patient from the time of presentation to 90-day follow-up and had access to all measured routine clinical care cTn/hs-cTn concentrations and centrally measured serial hs-cTnT concentrations. Myocardial necrosis was diagnosed by at least one hs-cTnT value above the 99th percentile together with a significant rise and/or fall. Absolute changes in hs-cTnT were used to determine significant changes based on the diagnostic superiority of absolute over relative changes [16,17].

Patients were contacted after 6, 12, and 24 months either in written form or by telephone interview by trained researchers. In case of an event, information was obtained from hospital records, the GP/cardiologist's records, and national death registry.

2.3. Biomarker measurements

Blood samples for determination of hs-cTnT (Roche Diagnostics) and GDF-15 (Roche Diagnostics) were drawn at emergency department presentation. The employed assays are described in the Supplementary material [18].

2.4. Statistical analysis

Continuous and nominal variables were compared with Mann–Whitney U and chi-squared tests respectively. Confidence intervals (CI) of proportions are exact binomial 95% CIs. Time dependent areas under the receiver operating characteristic (ROC) curve (AUC) were used to quantify the predictive accuracy of the biomarkers for all-cause death within 2 years while accounting for censoring [19]. Additionally, the GRACE score estimating the risk of death following an acute coronary syndrome was assessed in AMI patients [20]. McNemar's test was used to compare derived GDF-15 and GRACE score 100% sensitivity cutoffs for all-cause death within 2 years. Multivariable Cox regression was used to assess GDF-15 concentrations as independent markers for death. The cumulative incidence of death within 2 years was compared using log-rank testing. Statistical analyses were performed with SPSS v25.0 and R v3.4.2. All hypothesis testing was two-tailed and *P*-values < 0.05 were considered statistically significant.

3. Results

Overall, 718 patients with available GDF-15 and hs-cTnT concentrations were included (Supplemental Fig. 1) with 23% (162/718) having an hs-cTn adjudicated diagnosis of AMI (17% [123/162] non-ST-elevation and 6% [39/718] ST-elevation AMI). While in patients without AMI the correlation between GDF-15 and hs-cTnT concentrations was high (spearman rho 0.618, $P < 0.001$), GDF-15 and hs-cTnT concentrations showed no correlation in patients with AMI (spearman rho 0.098, $P = 0.214$).

The median follow-up time was 828 days (IQR 755–939). Patient characteristics stratified by AMI diagnosis and death are presented in Table 1 and patient characteristics stratified by the median GDF-15 concentration are shown in Supplemental Table 1. The cumulative incidence of death within 2 years was 19% in patients with AMI (30 deaths in 162 patients) versus 5% in patients without AMI (25 deaths in 556 patients; $P < 0.001$, Supplemental Fig. 2).

Table 1
Patient characteristics stratified by acute myocardial infarction diagnosis and 2-year all-cause death.

	With AMI ($N = 162$)			Without AMI ($N = 556$)		
	Censored	2-year all-cause death	*P*-value	Censored	2-year all-cause death	*P*-value
N	132	30		531	25	
Female (%)	35 (27)	9 (30)	0.873	187 (35)	5 (20)	0.177
Age [IQR], years	67 [56, 76]	83 [72, 87]	<0.001	60 [48, 72]	80 [72, 84]	<0.001
Previous medical history						
Known CAD (%)	45 (34)	22 (73)	<0.001	169 (32)	15 (60)	0.007
Previous AMI (%)	32 (24)	17 (57)	0.001	122 (23)	11 (44)	0.030
Previous stroke (%)	10 (8)	6 (20)	0.085	24 (5)	3 (12)	0.221
Hypertension (%)	92 (70)	27 (90)	0.041	322 (61)	20 (80)	0.083
Hypercholesterinemia (%)	73 (55)	18 (60)	0.792	244 (46)	15 (60)	0.242
Diabetes (%)	28 (21)	12 (40)	0.055	70 (13)	5 (20)	0.499
Ever smoker (%)	82 (62)	15 (50)	0.309	308 (58)	18 (72)	0.238
Family history of CAD (%)	50 (46)	7 (41)	0.921	157 (39)	4 (31)	0.753
Medication at presentation						
Aspirin (%)	55 (42)	16 (53)	0.338	193 (36)	12 (48)	0.333
Statin (%)	42 (32)	15 (50)	0.095	180 (34)	12 (48)	0.217
Betablocker (%)	47 (36)	20 (67)	0.004	202 (38)	15 (60)	0.047
GDF-15 (ng/L), 0 h	1425 [1020, 2025]	3510 [2515, 5203]	<0.001	1070 [743, 1695]	2440 [1490, 5310]	<0.001
hs-cTnT (ng/L), 0 h	84 [29, 274]	116 [41, 323]	0.343	5 [3, 11]	13 [8, 21]	<0.001

AMI - acute myocardial infarction; CAD - coronary artery disease; GDF-15 - growth differentiation factor-15; hs-cTnT - high-sensitivity cardiac troponin T; IQR - inter quartile range.

3.1. Prognostic performance

In contrast to hs-cTnT, GDF-15 concentrations remained significant predictors for death in patients with and without AMI when adjusted for age, sex, previous medical history and risk factors (Supplemental Table 2). In AMI patients, GDF-15 provided an AUC of 0.89 (95% CI 0.83–0.94) for 2-year death versus 0.55 (95% CI 0.44–0.66) for hs-cTnT ($P < 0.001$) (Fig. 1). A GDF-15 cutoff of ≤1560 ng/L predicted 2-year survival in 47% (76/162) of AMI patients and had 100% sensitivity (95% CI 88–100%) for 2-year death. While the overall predictive accuracy of GDF-15 (0.89, 95% CI 0.83–0.94) was not statistically different from the GRACE score (0.81, 95% CI 0.73–0.89, $P = 0.066$), the GDF-15100% sensitivity cutoff correctly identified significantly more AMI patients at very low mortality risk as compared to the GRACE score 100% sensitivity

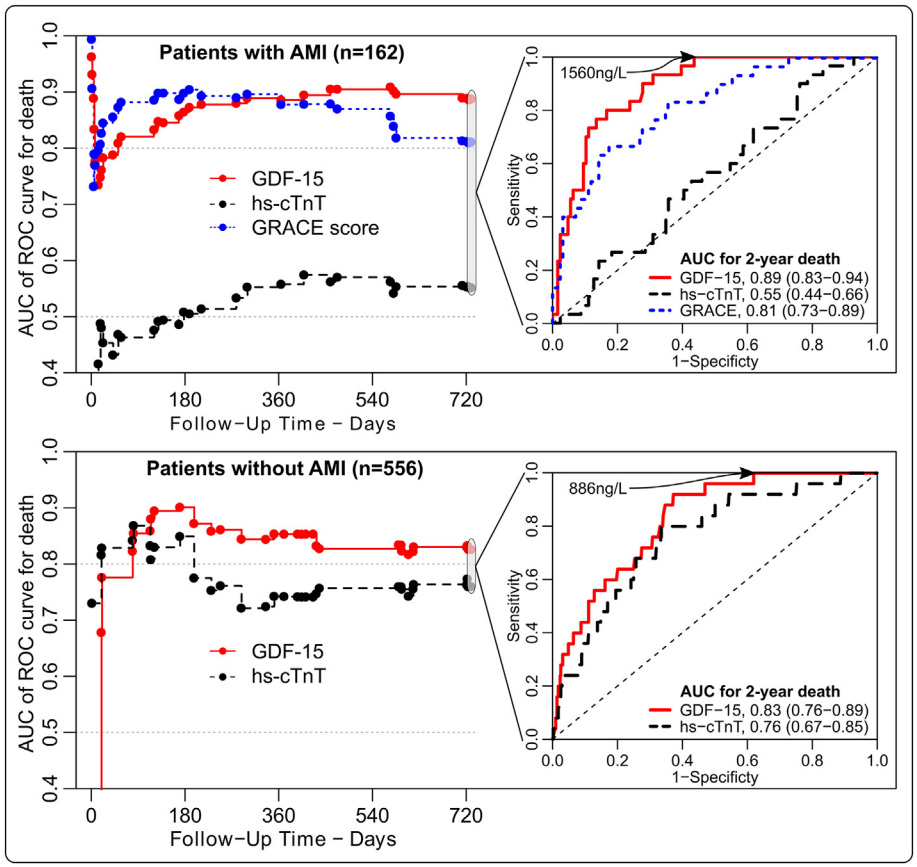

Fig. 1. Time-dependent areas under receiver operating characteristics curve (AUC of ROC) of GDF-15, hs-cTnT and the GRACE score for death plotted over 2 years for patients with and without acute myocardial infarction (AMI). Each dot represents a change in AUC due to death or censoring. Brackets - 95% confidence intervals of AUC. Arrow - GDF-15100% sensitivity cutoff.

cutoff (47% [76/162] versus 22% [36/162], $P < 0.001$). The cumulative incidence of death within 30 days and 2 years in AMI patients with GDF-15 concentrations >1560 ng/L was 12% and 35% respectively as compared to 0% in patients below that cutoff (Supplemental Fig. 3). For patients without AMI, the equivalent cutoff was ≤886 ng/L and predicted 2-year survival in 37% (203/556) of non-AMI patients while providing 100% sensitivity (95% CI 86–100%) for 2-year death (Supplemental Fig. 4). The cumulative incidence of death within 2 years in non-AMI patients with GDF-15 concentrations >886 ng/L was 7% ..

4. Discussion

This study assessed the prognostic utility of GDF-15 concentrations measured in unselected patients presenting with suspected AMI to the emergency department and AMI adjudication based on hs-cTn. We report three major findings. **First**, in both patients with and without AMI, GDF-15 concentrations measured at presentation were independent predictors of death. This corroborates previous studies [7,10] and confirms the incremental predictive information of GDF-15 concentrations in a real-world setting. **Second**, GDF-15 concentrations provided a consistently high predictive accuracy for death in patients with and without AMI, whereas hs-cTnT concentrations had little prognostic significance in AMI patients. This supports the notion that GDF-15 is a biomarker that integrates both cardiac dysfunction and non-cardiac comorbidity [6–11]. **Third**, a GDF-15 cutoff of ≤1560 ng/L at presentation provided a very high negative predictive value (100%) for death in about half of AMI patients. Conversely, AMI patients with a GDF-15 concentration > 1560 ng/L had a high mortality risk. This cutoff is similar to the median GDF-15 concentration found recently in a large cohort of selected acute coronary syndrome patients, with the 1-year death rate in patients <1550 ng/L being markedly lower than in patients above that median (1.8% vs. 7.4%) [11]. Similarly, another sub-analysis of a non-ST-elevation acute coronary syndrome trial of patients recruited between 1999 and 2000 found a 0.76 AUC for GDF-15 concentrations predicting 1-year death [8]. We assume that having a more precise diagnosis of AMI and including patients with both cardiac and non-cardiac comorbidity contributed to the even higher prognostic accuracy observed in our study. Future studies need to evaluate how GDF-15 could best be used clinically. Given the extremely low risk of death based on GDF-15 concentrations below 1560 ng/L in nearly half of hs-cTn adjudicated AMI patients, an apparent option would potentially be the identification of appropriate candidates for swift discharge from a monitored unit after revascularization and shorter hospitalization. This could help addressing uncertainties among physicians regarding the intensity and length of hospitalization following revascularizations for AMI. Similarly, GDF-15 concentrations could help in the selection of patients with small AMIs without benefit from ACE-inhibitors and beta-blockers [2].

Some limitations warrant consideration when interpreting the findings of this study. This was a secondary analysis from a large ongoing multicenter study. As such, no specific sample size calculation was performed and only a moderate number of patients could be included. There certainly is the need for additional studies in hs-cTn adjudicated AMI patients.

5. Conclusions

GDF-15 concentrations provide a high discriminative performance for all-cause death in patients presenting with suspected AMI. A simple cutoff of 1560 ng/L ruled-out 2-year death in about half of hs-cTn adjudicated AMI patients with very high sensitivity. Future research is necessary to fully characterize the contemporary clinical potential of GDF-15 for efficient risk-stratification of AMI patients in the era of hs-cTn.

Funding/support

APACE was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the European Union, the KTI, the Stiftung für kardiovaskuläre Forschung Basel; Abbott, Beckman Coulter Foundation, Biomerieux, Brahms, Roche, Siemens, and Singulex.

Role of the funder/sponsor

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosures

The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. Drs. Walter, Twerenbold, Nestelberger, Boeddinghaus, Wildi, Badertscher and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers.

Dr. Walter reports a research grant from the Swiss Heart Foundation and the Swiss Academy of Medical Sciences and Bangerter-Rhyner Foundation (YTCR 23/17). Dr. Nestelberger received speaker honoria from Beckman-Coulter. Dr. Boeddinghaus discloses research grants from the University of Basel and the Division of Internal Medicine, the Swiss Academy of Medical Sciences, the Gottfried and Julia Bangerter-Rhyner-Foundation, and speaker honoraria from Siemens. Dr. Twerenbold received research support from the Swiss National Science Foundation (P300PB-167803/1) and speaker honoraria/consulting honoraria from Roche, Abbott, Brahms and Siemens. Dr. Wildi has received research funding from FAG (Freiwillige Akademische Gesellschaft) Basel and the Bangerter-Rhyner Stiftung. Dr. Mueller has received research support from the Swiss National Science Foundation, the University of Basel, Swiss Heart Foundation, the KTI, the European Union, the Stiftung für kardiovaskuläre Forschung Basel; Abbott, Alere, Astra Zeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, and the University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, Amgen, Astra Zeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Sanofi, Siemens, and Singulex.

All other authors declare that they have no conflict of interest with this study. The investigated hs-cTnT and GDF-15 assays were donated by the manufacturers, who had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.088.

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