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This is the published version of a paper published in *Resuscitation*.

Citation for the original published paper (version of record):

Andersson, J., Fall, T., Delicano, R., Wennberg, P., Jansson, J-H. (2020)  
GDF-15 is associated with sudden cardiac death due to incident myocardial infarction  
*Resuscitation*, 152: 165-169  
<https://doi.org/10.1016/j.resuscitation.2020.05.001>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

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# Resuscitation

journal homepage: [www.elsevier.com/locate/resuscitation](http://www.elsevier.com/locate/resuscitation)

## Clinical paper

# GDF-15 is associated with sudden cardiac death due to incident myocardial infarction



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## Abstract

**Aims:** Preventing sudden cardiac death (SCD) due to acute myocardial infarction (MI) in previously healthy patients is challenging. Proteomic analysis may lead to an understanding of biological mechanisms and provide predictive biomarkers.

**Methods:** In this prospective, nested case-control study from northern Sweden, 87 candidate cardiovascular protein biomarkers were studied in 244 individuals who later died within 24 h from an incident MI and 244 referents without MI and individually matched for age, sex and date of health examination and alive at the date of event in the index person. Association analysis was conducted using conditional logistic regression. Bonferroni correction was applied to avoid false positive findings.

**Results:** Ten proteins were associated with future SCD due to acute MI in the non-adjusted analysis. The strongest association were found for growth differentiation factor 15 (GDF-15) with an odds ratio (OR) of 1.79 (95% confidence interval [CI] 1.41, 2.25) per standard deviation increase in protein, and urokinase-type plasminogen activator receptor with an OR of 1.66 (95% CI 1.34, 2.06). In models adjusted for lipid levels, body mass index, education, smoking, hypertension and C-reactive protein, only association with GDF-15 remained (OR 1.47 (95% 1.11, 1.95)).

**Conclusion:** Elevated levels of GDF-15 are associated with increased risk of SCD within 24 h of incident MI. Further research may enable the use of GDF-15 together with other clinical and biological markers to guide primary preventive interventions for individuals at high risk for SCD.

**Keywords:** Sudden cardiac death, Myocardial infarction, Proteomics, GDF-15

## Introduction

Cardiovascular disease (CVD) accounts for one-third of all deaths globally and is the single leading cause of premature mortality.<sup>1,2</sup> About 50% of all heart-related deaths is caused by sudden cardiac death (SCD) triggered by coronary heart disease events.<sup>3</sup> In northern Sweden the yearly incidence of SCD in individuals aged 35–64 without previous CVD is 12 per 100,000 for women and 65 for men,<sup>4</sup> and the incidence rate increases rapidly with higher age.<sup>5</sup> Prevention is challenging as SCD might be the first clinical manifestation of CVD and because the underlying etiology is not fully understood. “Among

individuals without known heart disease many suffers from a concealed ischemic heart disease. When this is not the case genetic and other still unknown causes predispose individuals to SCD.” Risk factor profiling is proposed to be a feasible strategy to identify individuals with increased risk for SCD.

We previously reported that type 2 diabetes mellitus as well as a high body mass index (BMI) predict an eightfold risk for SCD due to acute myocardial infarction (MI).<sup>6</sup> However, cardiovascular risk factor screening methods still needs to be improved,<sup>7,8</sup> particularly to identify high-risk individuals. Recent technical advancements have enabled proteomic plasma profiling in large studies and paving the path for the discovery of novel biomarkers and pathways leading to SCD.

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<https://doi.org/10.1016/j.resuscitation.2020.05.001>

Received 16 January 2020; Received in revised form 9 April 2020; Accepted 1 May 2020

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The aim of this study was to evaluate the association of a large set of cardiovascular candidate biomarkers with SCD due to acute MI using a nested case-reference design in a population-based setting in northern Sweden.

## Methods

### Study population

The study sample was derived from the Västerbotten Intervention Program (VIP),<sup>9</sup> a health intervention program for prevention of CVD and the World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA), a population survey in northern Sweden.<sup>10</sup> Participation rates were about 59% and 77%, respectively. The data collection and registration in VIP and MONICA are similar and are described in detail in Refs.<sup>9,10</sup> All acute MI events in northern Sweden are evaluated and registered in the MONICA registry, according to standardized WHO criteria and based on reports from general practitioners as well as hospital discharge records and death certificates.<sup>10</sup>

In this prospective nested case-control study, we identified cases of first ever acute MI in VIP and MONICA occurring between 1986 and 2006 through the MONICA registry. Individuals included are 25–64 years and from 2000, individuals  $\leq 74$  years have also been included. MI cases that died within 24 h from onset of symptoms were classified as SCD due to MI. Subjects with a history of MI before health examination were excluded, as experiencing a MI may influence the studied determinants. Plasma was available from 244 cases with SCD due to MI. One referent without MI for each case, alive at the time of SCD in the index person, matched by sex, birth year ( $\pm 2$  years), year of health examination and type of health examination, were selected from the biobank. The study was approved by the Research Ethics Committee of Umeå University. All participants gave informed consent.

### Baseline variables

Smoking habits were classified into “ever smoking” (including previous smokers and occasional smokers) or “never-smoking”. BMI was calculated as weight (kg)/square height (m<sup>2</sup>). Hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg or a diastolic blood pressure  $\geq 90$  mmHg or reported use of anti-hypertensive medication during the last 14 days. Educational level was dichotomised into 9 years compulsory education or higher.

Blood samples were taken after a minimum 4-hour fast and were analyzed for total cholesterol and plasma glucose using a bench-top analyser (Reflotron<sup>®</sup>; Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany). Since 2005, a HemoCue bench-top analyser (Quest Diagnostics) has been used for glucose values. An oral glucose tolerance test was performed with a 75 g oral glucose load according to WHO standards. Diabetes was defined as self-reported disease from the questionnaire or a fasting glucose  $\geq 7$  mmol/L and/or 2-h post-load plasma glucose  $\geq 11.0$  mmol/L ( $\geq 12.2$  mmol/L in the VIP, as capillary plasma was drawn). Biochemical analysis was performed on the Cobas 8000 modular multianalyser using Tinaquant kits for A1 (APOAT) and B (APOBT), as well as c-reactive protein (CRP)-kit (CRPL3) from the same manufacturer (Roche Diagnostics GmbH, Mannheim, Germany). Plasma samples were obtained after a minimum of 4 h fast (extended to 8 h 1992), and

stored in a deep-freezer at  $-80^{\circ}\text{C}$  until analyses. All measurements were made by laboratory staff, blinded to participants' disease status.

### Proteomic profiling

Plasma samples were analyzed using the Proximity Extension Assay technique<sup>11</sup> on the Olink Multiplex CVD III panel, a high-specificity assay that simultaneously measures concentrations of 92 cardiovascular candidate proteins. In brief, the assay uses a standard 96-well microplate format including four quality control standards. Each sample is mixed with 92 pairs of oligonucleotide-labeled antibodies. If both high-specificity antibodies bind the target protein, the attached oligonucleotides form a unique DNA reporter sequence that is subsequently amplified and quantified by standard PCR. Samples were analyzed in individual wells on eight plates, keeping each set of case and referent together on the same plate. Fluorescence detection-threshold PCR values were log2-transformed and corrected for technical variation by negative and inter-plate controls.<sup>11</sup> Lower limits of detection (LOD) was determined through negative control samples. Quality control included the removal of five proteins (SPON1, NTproBNP, EPHB4, PCSK9 and PSPD) with  $>15\%$  missing values. One individual with  $<95\%$  of measurements below LOD in the remaining 87 proteins were excluded. In the remaining data, values below the LOD were imputed to LOD/2 (in total 107 replacements out of 42,891 data points). Because principal component analysis indicated associations of protein measurements with plate and storage time, we used standardized residuals from linear regression models adjusted for plate and storage time as independent variables in this study.

### Statistical analysis

We used STATA 14.1 for all statistical analyses. As a first step, a series of non-adjusted conditional logistic regressions were used to estimate the association of each protein with case status using the *clogit* command in STATA. We used a Bonferroni corrected *p* value of  $0.05/87$  tests =  $5.7\text{e}-4$  to define statistical significance.

For the proteins associated with case status at a Bonferroni-adjusted *p*-value threshold, we performed a set of adjusted conditional logistic regression models. For many variables, especially CRP, apolipoprotein A (ApoA), and ApoB1, there were many missing observations. Therefore, we applied the following approach. First, we used the complete-case approach that excluded individuals with missing covariate data and adjusted for hypertension status, smoking habits, diabetes mellitus, education level, fasting status, BMI and total cholesterol. We further used multiple imputation by chained equation with 20 iterations to impute missing values in diabetes mellitus, ApoA1, ApoB, education, BMI and CRP based on information in these variables and hypertension, smoking habits, age and sex. Thus, the imputation included some of the matching variables but excluded the identifier of matched pairs, consistent with the method “Multiple imputation using matching variables” described by Seaman and Keogh.<sup>12</sup> The number of imputed values is shown in Supplementary Table 1. Conditional logistic regression models adjusting coefficients and standard errors for the variability between imputations was done according to the combination rules by Rubin.<sup>13</sup> These models were run for each of the proteins passing step 1 adjusting for hypertension status, smoking habits, diabetes mellitus, education level, fasting status, BMI, total cholesterol, ApoA1, ApoB and CRP.

**Table 1 – Description of the 244 cases with myocardial infarction and sudden cardiac death and 244 referents.**

	Cases with data	Mean (SD)/n(%)	Referents with data	Mean (SD)/n(%)
Age at sampling	244	54.7 (7.0)	244	54.9 (7.1)
Age at event	244	63.2 (7.3)	NA	NA
Female	244	54 (22.1%)	244	54 (22.1%)
Previous or occasional smokers	244	174 (71.3%)	244	135 (55.3%)
Body mass index	242	28.1 (4.6)	239	26.0 (3.9)
Triglycerides	201	2.0 (1.2)	187	1.6 (0.9)
Total cholesterol	235	6.5 (1.3)	234	6.1 (1.1)
Hdl cholesterol	105	1.5 (3.1)	86	1.3 (0.4)
Apoa1	173	1.4 (0.2)	175	1.4 (0.3)
ApoB	174	1.3 (0.3)	175	1.2 (0.3)
Diabetes mellitus	244	85 (34.8%)	241	44 (18.3%)
Fasting glucose	207	6.1 (2.5)	214	5.5 (1.0)
2-h-post OGTT glucose	186	7.0 (2.7)	213	6.6 (1.8)
C-reactive protein	172	3.1 (6.0)	171	2.1 (4.7)
Hypertension	244	158 (64.8%)	244	108 (44.3%)
Systolic blood pressure	238	142.3 (18.4)	240	133.9 (16.9)
Diastolic blood pressure	238	88.4 (9.1)	240	84.9 (8.9)
Secondary education	227	100 (44.1%)	230	138 (60.0%)

## Results

The mean age at SCD was 55 years and 78% were men (Table 1). In the first step, 10 proteins were associated with future SCD in the non-adjusted analysis. These associations are reported in Supplementary Table 2. Nine proteins were associated with increased risk while concentrations of paraoxonase 3 (PON3) was associated with lower risk. The strongest associations were found for GDF-15, with an odds ratio (OR) per standard deviation (SD) increase in protein of 1.79 (95% CI 1.41, 2.25) and urokinase plasminogen activator surface receptor (U-PAR) 1.66 (95% CI 1.34, 2.06). In fully adjusted models using the complete case approach, estimates were attenuated, indicating that the association was confounded or mediated by the included covariates (hypertension status, smoking habits, diabetes mellitus, education level, fasting status, BMI, and total cholesterol) although the association of GDF-15 and U-PAR with SCD was still significant. In

models additionally adjusted for ApoA1, ApoB and CRP, only the association of GDF-15 was still significant (OR 1.47, 95% CI 1.11, 1.95). The results are shown in Table 2.

## Discussion

Our main finding was identification of the strong association of GDF-15 independently with SCD. We further identified nine other associated proteins, but their association was dependent on cardiovascular risk factors.

GDF-15 was identified in 1997 as a macrophage derived inflammatory response cytokine.<sup>14</sup> It was later found to be induced in the myocardium in response to ischemia.<sup>15</sup> Since then it has become recognized as a risk marker for cardiovascular and all-cause mortality,<sup>16–20</sup> and in acute coronary syndromes as a predictor of prognosis.<sup>21–27</sup>

**Table 2 – Multivariable-adjusted models for those proteins that were associated with sudden cardiac death in the discovery analysis.**

Protein	Protein, full name	Non-adjusted, n=488		Adjusted <sup>a</sup> , n=426		Imputed, adjusted <sup>b</sup> , n=488	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
GDF15	Growth/differentiation factor 15	1.79 (1.41, 2.25)	1.1E–06	1.39 (1.05, 1.84)	0.02	1.47 (1.11, 1.95)	0.01
UPAR	Urokinase plasminogen activator surface receptor	1.66 (1.34, 2.06)	4.0E–06	1.35 (1.02, 1.78)	0.04	1.32 (0.99, 1.75)	0.05
PON3	Paraoxonase	0.60 (0.48, 0.75)	7.2E–06	0.76 (0.56, 1.02)	0.07	0.79 (0.58, 1.07)	0.12
LDL receptor	Low-density lipoprotein receptor	1.59 (1.30, 1.95)	8.2E–06	1.25 (0.95, 1.63)	0.11	1.16 (0.88, 1.51)	0.29
OPG	Osteoprotegerin	1.54 (1.24, 1.90)	6.8E–05	1.16 (0.90, 1.50)	0.26	1.22 (0.93, 1.60)	0.14
FABP4	Fatty acid-binding protein, adipocyte	1.56 (1.25, 1.95)	6.9E–05	1.14 (0.84, 1.55)	0.41	1.08 (0.80, 1.46)	0.61
RARRES2	Retinoic acid receptor responder protein 2	1.50 (1.22, 1.84)	1.3E–04	1.13 (0.88, 1.45)	0.35	1.05 (0.81, 1.35)	0.73
tPA	Tissue-type plasminogen activator	1.47 (1.21, 1.80)	1.4E–04	1.09 (0.83, 1.42)	0.55	1.03 (0.79, 1.34)	0.84
CSTB	Cystatin-B	1.48 (1.20, 1.81)	1.8E–04	1.17 (0.91, 1.51)	0.22	1.13 (0.89, 1.45)	0.31
CTSD	Cathepsin D	1.43 (1.18, 1.75)	3.6E–04	1.03 (0.81, 1.32)	0.81	1.01 (0.79, 1.30)	0.92

<sup>a</sup> Adjusted for hypertension status, smoking habits, diabetes mellitus, education level, fasting status, body mass index and total cholesterol.

<sup>b</sup> Imputed covariates, adjusted for hypertension status, smoking habits, diabetes mellitus, education level, fasting status, body mass index, total cholesterol, ApoA1, ApoB and C-reactive protein.

GDF-15 is involved in the inflammatory pathway but in contrast to the rapid rise and fall of natriuretic peptides, cardiac troponin and CRP during CVD events it seems more stable and may reflect a chronic CVD burden.<sup>28</sup> It is reasonable to assume that GDF-15 identifies individuals with subclinical cardiovascular disease at risk for SCD from an acute myocardial infarction, explaining our results. Our study adds to the potential use of GDF-15 for SCD risk prediction, as this is the first study to show GDF-15 as a risk marker for SCD among previously healthy individuals. However, the discriminative ability and clinical utility of GDF-15 in that setting needs to be determined in future studies. In the absence of previous cardiovascular events, primary prevention is the only possible measurement to reduce SCD. Thus, improved methods to identify individuals with high risk are essential and GDF-15 may be a suitable candidate risk marker. Further research may lead to the use of GDF-15, together with other clinical and biological markers, to guide primary preventive interventions for individuals with high risk for SCD. Currently, implantable cardioverter defibrillators are used to reduce SCD among patients with heart failure. The use of GDF-15 may better identify patients that can benefit from such treatment and beyond present indications. GDF-15 may also become a tool to evaluate primary preventive measures that aim to reduce the risk of SCD.

Using a single marker strategy in individual risk prediction in the general population is not reasonable based on the heterogeneity of SCD.<sup>29,30</sup> GDF-15 itself can only explain a limited risk increase for SCD, and it is unlikely that any other single biomarker will have enough power to identify a satisfactory number of high-risk individuals in a general population. Further studies are needed, and a constellation of biomarkers and other risk factors could be the basis for a risk score.

U-PAR has also been identified as an inflammatory marker from studies mainly in cancer<sup>31</sup> and kidney disease.<sup>32–35</sup> In the Malmö Diet and Cancer Study U-PAR was associated with increased incidence of CVD in elderly.<sup>36</sup> We could not reproduce their results in our fully adjusted model. The discrepancy can be explained in several ways including the differently adjusted models, the fact that U-PAR is associated with CVD but not SCD, and that the Malmö Diet and Cancer Study population was about 10 years older.

Our findings are most likely explained by atherosclerotic mechanisms involving GDF-15 and U-PAR. Both GDF-15 and U-PAR are involved in inflammatory processes which in turn are linked to atherosclerosis. A higher degree of inflammation could suggest more aggressive disease progression explaining the association of GDF-15 with SCD events among MI cases in our study.

Our findings need confirmation in another population to verify the results. Also, it remains unknown if GDF-15 is only a risk marker or if it is a causal factor and if therapies targeting GDF-15 can lower the risk of SCD. Additional studies such as Mendelian randomization and randomized controlled trials lowering GDF-15 are needed to answer such questions.

Our study had some unique strengths. A majority of SCD occurs out of the hospital. We were able to include patients who died outside of the hospital due to cardiac arrest even when no resuscitation was attempted, and we only included incident MIs. Secondary prevention in cases with previous CVD may otherwise have altered the concentrations of the studied proteins. The method also allowed us to analyze proteins sampled before the event.

The study also had some limitations. Almost 80% of the cases were male, as can be expected, which limited the possibility for sex-specific analysis. The participants in this study were mainly middle-aged

Caucasians from northern Sweden and the results could be different in other populations. Moreover, the protein panel only included a limited set of proteins, and other proteins may be of larger importance. The findings should be confirmed in further studies, preferably in another population.

## Conclusion

Elevated levels of GDF-15 are associated with increased risk of SCD within 24 h of incident MI. Further research may enable the use of GDF-15 together with other clinical and biological markers to guide primary preventive interventions for individuals at high risk for SCD.

## Authors' contributions

Jonas Andersson contributed to acquisition, analysis, or interpretation, drafted manuscript, critically revised the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Tove Fall contributed to acquisition, analysis, or interpretation, drafted manuscript, critically revised the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Rachel Delicano contributed to acquisition, analysis, or interpretation, critically revised the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Patrik Wennberg contributed to acquisition, analysis, or interpretation, critically revised the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Jan-Håkan Jansson contributed to conception or design, contributed to acquisition, analysis, or interpretation, critically revised the manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

## Funding

This work was supported by ERC Starting Grant (801965), a project grant from Swedish Heart and Lung foundation (20150429) and the Swedish Research Council (2015-03477). The project was also supported by the Swedish Heart and Lung foundation (20160275).

## Conflict of interest

None declared.

## Acknowledgements

Dr. Fall reports grants from ERC Starting Grant (801965), a project grant from Swedish Heart and Lung foundation (20150429) and the Swedish Research Council (2015–03477), during the conduct of the study.

Dr. Jansson reports grants from Swedish Heart and Lung foundation (20160275), during the conduct of the study.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.resuscitation.2020.05.001>.

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