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Limited incremental value of growth differentiation factor 15 in the initial evaluation of low and intermediate risk acute chest pain patients

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ABSTRACT

Introduction: Expression of the cytokine growth differentiation factor 15 (GDF-15) is up-regulated in conditions of tissue injury and stress. We evaluated if GDF-15 predicts obstructive coronary artery disease (CAD) or need for revascularization within 30 days and 12 months in low/intermediate risk patients with acute chest pain.
Materials and Methods: We included 537 hospitalized patients who had high-sensitivity troponin T (hs-cTnT) < 99th percentile and underwent coronary CT angiography (CCTA). Odds ratios (ORs) and 95 % confidence intervals (CI) were calculated by logistic regression analyses and are reported per standard deviation increment of GDF-15 (log-transformed).
Results: The median (25th-75th percentile) age was 56 (49–65) years, 217 (40.4 %) were women, 83 (15.5 %) had obstructive CAD at CCTA. In total 49 (9.1 %) patients underwent revascularization within 30 days and 52 (9.7 %) within 12 months. In age and sex adjusted analysis GDF-15 was a significant predictor with ORs (95 % CI) of 1.35 (1.05–1.73), 1.39 (1.06–1.83) and 1.41 (1.07–1.84) for obstructive CAD, revascularization within 30 days and 12 months, respectively. However, after adjustment for clinical covariables, the ORs of GDF-15 were no longer statistically significant for either outcome ($P \geq 0.07$). Adding hs-cTnT levels alone to the age and sex adjusted model also rendered the ORs of GDF-15 non-significant ($P \geq 0.31$).
Conclusions: In patients with acute chest pain but without acute myocardial infarction, GDF-15 did not substantially improve the identification of obstructive CAD or need for revascularization within 30 days and 12 months. Our findings question the clinical usefulness of GDF-15 for prognostication of low-risk patients with acute chest pain.

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1. Introduction

Chest pain remains a major diagnostic challenge due to its frequent occurrence, diverse presentations and potentially life-threatening consequences. However, a large proportion of patients investigated for chest pain of suspected ischemic aetiology, have non-cardiac, and often benign, causes of their symptoms. Improved tools for the identification of patients with coronary artery disease (CAD) who do not have acute myocardial infarction (MI) may have great impact on safety and patient outcomes as well as on cost efficiency of the health care system. Cardiac troponin measurements have for more than 2 decades been integral to the definition of MI, and newer, high-sensitivity assays can rapidly rule out MI in the emergency department (ED). In patients where MI has been excluded, clinicians are encouraged to use risk assessment tools like the HEART score [1] in their diagnostic workup. However, such risk scores have suboptimal performance and are generally underused in day-to-day practice [2].

Cytokine growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor-β superfamily. It is expressed in several tissues including cardiomyocytes and is up-regulated in conditions of tissue injury and stress. In experimental models, GDF-15 has been identified in atherosclerotic plaques [3] and has been shown to be up-regulated in ischemia [4]. Hence, serum GDF-15 measurements have been extensively studied as a predictor of adverse cardiovascular events in patients with acute and chronic coronary syndromes [5–8]. Indeed, recent European guidelines highlight GDF-15 as a promising biomarker for long-term prognostication following an acute coronary syndrome (ACS) [9]. However, compared to the extensive literature on GDF-15 for long-term risk prediction, less is known on the diagnostic or prognostic performance of this biomarker during or shortly after the acute hospitalization of low/intermediate risk patients with acute chest pain [10–12]. Rule-out of CAD in general and, more specifically, obstructive CAD is of particular interest when assessing the potential clinical utility of a biomarker in the ED. It would be highly beneficial for clinicians to improve the identification of patients with CAD to initiate prophylactic treatment as well as being able to safely discharge patients who do not require further investigations during in-hospital stay.

We hypothesized that measurement of serum GDF-15 could improve the workflow of patients with acute chest pain. We evaluated if elevated GDF-15 predicted the presence of any CAD or obstructive CAD during index hospitalization and need for revascularization during 30 days and 12 months follow-up. Further, we evaluated if GDF-15 measurements could be used to identify a subgroup who could be safely discharged from the ED without further diagnostic workup. The study was performed in a cohort of patients with suspected CAD in whom acute MI had been excluded. All the participants underwent coronary CT angiograms (CCTA) during in-hospital stay.

2. Methods

2.1. Study design

The WESTCOR study (Clinical Trials number: NCT02620202) is a prospective observational study, which has been described in detail earlier [13,14]. The current study included a subgroup of 537 participants aged ≥ 18 years who were admitted to the ED at Haukeland University Hospital in Bergen, Norway due to acute chest pain, who were not diagnosed with acute MI during the index admission. The participants were recruited during the period February 2015–May 2019. All patients included in the present sub-study had serial high-sensitivity cardiac troponin T (hs-cTnT) measurements < 99th percentile and underwent a CCTA as part of the initial diagnostic work-up. Hence, patients included in the WESTCOR-study who were diagnosed with MI according to the third universal definition of MI [15] were excluded, as were patients in which a CCTA was clinically contraindicated (contrast allergy, decompensated heart failure, fast and irregular rhythms such as atrial fibrillation or estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73 m^2).

All patients underwent clinical examination, including measurements of body mass index (BMI), systolic and diastolic blood pressure.

The study was carried out according to the declaration of Helsinki and was approved by the regional Ethics Committee (approval number 2014/1365). All participants provided written, informed consent.

2.2. Biochemical analysis

Serum samples were obtained at arrival, frozen and stored at −80 °C. GDF-15 was measured in thawed biobanked samples using an electrochemiluminescence immunoassay on Cobas e801 (Roche Diagnostics). The GDF-15 assay has a measuring range from 400 (limit of quantitation) to 20 000 ng/L. The highest coefficient of variation (CV_A) was 2 % at a concentration of 520 ng/L (lowest measured internal quality assessment sample). The expected reference interval for this assay as suggested by the manufacturer is shown in the Supplemental Table S1.

Hs-cTnT was analysed in fresh samples, using a high-sensitivity assay from Roche Diagnostics with limit of blank 3 ng/L), limit of detection of 5 ng/L, and local 10 % analytical within-series CV_A at 4.5 ng/L. CV_A was below 5 % for concentrations of 10 ng/L or higher, and the sex-neutral 99th percentile was 14 ng/L [16]. HbA1c, non-HDL cholesterol, triglycerides (TG), and creatinine were measured in fresh samples at the routine laboratory at Haukeland University Hospital (Bio-rad D100 (Biorad), Cobas 8000 and e602/e801, Roche Diagnostics), see Supplemental Table S2. GFR was estimated using the creatinine (enzymatic assay) CKD-EPI formula [17].

2.3. Coronary Computed Tomography angiography

All participants were examined using the dual source 128 or 256 Slice Somatom FORCE (https://www.siemens-healthineers.com). Coronary artery calcium (CAC) score quantifications were performed by the Agatston method on non-contrast scans [18]. Segment involvement score (SIS) was calculated counting each involved coronary artery segment with > 10 % lumen narrowing [19]. Any CAD was defined as > 10 % narrowing of the lumen in ≥ 1 coronary segment. Obstructive CAD was defined as > 50 % diameter narrowing of the lumen. Multivessel CAD was defined as obstructive CAD in ≥ 2 coronary arteries.

2.4. Follow-up and End Points

Information on CAD on CCTA obtained during the index hospitalization was collected from hospital medical records. We further collected information on revascularization procedures performed within the first 30 days and 12 months post discharge by linkage to the Norwegian Patient Registry.

2.5. Statistical analysis

Variables were reported as counts (%), medians and interquartile range (IQR). Patients were categorized in two groups based on the GDF-15 concentration (≥ or < median) at admission. Differences in baseline characteristics were evaluated using the $\chi 2$ test for categorical variables and the Kruskal-Wallis test for continuous variables.

The association of serum GDF-15 with clinical baseline characteristics was calculated by multivariable linear regression. Non-normally distributed variables were logarithmically transformed before being entered into the linear regression analyses. Additionally, we explored for potential nonlinear relationships by generalized additive regression.

Associations of GDF-15 with CAD, obstructive CAD, multivessel CAD, 30-days and 12 months revascularization were calculated by logistic regression analyses. The odds ratios (ORs) and 95 % confidence intervals (CI) are reported by standard deviation increment of GDF-15 (log transformed). The simple model was adjusted for age and sex

Table 1
Baseline characteristics.

	Total (n = 537)	GDF-15 < median 733 ng/L, (n = 268)	GDF-15 ≥ median 733 ng/L, (n = 269)	P
Demographics				
Age (years) (IQR range)	56 (49–65)	51 (45–59)	61 (54–69)	<0.001
Women	217 (40.4 %)	102 (38.1 %)	115 (42.8 %)	0.31
BMI (kg/m^2) (IQR range)	27.2 (24.8–30.4)	27.2 (25.0–30.0)	27.2 (24.3–30.8)	0.62
Symptoms				
Highly	104 (19.4 %)	54 (20.1 %)	50 (18.6 %)	0.59
Moderately	42 (7.8 %)	18 (6.7 %)	24 (8.9 %)	0.26
Slightly	391 (72.8 %)	196 (73.1 %)	195 (72.5 %)	0.52
ECG				
Normal	502 (93.5 %)	251 (93.7 %)	251 (93.3 %)	0.98
Unspecific	14 (2.6 %)	7 (2.6 %)	7 (2.6 %)	0.79
ST deviation	21 (3.9 %)	10 (3.7 %)	11 (4.1 %)	0.83
Risk factors				
Diagnosed hypertension	185 (34.5 %)	70 (26.1 %)	115 (42.8 %)	<0.001
Systolic BP (mmHg)	145 (133–160)	143 (132–158)	148 (134–164)	0.02
(IQR range)				
Diastolic BP (mmHg)	85 (77–94)	87 (78–96)	84 (76–93)	0.05
(IQR range)				
Diabetes	43 (8.0 %)	7 (2.6 %)	36 (13.4 %)	<0.001
Current smoking	104 (19.4 %)	50 (18.7 %)	54 (20.1 %)	0.68
Hypercholesterolemia	129 (24.0 %)	43 (16.0 %)	86 (32.1 %)	<0.001
Biochemistry				
Serum creatinine (mmol/L) (IQR range)	75 (66–83)	75 (67–82)	75 (65–83)	0.02
eGFR (ml/min/1.73 m^2) (IQR range)	91 (81–99)	94 (85–102)	88 (78–96)	<0.001
HbA1c (mmol/mol)	36.8 (34.4–39.9)	35.5 (33.3–38.0)	38.8 (35.6–41.0)	<0.001
(IQR range)				
Hs-cTnT (ng/L)	5.0 (3.0–7.0)	4.0 (3.0–6.0)	5.0 (3.0–7.0)	<0.001
(IQR range)				
Total chol. (mmol/L)	5.2 (4.4–6.1)	5.1 (4.5–6.1)	5.2 (4.4–6.2)	0.22
(IQR range)				
LDL chol. (mmol/L)	3.4 (2.7–4.3)	3.4 (2.8–4.3)	3.4 (2.7–4.3)	0.18
(IQR range)				
HDL chol. (mmol/L)	1.4 (1.1–1.7)	1.4 (1.2–1.7)	1.4 (1.1–1.8)	1.00
(IQR range)				
TG (mmol/L) (IQR range)	1.40 (1.00–2.00)	1.31 (0.97–1.84)	1.50 (1.06–2.13)	0.01
CRP (mg/L) (IQR range)	1.0 (0.62–3.0)	1.0 (0.66–3.75)	1.0 (0.60–3.0)	0.20
Calcium score				
CAC 0	249 (46.4 %)	151 (56.3 %)	98 (36.4 %)	<0.001
CAC 1–100	163 (30.4)	79 (29.5 %)	84 (31.2 %)	0.73
CAC 101–400	64(11.9)	21 (7.8 %)	43 (16.0 %)	0.005
CAC > 400	56 (10.4)	15 (5.6 %)	41 (15.2 %)	0.001
CCTA				
SIS (IQR range)	1 (1–3)	0 (0–2)	1 (0–3)	<0.001
Any CAD	272 (50.7 %)	117 (43.7 %)	155 (57.6 %)	<0.001
Obstructive CAD	83 (15.5 %)	33 (12.3 %)	50 (18.6 %)	0.03
1 vessel CAD	54 (10.1 %)	21 (7.8 %)	33 (12.3 %)	0.11
2 vessel CAD	24 (4.5 %)	11 (4.1 %)	13 (4.8 %)	0.68
3 vessel CAD	5 (0.9 %)	1 (0.4 %)	4 (1.5 %)	0.19
CCTA not performed due to severely elevated CAC score	21 (3.9 %)	4 (1.5 %)	17 (6.3 %)	0.004
Revascularization				
30-days revascularization	49 (9.1 %)	19 (7.1 %)	30 (11.2 %)	0.13
12 months revascularization	52 (9.7 %)	20 (7.5 %)	32 (11.9 %)	0.06

Abbreviations
BMI: Body mass index
BP: Blood pressure
CAC: Coronary artery calcium
CAD: Coronary Artery Disease
CCTA: Coronary CT Angiography
Chol.: Cholesterol
eGFR: Estimated Glomerular Filtration Rate
hs-cTnT: High-sensitive cardiac Troponin T

(*continued on next page*)

Table 1 (*continued*)

	Total (n = 537)	GDF-15 < median 733 ng/L, (n = 268)	GDF-15 ≥ median 733 ng/L, (n = 269)	P

SIS: Segment involvement score
TG: Triglycerides
Definitions
Any CAD: >10 % narrowing of the lumen in ≥ 1 coronary segment
Obstructive CAD: > 50 % diameter narrowing of the lumen in ≥ 1 coronary segment

Table 2
Covariates associated with GDF-15.

	Standardized β	95 % CI	P
Age	0.037	−0.09–0.17	0.58
Sex (female)	0.048	−0.08–0.18	0.46
BMI	−0.029	−0.15–0.09	0.63
Systolic BP	0.14	0.0044–0.27	0.042
Diastolic BP	−0.16	−0.29- − 0.021	0.024
LDL-cholesterol	0.0049	−0.11–0.12	0.93
HDL-cholesterol	−0.13	0.0009–0.27	0.048
Triglycerides	0.14	0.013–0.27	0.030
HbA1c	0.31	0.19–0.43	<0.001
eGFR	−0.22	−0.35- −0.082	0.0017
hs-cTnT	0.12	−0.011–0.24	0.073
Calcium score	0.14	0.027–0.25	0.015
Multiple R^2 32.8 %			

Table 2. Associations between clinical covariates and GDF-15 levels, calculated by multivariate linear regression analysis, expressed as standardized β coefficients with corresponding 95 % confidence intervals (CI) and p-values. The strongest association is seen in relation to HbA1c with β = 0.31, but also systolic BP, triglycerides, and calcium score were all significantly associated with GDF-15. Diastolic BP, HDL-cholesterol and eGFR all show a significant inverse association with GDF-15. The total explained variance of GDF-15 for all variables was 32.8 %.
Abbreviations
BMI: Body mass index
BP: Blood pressure
eGFR: Estimated Glomerular Filtration Rate
hs-cTnT: High-sensitive cardiac Troponin T

only. As it is very unlikely that the clinician would assess acute chest pain patients without taking previous medical history or an electrocardiogram (ECG) into consideration, we used additional clinical routine variables as covariables for the multivariable model. These were selected based on the HEART score [20] and included: symptoms (slightly, moderately or highly suspicious of CAD), family history (first degree relative with cardiovascular disease (CVD) before age 65, binary), ECG (normal, non-specific repolarization disturbances, significant ST deviation), smoking (current, former, never), hypercholesterolemia (binary), hypertension (binary), diabetes (binary) and prior CVD (binary).

In a third model we adjusted for baseline hs-cTnT levels in addition to age and sex. All logistic regression analyses were also repeated replacing GDF-15 with baseline hs-cTnT levels. Discrimination was evaluated by calculating the area under the receiver operating characteristic curve (ROC-AUC) and DeLongs test. We also assessed whether GDF-15 or hs-cTnT (alone or in combination) could be helpful in identifying patients with low/intermediate risk of CAD, obstructive CAD and need of revascularization, and thus promote safe, early discharge from hospital. For the calculations of sensitivity, specificity, positive and negative predictive values, we applied cut-offs for hs-cTnT ≥ 5 ng/L and GDF-15 ≥ 700 ng/L, approximately corresponding to the median values in this study population.

The number of missing observations of clinical and biochemical baseline characteristics were generally low (< 1 %) except for BMI which was only recorded in 284 patients. Missing observations were handled by listwise deletion.

All probability values are two tailed with a significance level set to 0.05. For the statistical analyses, we used the software packages SPSS Statistics V.26 (IBM), R V.4.0.4 for Windows (Vienna, Austria: https://www.R-project.org) and MedCalc Statistical Software version 17.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2017).

3. Results

3.1. Baseline characteristics

The baseline characteristics are summarised in Table 1. The median (IQR) age was 56 (49–65) years, and 217 (40.4 %) of the patients were women. Prior established CAD was registered in 16 patients (3.0 %) and 185 patients (34.5 %) had a history of hypertension. Median (IQR) BMI was 27.2 kg/m^2 (24.8–30.4 kg/m^2), 43 (8.0 %) patients had diabetes, and 104 patients (19.4 %) were current smokers.

At CCTA, a total of 249 (46.4 %) patients had CAC = 0, whereas 120 (22.3 %) had CAC > 100. The median (IQR) SIS was 1 (1–3).

As shown in Table 2, we applied multivariable linear regression analysis to identify covariates associated with GDF-15. The total explained variance of GDF-15 for all variables listed in Table 2 was 32.8 %. The strongest association of GDF-15 was seen in relation to HbA1c (β = 0.31, 95 % CI (0.19–0.43). P < 0.001). GDF-15 was also moderately positively associated with systolic blood pressure, serum TG and CAC score, whereas an inverse association was found with estimated GFR, HDL-cholesterol and diastolic blood pressure. Fig. 1 visualizes the univariate associations of GDF-15 to HbA1c, CAC score and serum TG as obtained by generalized additive regression.

3.2. The associations of GDF-15 with obstructive CAD and revascularization during follow-up

A total of 272 (50.7 %) patients were diagnosed with CAD at baseline CCTA, 83 (15.5 %) patients had obstructive CAD, whereas 29 (5.4 %) had multivessel CAD. In total, 49 (9.1 %) and 52 (9.7 %) patients underwent coronary revascularization during the first 30 days and 12 months, respectively, following the index hospitalization.

In this low-risk population there were no fatalities or incidences of acute MI during 12 months of follow-up.

GDF-15 was not a significant predictor of the presence of CAD, defined as > 10 % lumen reduction in ≥ 1 coronary segment, in either model (Table 3, panels a–c). In age and sex adjusted analyses, GDF-15 significantly predicted obstructive CAD and multivessel CAD, as well as revascularization during 30 days and 12 months, with OR (95 % CI) per standard deviation (SD) increment of ln(GDF-15) of 1.35 (1.05–1.73), 1.44 (1.03–2.01), 1.39 (1.06–1.83) and 1.41 (1.07–1.84), respectively (P ≤ 0.03). However, after adjustment for individual components of the HEART score, i.e. clinical information that is usually routinely available to the clinicians in the ED, the ORs of GDF-15 were no longer statistically significant for any of the outcomes (Table 3, panel b). Also, adding serum hs-cTnT levels alone to the age and sex adjusted model, rendered the ORs of GDF-15 non-significant in relation to obstructive CAD, multivessel CAD as well as 30 days and 12 months revascularization (Table 3, panel c).

We also performed sex specific analysis for the association between GDF-15 and all the evaluated clinical outcomes. Notably, no significant

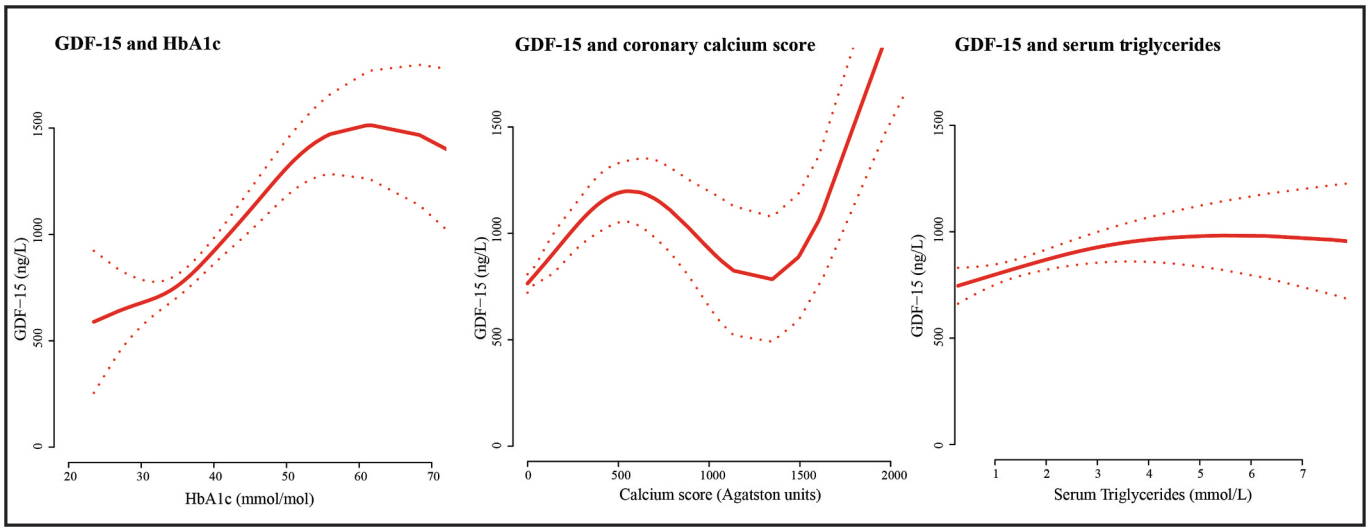

Fig. 1.

Table 3
GDF-15 results.

	Panel A: Age and sex			Panel B: Multivariable model*			Panel C: Age, sex and hs-cTnT levels		
	OR	95 % CI	P	OR	95 % CI	P	OR	95 % CI	P
Presence of any CAD at baseline	0.99	0.78–1.26	0.943	0.84	0.64–1.09	0.189	0.97	0.77–1.24	0.832
Obstructive CAD at baseline	1.35	1.05–1.73	0.020	1.18	0.90–1.54	0.229	1.11	0.85–1.44	0.446
Multivessel CAD at baseline	1.44	1.03–2.01	0.034	1.23	0.84–1.81	0.291	1.19	0.83–1.70	0.354
Revascularization 30 days	1.39	1.06–1.83	0.018	1.28	0.94–1.73	0.117	1.13	0.84–1.52	0.425
Revascularization 12 months	1.41	1.07–1.84	0.013	1.32	0.98–1.77	0.069	1.16	0.87–1.55	0.314

Definitions
Any CAD: >10 % narrowing of the lumen in ≥ 1 coronary segment
Obstructive CAD: > 50 % diameter narrowing of the lumen in ≥ 1 coronary segment
Multivessel CAD: obstructive CAD ≥ 2 coronary arteries
Abbreviations
CAD: Coronary Artery Disease
GDF-15: Growth differentiation factor 15
hs-cTnT: High-sensitive cardiac Troponin T

* Age, sex, history suspicious of CAD, family history, ECG, smoking, previously known hypercholesterolemia, diabetes, hypertension and cardiovascular disease.

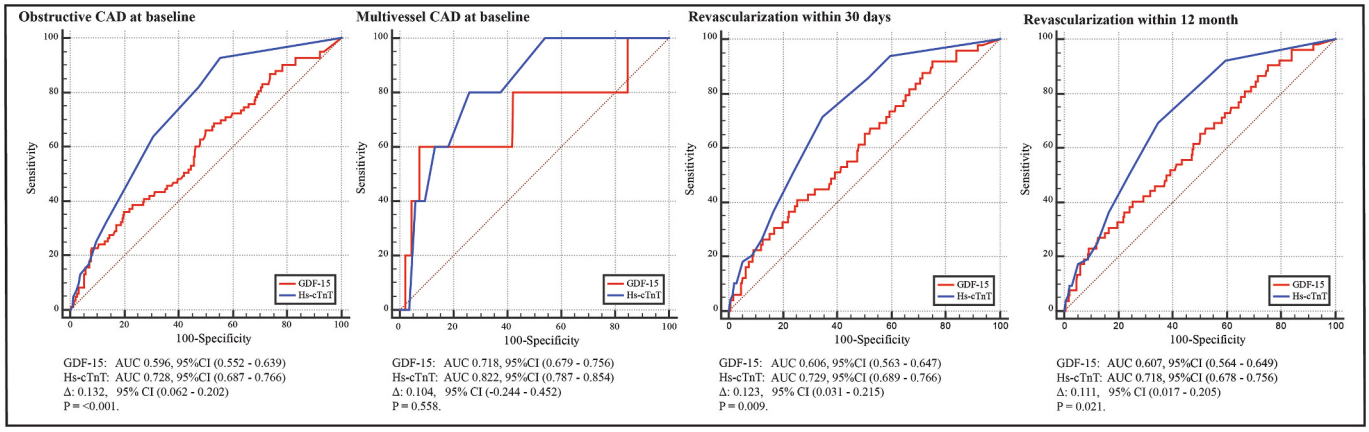

Fig. 2.

effect modifications according to sex were observed ($P_{int} \geq 0.69$; Supplemental Table S3).

We additionally performed the logistic regression analyses replacing serum GDF-15 with serum hs-cTnT levels. As shown in Supplemental Table S4, hs-cTnT was a far stronger predictor in this study population with multivariable adjusted OR (95 % CI) per SD increment of ln(hs-cTnT) of 1.96 (1.45–2.62), 1.76 (1.14–2.74), 2.14 (1.52–3.03) and 2.08 (1.49–2.90) in relation to obstructive CAD, multivessel CAD, revascularization during 30 days and revascularization during 12 months (all $P \leq 0.011$, Supplemental Table S4, panel b).

Adjustment for GDF-15 did not substantially affect the ORs of serum hs-cTnT to outcomes (Supplemental Table S4, panel c).

3.3. Risk discrimination

We further evaluated risk discrimination of GDF-15 by calculating ROC-AUC (Supplemental Table S5). In line with the results from the logistic regression analyses, GDF-15 provided a modest ROC-AUC of 0.596 (0.552–0.639) for obstructive CAD at baseline, P = 0.006. The corresponding estimates for multivessel CAD, revascularization during 30 days and 12 months were 0.718 (0.679–0.756), P = 0.171, 0.606 (0.563–0.647), P = 0.01, and 0.607 (0.564–0.649), P = 0.009, respectively. As shown in Fig. 2 and Supplemental Table S5, the ROC-AUC for hs-cTnT were significantly higher than those for GDF-15 in relation to obstructive CAD at baseline as well as revascularization after 30 days and 12 months (P < 0.021) Combining GDF-15 and hs-cTnT did not significantly improve the ROC-AUCs as compared to hs-cTnT alone (P ≥ 0.432).

3.4. GDF-15 for rule-out

As shown in Supplemental Table S6, we evaluated whether measurements of GDF-15 and/or hs-cTnT could be helpful in ruling out the presence of CAD or obstructive CAD at baseline. Applying a cutoff of 5 ng/L, we found sensitivity (95 % CI) for hs-cTnT alone of 81.9 % (72.0–89.5 %) for obstructive CAD at baseline. The corresponding sensitivity for GDF-15 ≥ 700 ng/L alone was 63.9 % (52.7–74.1 %). The combination of GDF-15 ≥ 700 ng/L or hs-cTnT ≥ 5 ng/L were numerically slightly higher than for hs-cTnT alone, 88.0 % (79.0–94.1 %), although 95 % CI were overlapping. Similar trends and modest results were obtained in relation to multivessel CAD as well as to revascularization within 30 days and 12 months (Supplemental Table S6). We found relatively low sensitivity and specificity (56–65 %) for GDF-15 and hs-cTnT individually, as well as for their combination (56–59 %) for the presence of CAD. Of note hs-cTnT alone showed slightly higher numerical values compared to GDF-15 or the combined use of GDF-15 and hs-cTnT, albeit with overlapping 95 % CI.

4. Discussion

4.1. Principal findings

In a cohort of patients with acute chest pain, who were not adjudicated as MI, GDF-15 measured on admission did not predict presence of CAD on baseline CCTA. Obstructive CAD, multivessel CAD, as well as revascularization during 30 days and 12 months follow-up were predicted in age and sex adjusted analyses but not after adjusting for other clinical variables or hs-cTnT. Serum GDF-15 correlated positively with the CAC score, reflecting atherosclerosis severity.

The lack of significant association between GDF-15 concentrations and the outcomes after correcting for several traditional risk factors including age, diabetes and hypertension as well as serum hs-cTnT levels may partially be explained by GDF-15′s association with several chronic diseases, as well as increasing age. Further, GDF-15 alone or in combination with hs-cTnT had modest diagnostic and prognostic accuracy. Hence a potential use for early rule out in the ED may not be justified. Our findings also question a role of GDF-15 measurement for risk stratification and short-term prognostication of this large group of patients. Indeed, the current analysis indicates hs-cTnT as a more valuable option.

4.2. GDF-15

Contrary to the present work, we previously identified serum GDF-15 as a strong predictor of all-cause and CVD mortality during long-term (median of 1523 days) follow-up, in a partly overlapping study population based on the WESTCOR cohort [7,8]. Associations of GDF-15 to increased long-term mortality risk have also been demonstrated in several previous reports of patients with non-ST acute coronary syndrome, including the MERLIN-TIMI and PLATO studies [21,22]. In contrast, conflicting results have been obtained concerning the association of GDF-15 to recurrent acute coronary events and MIs in ACS patients.

In general population studies, GDF-15 has been identified as a strong predictor of overall mortality [23] as well as death due to coronary heart disease [24]. Further, similar to the present study, significant associations have been found between the serum GDF-15 and the CAC score [25]. The expression of GDF-15 has been identified in atherosclerotic plaques [3] and has been shown to be up-regulated in experimental models of ischemia [4]. GDF-15 may regulate vascular function by increasing the release of nitric oxide [26]. Hence, protective autocrine and paracrine effects have been postulated on the cardiomyocytes and the vascular endothelium [27].

GDF-15 is, however, up-regulated in a variety of cell types in conditions of tissue injury and stress. A *meta*-analysis performed by Zhou et al. revealed that GDF-15 predicted chronic kidney disease progression in renal failure patients [28]. GDF-15 was also a potent predictor of decreased survival over 20 years in patients with osteoarthritis [29]. Further, elevated circulating levels of GDF-15 were associated with increase in the dual risk of cancer and cardiovascular disease in patients with type 2 diabetes [30].

GDF-15 thus appears as a biomarker reflecting the disease severity and prognosis of several chronic disorders, but is not specific for CAD. Consistent with our findings of strong associations between GDF-15 and HbA1c levels as well as with serum TG, numerous experimental studies indicated a role of GDF-15 in the pathogenesis of metabolic syndrome and type 2 diabetes [31]. Interestingly, the signalling pathway between GDF-15 and major central nervous system receptor GFRAL are currently explored as a potential target in obesity treatment [32]. Since strong associations have been observed between GDF-15 levels and metformin dosage [33], GDF-15 has been proposed as a biomarker of metformin use. A recent randomized trial, however, revealed no significant association between GDF-15 levels and glycaemic control in patients treated with metformin [34]. Mendelian randomization studies exploring associations of GDF-15 gene polymorphisms with atherosclerotic CVD have provided inconsistent results, questioning an active role of the GFD-15 cytokine in atherogenesis and vascular diseases [35]. Causality is certainly not a necessity for the clinical usefulness of a biomarker [36]. However, the strong association of GDF-15 to several established cardiometabolic risk factors may imply that its incremental prognostic information to clinical risk scores is modest, a notion that is supported by the findings of the present study.

4.3. Clinical implications

Patients with acute chest pain and suspected ACS frequently undergo CCTA, particularly when ECGs and troponin levels are normal. We aimed at specifically exploring a patient population who were referred to CCTA as an initial diagnostic step. The use of CCTA for low to intermediate risk patients with acute chest pain is endorsed by current clinical guidelines [9]. Hence, tools that could improve the identification of patients with positive findings and who likely benefit the most from this imaging modality, would be highly welcomed.

Cardiac Troponin (cTn) has traditionally been used in ED for the diagnosis of acute MI [37,38]. In line with our findings, it has also previously been shown that in patients where MI has been ruled out, intermediate concentrations of hs-cTnT between 5 ng/L and the 99th percentile upper limit are more likely to have non-obstructive CAD and obstructive CAD than those with hs-cTnT concentrations below this threshold [39,40]. Currently cTn measurements are routinely incorporated into the HEART score algorithm for risk stratification of chest pain patients. Our data suggest that there is no incremental role of GDF-15 measurements in this clinical scenario. Further, hs-cTnT measurements alone or in combination with GDF-15 may not be sufficient as stand-alone tests for ruling out the presence of CAD or obstructive CAD

in the ED. Our findings somewhat contradict numerous reports of strong associations of GDF-15 to adverse CVD prognosis, but previous studies on ACS have mostly included patients with more high-risk features and longer follow-up than in the present study. Earlier studies indicate that GDF-15 is a good risk predictor of overall frailty and risk of death whilst the current data show a weaker association with coronary atherosclerosis. We included individual components of the HEART score into the multivariable model, since physicians are often encouraged to use this risk estimator, along with their clinical judgment, for risk stratification in the ED. Unfortunately, GDF-15 seemed not to provide incremental predictive information beyond the traditional factors of the HEART score, suggesting it may be of limited value in this clinical setting.

5. Strengths and limitations

The prospective design and contemporary study population represent major strengths of our study. Further, the cohort is extensively characterized concerning clinical baseline characteristics. Notably, baseline serum hs-cTnT levels and CCTA findings, including CAC scores, are available for all study participants. Linkage to high-quality health registries provided information on revascularization procedures during follow-up. Notably, reporting to these registries is mandatory to all Norwegian hospitals.

Limitations include the relatively small sample size and single centre design. The study population included patient who had been referred to CCTA as the initial diagnostic modality. Patients with acute MI and those considered at high risk due to dynamic ECG changes, recurrent pain attacks or hemodynamic instability were generally referred directly to invasive coronary angiography and were not eligible for the present study. Hence our findings need replication in independent cohorts with larger sample sizes and may not be generalizable to higher risk study populations. Furthermore, our patients were hospitalized, often due to long geographical travel distances, whereas in other European countries or the USA, they might have been managed in outpatient clinics. Consequently, our results may not be directly applicable to all hospitalized chest pain patients but rather to those referred to CCTA after MI was excluded. However, our use of CCTA in troponin-negative patients with acute chest pain is comparable to practices in other countries.

6. Conclusion

In patients with acute chest pain who underwent CCTA due to suspected CAD, but in whom acute MI had been excluded, GDF-15 provided no incremental information beyond clinical risk factors or hs-cTnT in identifying patients with the presence of CAD, obstructive CAD, multivessel CAD or need of revascularization during 12 months of follow-up. Our study questions the clinical usefulness of GDF-15 measurements for prognostication of patients with acute chest pain, and its role in an early rule-out algorithm in the ED.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use any generative AI or AI-assisted technologies.

Contribution statement

I.K. and E.R.P. analysed and interpreted data. I.K and E.R.P. wrote the manuscript. I.K. and E.R.P. made substantial contributions to analysis and interpretation of data. I.K., E.R.P., O.T.S., G.M.S.M., and T.H.L., collected and processed data. K.M.A, E.R.P. and T.O. conceived and designed the study. K.M.A obtained the funding of the study except for measuring the GDF-15 analysis that was obtained by T.O. I.K., E.R.P., K.M.A., T.O., K.V., P.O.C and T.H.L. edited and revised the manuscript. I.K. and E.R.P. is the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the article.

CRediT authorship contribution statement

Iman Karaji: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Ole-Thomas Steiro:** Writing – review & editing, Data curation. **Gard MS Myrmel:** Writing – review & editing, Data curation. **Torbjørn Omland:** Writing – review & editing, Funding acquisition, Conceptualization. **Hilde L Tjora:** Writing – review & editing, Data curation. **Jørund Langørgen:** Writing – review & editing. **Rune Bjørneklett:** Writing – review & editing. **Øyvind Skadberg:** Writing – review & editing. **Vernon VS Bonarjee:** Writing – review & editing. **Øistein R Mjelva:** Writing – review & editing, Conceptualization. **Paul Collinson:** Writing – review & editing. **Kjell Vikenes:** Writing – review & editing. **Terje H Larsen:** Writing – review & editing. **Kristin M Aakre:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Eva Ringdal Pedersen:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Iman Karaji reports a relationship with Boehringer Ingelheim Norway KS that includes: speaking and lecture fees. Kristin M Aakre reports a relationship with Roche Diagnostics that includes: consulting or advisory, funding grants, and speaking and lecture fees. Kristin M Aakre reports a relationship with Radiometer that includes: consulting or advisory. Kristin M Aakre reports a relationship with Siemens Healthineers that includes: consulting or advisory, funding grants, and speaking and lecture fees. Kristin M Aakre reports a relationship with Spinchip that includes: consulting or advisory. Kristin M Aakre reports a relationship with CardiNor that includes: consulting or advisory. Kristin M Aakre reports a relationship with Mindray that includes: speaking and lecture fees. Kristin M Aakre reports a relationship with Snibe Diagnostics that includes: speaking and lecture fees. Torbjoern Omland reports a relationship with Abbott Diagnostics that includes: funding grants and speaking and lecture fees. Torbjoern Omland reports a relationship with Bayer that includes: speaking and lecture fees. Torbjoern Omland reports a relationship with Cardinor that includes: speaking and lecture fees. Torbjoern Omland reports a relationship with Novo Nordisk that includes: speaking and lecture fees. Torbjoern Omland reports a relationship with Roche Diagnostics that includes: funding grants and speaking and lecture fees. Torbjoern Omland reports a relationship with ChromaDex Inc that includes: funding grants. Torbjoern Omland reports a relationship with Novartis that includes: funding grants. Torbjoern Omland reports a relationship with Akershus University Hospital that includes: funding grants. Paul Collinson reports a relationship with QuidelOrtho that includes: speaking and lecture fees. Paul Collinson reports a relationship with Radiometer that includes: consulting or advisory. Paul Collinson reports a relationship with Psyros Diagnostics that includes: consulting or advisory. Paul Collinson reports a

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Appendix A. Supplementary data

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Glossary

ACS: Acute coronary syndrome
BMI: Body mass index
BP: Blood pressure
CAC: Coronary artery calcium score
CAD: Coronary artery disease
CCTA: Coronary CT angiography
cTn: Cardiac troponin
CV_A*:* Coefficient of variation
CVD: Cardiovascular disease
ED: Emergency department
GDF-15:: Growth differentiation factor 15
GFRAL: GDNF Family Receptor Alpha Like
Hs-cTnT:: High-sensitivity cardiac troponin T
IQR: Interquartile range
MI: Myocardial infarction
ROC-AUC:: Receiver operating characteristics curves
SIS: Segment involvement score
TG: Triglycerides