



## **GDF-15 is a predictor of cardiovascular events in patients presenting with suspicion of ACS**



Δρ Στέργιος Ζ. Τζήκας  
30.10.2015

36<sup>ο</sup> Διεθνές Καρδιολογικό Συνέδριο, Θεσσαλονίκη

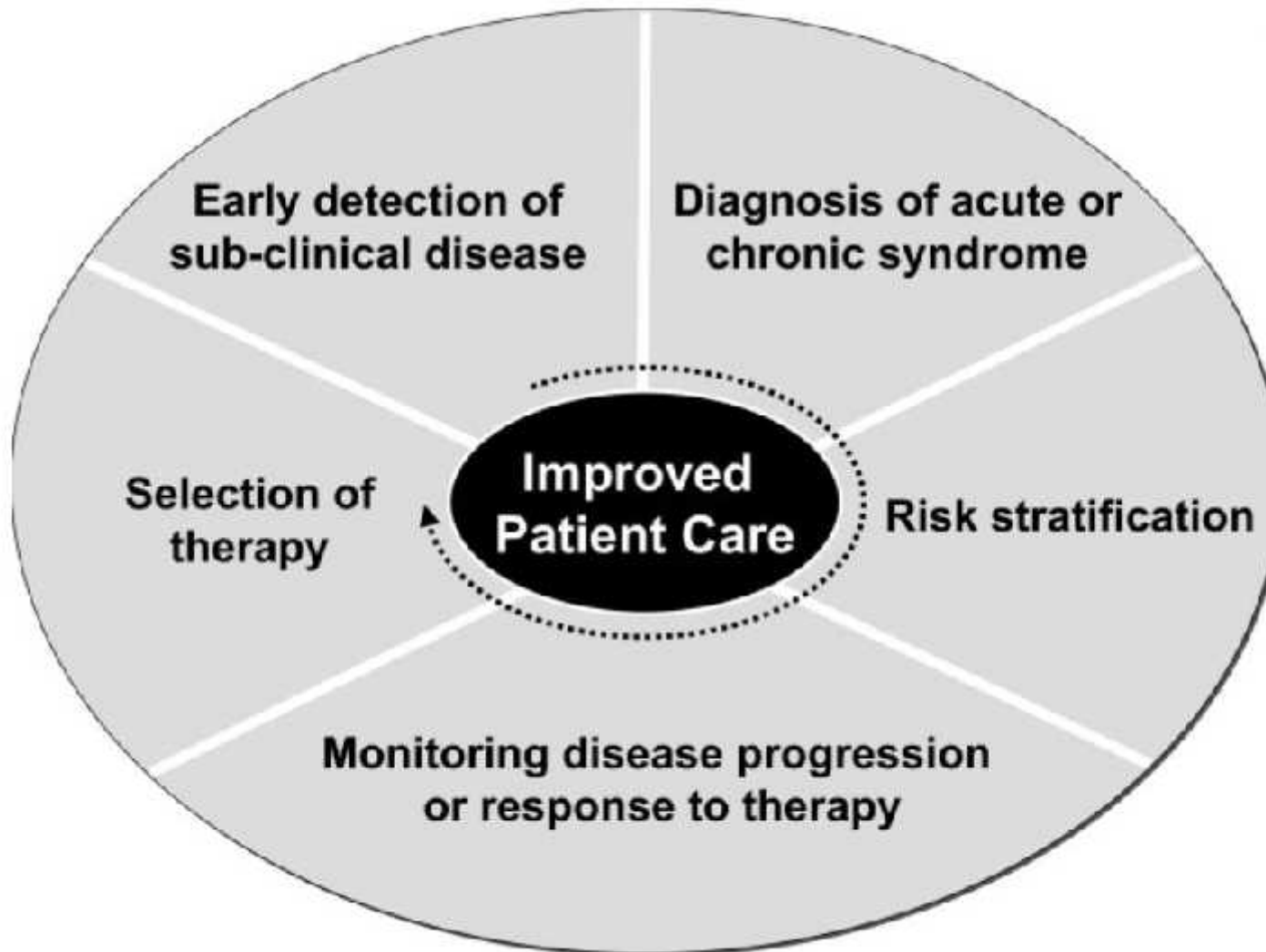


# Σύγκρουση συμφερόντων

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σύγκρουση συμφερόντων

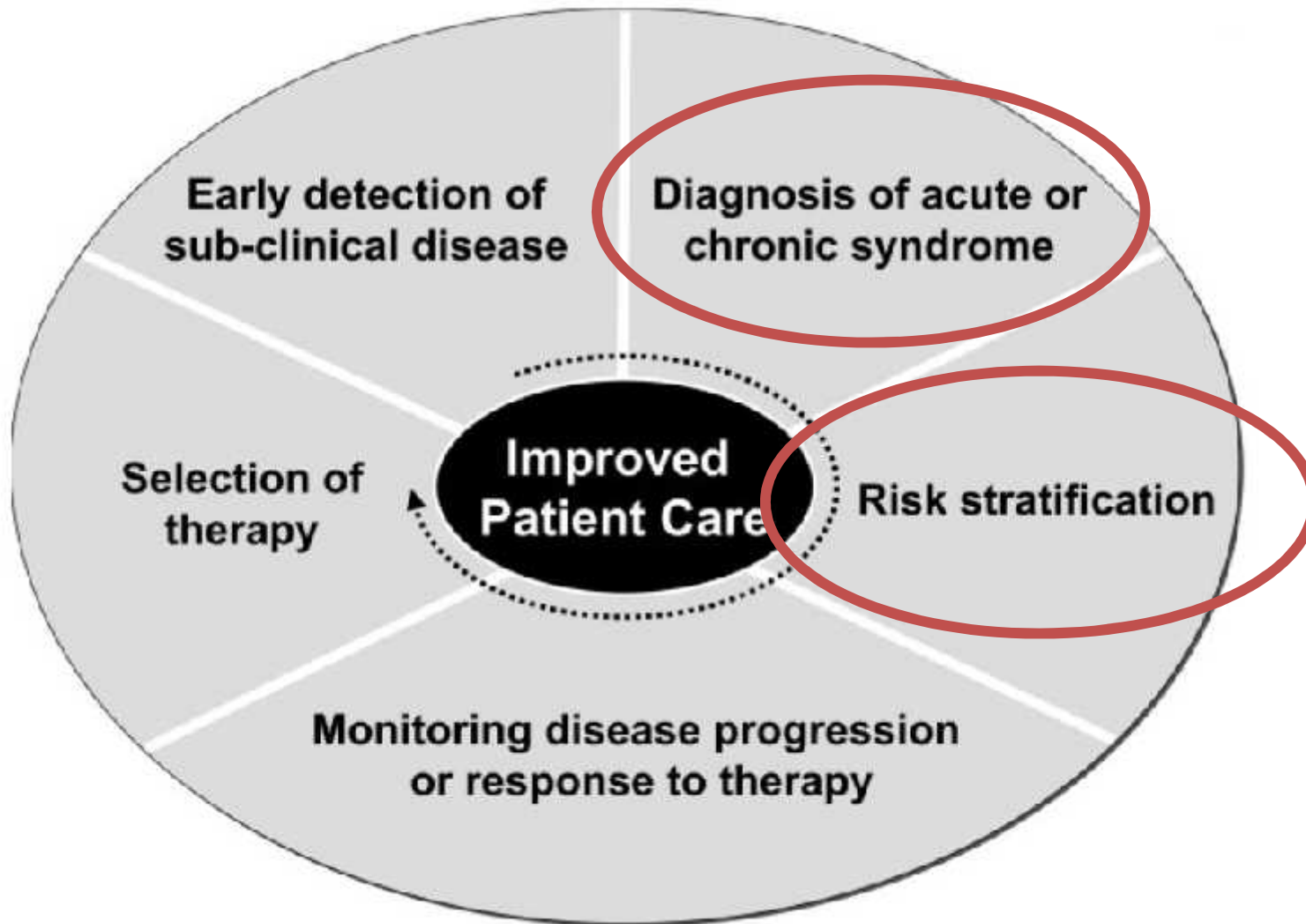


# Βιοχημικοί δείκτες





# Βιοχημικοί δείκτες





## GDF-15

- Πεπτίδιο με ρυθμιστικό ρόλο σε φλεγμονώδεις και αποπτωτικές οδούς
- Σε ενδοθηλιακά κύτταρα και μακροφάγα στους περισσότερους ιστούς
- Αύξηση επιπέδων μετά από τραυματισμό, φλεγμονή, μηχανικό και οξειδωτικό στρες
- Αυξάνει μετά από OEM



# GDF-15



European Heart Journal (2007) 28, 2858–2865  
doi:10.1093/eurheartj/ehm465

Clinical research  
Coronary heart disease

## Growth-differentiation factor-15 improves risk stratification in ST-segment elevation myocardial infarction

Tibor Kempf<sup>1†</sup>, Erik Björklund<sup>2†</sup>, Sylvia Olofsson<sup>2</sup>, Bertil Lindahl<sup>2</sup>, Tim Allhoff<sup>1</sup>, Timo Peter<sup>1</sup>, Jörn Tongers<sup>1</sup>, Kai C. Wollert<sup>1\*</sup>, and Lars Wallentin<sup>2\*</sup>

<sup>1</sup>Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany; and  
<sup>2</sup>Department of Cardiology and Uppsala Clinical Research Center, University of Uppsala, University Hospital, 75185 Uppsala, Sweden

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**Conclusion** GDF-15 is a new biomarker in STEMI that provides prognostic information beyond established clinical and biochemical markers.



# GDF-15

## Coronary Heart Disease

### **Growth Differentiation Factor 15 for Risk Stratification and Selection of an Invasive Treatment Strategy in Non-ST-Elevation Acute Coronary Syndrome**

Kai C. Wollert, MD; Tibor Kempf, MD; Bo Lagerqvist, MD, PhD; Bertil Lindahl, MD, PhD;  
Sylvia Olofsson, BSc; Tim Allhoff, BSc; Timo Peter, BSc; Agneta Siegbahn, MD, PhD;  
Per Venge, MD, PhD; Helmut Drexler, MD; Lars Wallentin, MD, PhD





# GDF-15

## Coronary Heart Disease

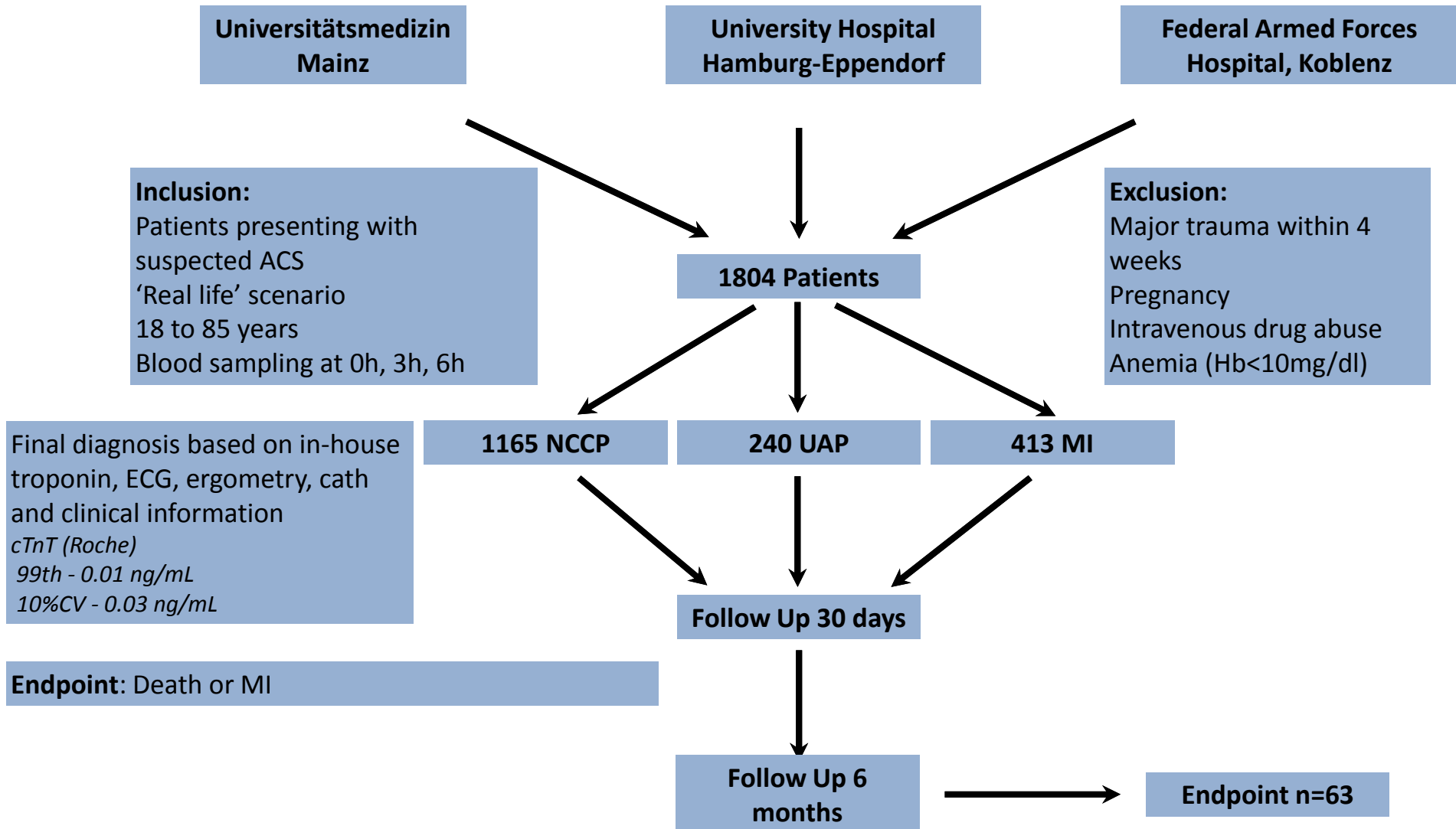
### Growth Differentiation Factor 15 for Risk Stratification and Selection of an Invasive Treatment Strategy in Non-ST-Elevation Acute Coronary Syndrome

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Per Venge, MD, PhD; Helmut Drexler, MD; Lars Wallentin, MD, PhD

**Conclusions**—GDF-15 is a potential tool for risk stratification and therapeutic decision making in patients with non-ST-elevation acute coronary syndrome as initially diagnosed by ECG and troponin levels. A prospective randomized trial is needed to validate these findings. (*Circulation*. 2007;116:1540-1548.)



# Study Design





# Βασικά χαρακτηριστικά - Διάγνωση

	NCCP	UAP	AMI	All
No. of patients (%)	1165 (64.1)	240 (13.2)	413 (22.7)	1818 (100)
Age (years)	59.7 ± 14.3	65.2 ± 10.5	64.0 ± 11.8	61.4 ± 13.5
Male gender (%)	729 (62.6)	165 (68.8)	314 (76.0)	1208 (66.4)
Body mass index (kg/m <sup>2</sup> )	27.7 ± 4.9	27.9 ± 4.4	27.9 ± 4.6	27.8 ± 4.8
Hypertension (%)	822 (70.6)	204 (85.0)	313 (75.8)	1339 (73.7)
Diabetes mellitus (%)	140 (12.5)	53 (23.0)	80 (20.0)	273 (15.6)
Current smoker (%)	254 (21.9)	40 (17.1)	143 (35.1)	437 (24.3)
Former smoker (%)	326 (28.5)	76 (33.2)	124 (31.0)	526 (29.7)
Never smoker (%)	564 (49.3)	111 (48.9)	133 (33.2)	808 (45.6)
Dyslipidaemia (%)	824 (70.7)	193 (80.4)	311 (75.3)	1328 (73.0)
Family History of CAD (%)	379 (33.4)	71 (32.3)	118 (29.9)	568 (32.5)
Known CAD (%)	361 (31.8)	137 (58.5)	136 (33.7)	634 (35.8)



# Βασικά χαρακτηριστικά - Διάγνωση II

	NCCP	UAP	AMI	AII
Total cholesterol (mg/dL)	197.7 ± 49.0	196.7 ± 47.5	205.0 ± 50.1	199.2 ± 49.1
HDL cholesterol (mg/dL)	51.8 ± 15.9	49.3 ± 14.0	47.6 ± 13.8	50.5 ± 15.3
LDL cholesterol (mg/dL)	117.2 ± 40.8	116.9 ± 41.9	129.6 ± 43.8	119.9 ± 41.9
Troponin I hs (pg/mL)	4.8 (1.7/9.0)	9.0 (4.5/26.0)	271.5 (60.1/1864.5)	7.4 (3.5/37.8)
CK (U/L)	74.00 (51.00/114.00)	74.00 (53.00/108.00)	121.00 (79.00/223.67)	82.00 (56.00/131.00)
CKMB (ng/mL)	1.00 (0.60/1.50)	1.10 (0.70/1.70)	3.30 (1.50/10.50)	1.200 (0.70/2.00)
BNP (pg/mL)	26.4 (9.1, 68.9)	47.9 (17.3, 105.9)	80.3 (23.7, 238.6)	33.8 (12.1, 105.3)
CRP (mg/L)	2.3 (1.1/5.4)	2.3 (1.3/4.5)	3.4 (1.7/8.8)	2.5 (1.3/5.8)
Creatinine	0.94 (0.82/1.08)	0.93 (0.82/1.06)	0.99 (0.88/1.16)	0.95 (0.83/1.09)
eGFR (mL/min for 1.73m <sup>2</sup> )	80.1 ± 21.0	79.8 ± 21.1	75.5 ± 22.3	79.0 ± 21.4
GDF15 (pg/mL)	692.15 (495.76/1068.63)	803.75 (606.58/1182.11)	967.10 (662.97/1340.53)	772.90 (534.80/1164.23)



## Βασικά χαρακτηριστικά - Διάγνωση II

	NCCP	UAP	AMI	AII
Total cholesterol (mg/dL)	197.7 ± 49.0	196.7 ± 47.5	205.0 ± 50.1	199.2 ± 49.1
HDL cholesterol (mg/dL)	51.8 ± 15.9	49.3 ± 14.0	47.6 ± 13.8	50.5 ± 15.3
LDL cholesterol (mg/dL)	117.2 ± 40.8	116.9 ± 41.9	129.6 ± 43.8	119.9 ± 41.9
Troponin I hs (pg/mL)	4.8 (1.7/9.0)	9.0 (4.5/26.0)	271.5 (60.1/1864.5)	7.4 (3.5/37.8)
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# Βασικά χαρακτηριστικά - Έκβαση

	All	No Event	Event	p-value
No. of patients (%)	1804 (100)	1741 (96.5)	63 (3.5)	
Age (years)	62 ± 13	61 ± 13	72 ± 10	< 0.001
Female gender (%)	607 / 1804 (34)	591 / 1741 (34)	16 / 63 (25)	0.202
Hypertension (%)	1330 / 1804 (74)	1273 / 1741 (73)	57 / 63 (90)	0.003
Dyslipidemia (%)	1320 / 1804 (73)	1278 / 1741 (73)	42 / 63 (67)	0.298
Diabetes mellitus (%)	341 / 1802 (19)	314 / 1739 (18)	27 / 63 (43)	< 0.001
Obesity (BMI>30) (%)	464 / 1681 (28)	449 / 1619 (28)	15 / 62 (24)	0.64
Active Smoker (%)	446 / 1800 (25)	438 / 1737 (25)	8 / 63 (13)	0.035
Former Smoker (%)	579 / 1729 (33)	548 / 1666 (33)	31 / 63 (49)	0.011
Family History of CAD (%)	626 / 1800 (35)	612 / 1737 (35)	14 / 63 (22)	0.046
History of MI (%)	429 / 1799 (24)	400 / 1736 (23)	29 / 63 (46)	< 0.001
Known CAD (%)	671 / 1802 (37)	633 / 1739 (36)	38 / 63 (60)	< 0.001



# Βασικά χαρακτηριστικά – Έκβαση II

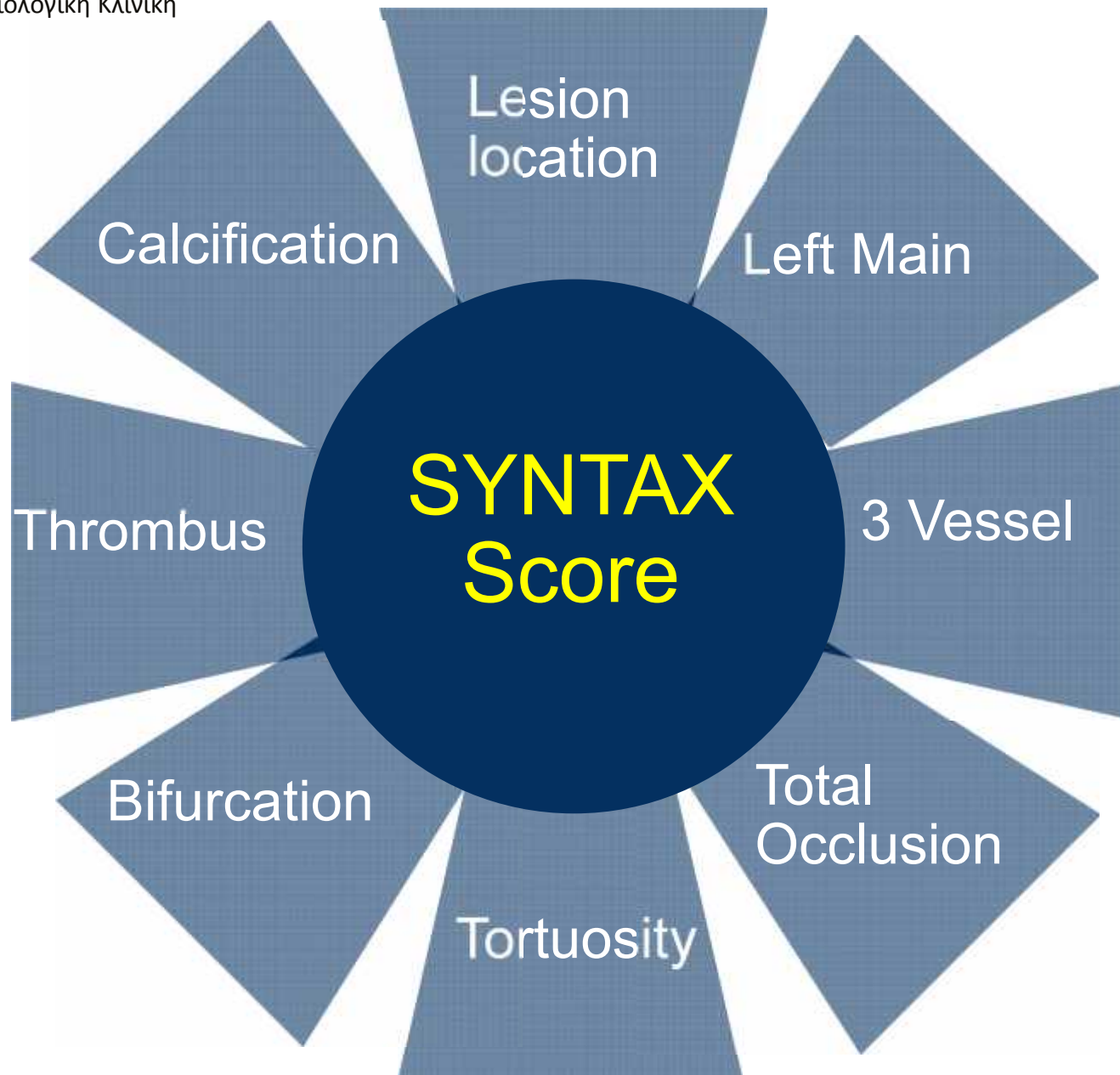
	All	No Event	Event	p-value
Total cholesterol (mg/dL)	196 (164.5/228)	196 (165/228.5)	188.5 (144.5/225.5)	0.156
LDL cholesterol (mg/dL)	116 (90/146)	117 (90/146)	106 (79.5/154)	0.574
HDL cholesterol (mg/dL)	48 (40/59)	48 (40/59)	44 (37/52.8)	0.057
Troponin I hs (pg/mL)	0.012 (0.004/0.066)	0.012 (0.003/0.058)	0.196 (0.047/3.003)	< 0.001
BNP (pg/mL)	33.8 (12.2/105.4)	32.9 (11.7/98.1)	164.1 (54/439)	< 0.001
CRP (mg/L)	2.5 (1.3/5.8)	2.5 (1.2/5.5)	5.6 (2.3/13)	< 0.001
eGFR (mL/min for 1.73m <sup>2</sup> )	79.4 (66.5/91.5)	79.8 (67.4/92)	60.6 (43.1/74.1)	< 0.001
GDF-15 (pg/mL)	774.1 (535/1163)	756.6 (525.8/1133)	1660 (1084/2502)	< 0.001



## Βασικά χαρακτηριστικά – Έκβαση II

	All	No Event	Event	p-value
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# Βασικά χαρακτηριστικά – Syntax Score

	All	Syntax Score: < 23	Syntax Score: 23-33	Syntax Score: ≥ 33
No. of patients (%)	619	526 (85)	67 (11)	26 (4)
Female gender (%)	201 / 619 (32)	187 / 526 (36)	10 / 67 (15)	4 / 26 (15)
Age (years)	63 ± 12	62 ± 12	66 ± 12	65 ± 11
Total cholesterol (mg/dL)	204.5 (175/239)	203 (175/238.8)	204 (169/231)	235 (215/251.5)
LDL cholesterol (mg/dL)	126 (99/157)	125 (99/156)	133 (93/149)	153 (127/170)
HDL cholesterol (mg/dL)	48 (39/58)	48 (40/59.2)	44 (39/56)	45 (38.5/55)
Troponin I hs (pg/mL)	0.061 (0.01/0.705)	0.048 (0.008/0.49)	0.108 (0.036/2.141)	0.908 (0.105/3.518)
BNP (pg/mL)	46.7 (16.4/138.6)	39.3 (15.5/119)	81.9 (23.9/169.7)	168.6 (61.2/358.3)
CRP (mg/L)	2.6 (1.4 , 6.6)	2.6 (1.3 , 6.1)	2.5 (1.8 , 6.6)	5.2 (2.2 , 14)
eGFR (mL/min for 1.73m <sup>2</sup> )	78.2 (66/90.9)	78.3 (65.7/91.4)	77.1 (65.2/91.6)	76.6 (69.3/87.9)
GDF-15 (pg/mL)	830.4 (563/1186)	797.3 (553.5/1172)	947.2 (688.5/1195)	934.6 (685.6/1341)



# Cox Regression Analysis

	HR (95%CI) 1 SD Inc. [M2]	p-value [M2]	HR (95%CI) 1 SD Inc. [M3]	p-value [M3]
Troponin I hs	1.97 ( 1.62 , 2.4 )	< 0.001	1.88 ( 1.52 , 2.34 )	< 0.001
Creatinine kinase	1.33 ( 1.09 , 1.64 )	0.006	1.27 ( 1.03 , 1.56 )	0.024
Creatine kinase-MB	1.51 ( 1.26 , 1.8 )	< 0.001	1.45 ( 1.2 , 1.75 )	< 0.001
eGFR	0.51 ( 0.4 , 0.67 )	< 0.001	0.8 ( 0.48 , 1.34 )	0.403
GDF15	2.1 ( 1.67 , 2.65 )	< 0.001	1.57 ( 1.13 , 2.19 )	0.008
BNP	1.94 ( 1.45 , 2.6 )	< 0.001	1.45 ( 1.06 , 1.98 )	0.021

Biomarker used as continuous value with HR per SD increase  
Event was defined as Death+MI in six months FU. There were 63 events.

All biomarkers entered the regressions after being log-transformed (except eGFR).

[M2] was age and sex adjusted.

[M3] was adjusted for the GRACE score variables: heart rate, (log) creatinine, ST changes in ECG, age, systolic blood pressure and Killip class.



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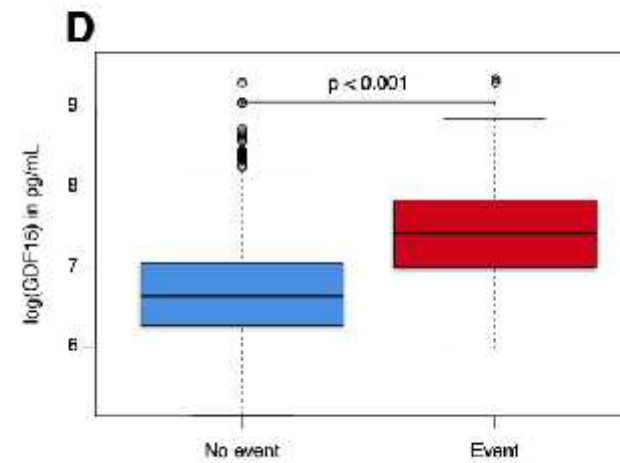
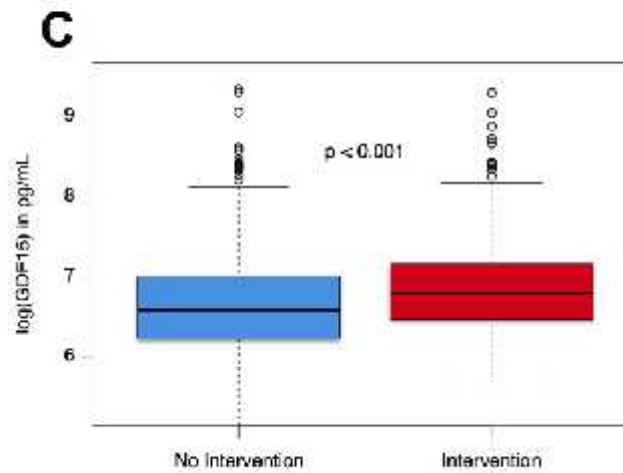
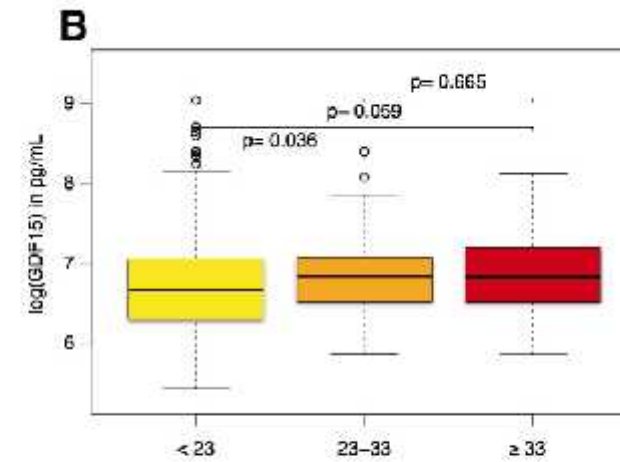
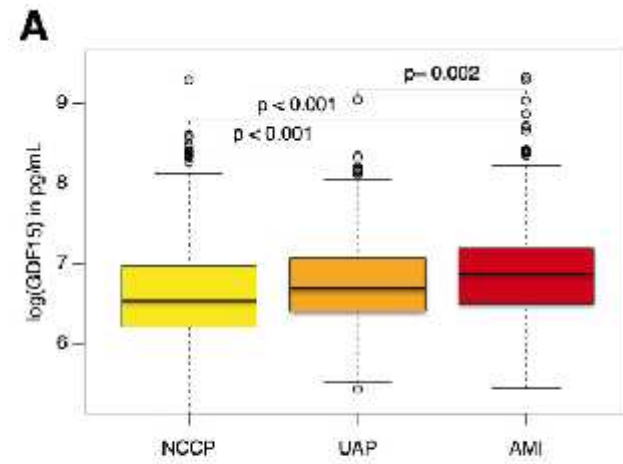


# Reclassification Analysis

	Reclassified upwards	Reclassified downwards	NRI
<b>GRACE Score + GDF-15</b>			
Kaplan-Meier rate of events	0.127	0.094	
Expected number of events	41.5	30.7	10.9 %
Expected number of non-events	285.5	296.3	1.6 %
NRI + p-value			<b>12.5 %; p: 0.044</b>
CI: NRI			( 0.3 %, 24.6 %)
<b>GRACE Score + BNP</b>			
Kaplan-Meier rate of events	0.382	0.011	
Expected number of events	265.5	7.6	6.7 %
Expected number of non-events	429.5	687.4	3.3 %
NRI + p-value			<b>10 %; p: 0.002</b>
CI: NRI			( 3.5 %, 16.4 %)

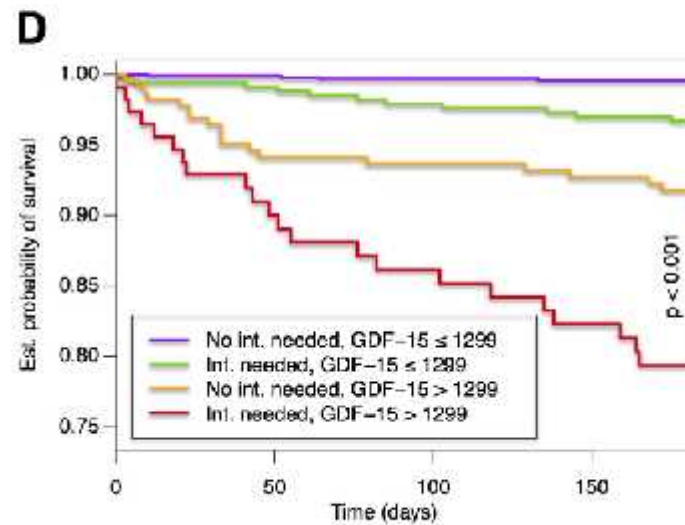
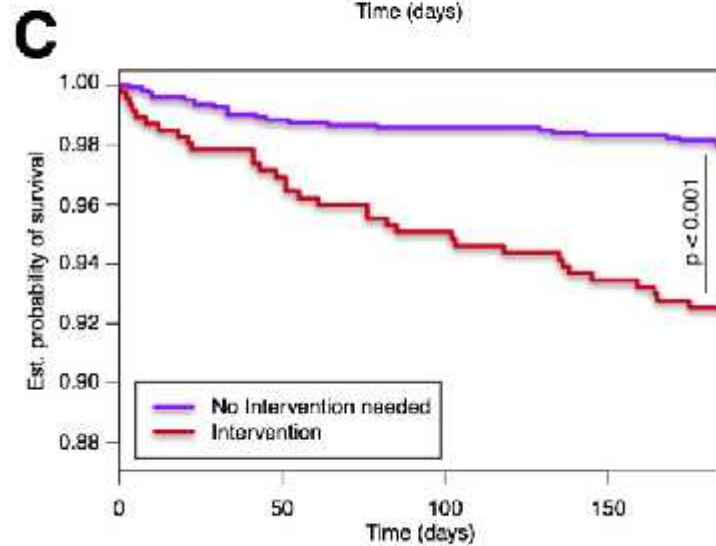
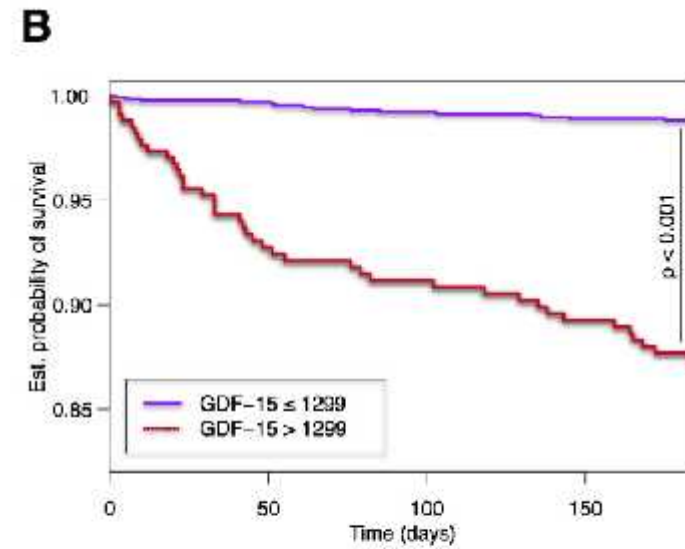
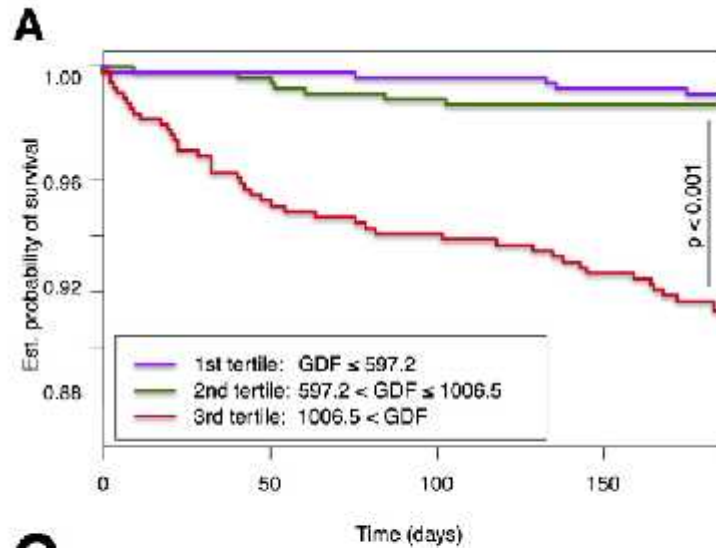


# Box plots





# Cumulative Survival





## Συμπεράσματα

- GDF-15 έχει σημαντική προγνωστική αξία σε ασθενείς με ΟΣΣ
- Συσχετισμός με τη βαρύτητα της στεφανιαίας νόσου (SYNTAX)
- Διαστρωμάτωση κινδύνου και ενδεχομένως κατεύθυνση της θεραπείας





## **GDF-15 is a predictor of cardiovascular events in patients presenting with suspicion of ACS**



Δρ Στέργιος Ζ. Τζήκας  
30.10.2015

36<sup>ο</sup> Διεθνές Καρδιολογικό Συνέδριο, Θεσσαλονίκη