sphingotest® vr-hGH

Risk Prediction of Incident Cardiovascular Disease

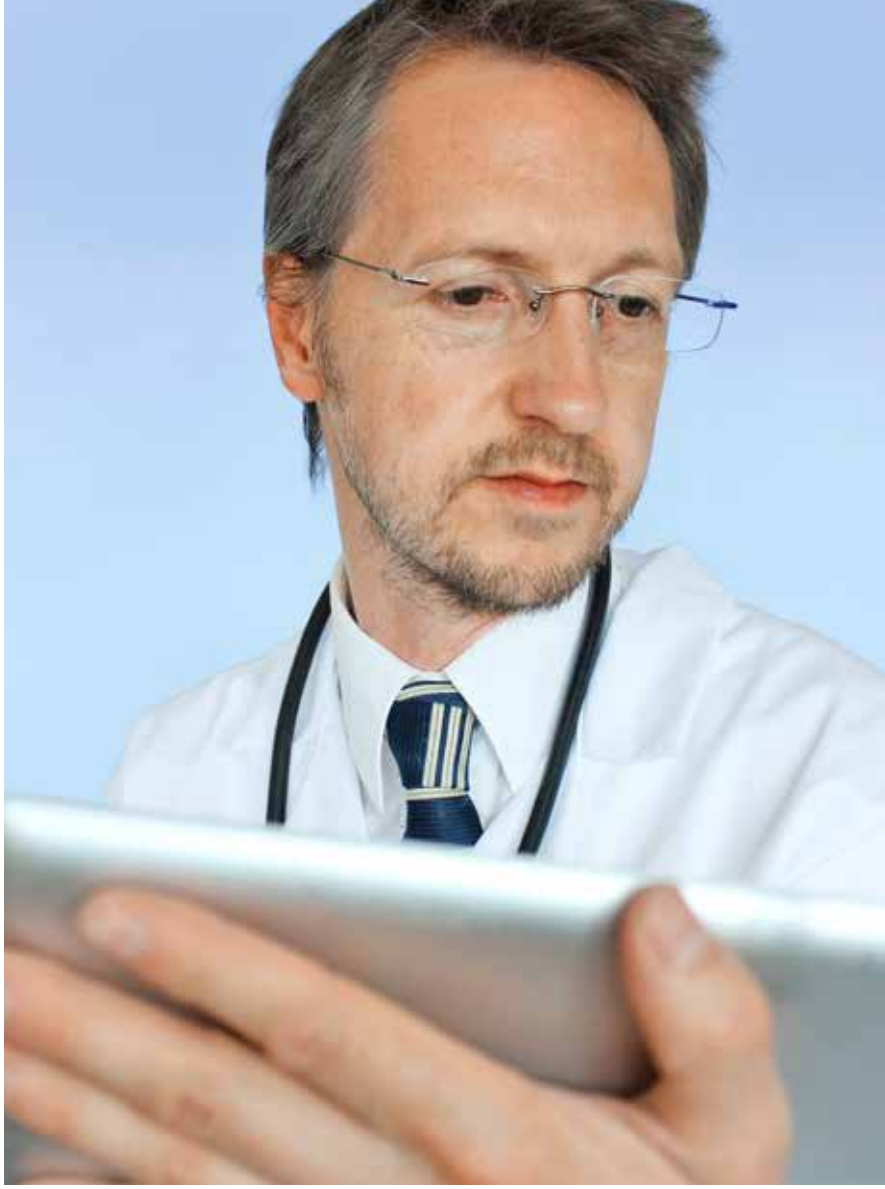
sphingotec
Innovations for life

Human Growth Hormone as Vascular Risk Biomarker

sphingotec offers the vascular risk human Growth Hormone biomarker (vr-hGH) for the risk prediction of incident cardiovascular disease in male subjects. It is imperative to identify and predict vascular risk in the general population early on. The biomarker vr-hGH developed by sphingotec enables an early intervention to reduce vascular risk.

Human Growth Hormone (hGH) is a 191-amino acid, single-chain polypeptide hormone that is synthesized, stored, and secreted by somatotropic cells within the lateral wings of the anterior pituitary gland. hGH release is primarily determined by the balance of growth hormone-releasing hormone (GHRH or somatocrinin) and growth hormone-inhibiting hormone (GHIH or somatostatin). These are, in turn affected by many physiological stimulators (e. g. exercise, nutrition, sleep) and inhibitors (e. g. free fatty acids) of GH secretion. hGH stimulates growth, cell reproduction and regeneration. Elevated levels of hGH are discussed as being associated with risk alteration of cardiovascular disorders.[1-5]

1 Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. The Journal of clinical endocrinology and metabolism 1998;83:2730-4.
2 Melmed S, Casanueva FF, Klibanski A et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary 2012.
3 Colao A, Marzullo P, Di Somma C, Lombardi G. Growth hormone and the heart. Clinical endocrinology 2001;54:137-54.
4 Takala J, Ruokonen E, Webster NR et al. Increased mortality associated with growth hormone treatment in critically ill adults. The New England journal of medicine 1999;341:785-92.
5 Maison P, Balkau B, Simon D, Chanson P, Rosselin G, Eschwege E. Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study. BMJ (Clinical research ed) 1998;316:1132-3.



About the vr-hGH Assay

hGH immunoassays are available and used routinely to diagnose growth defects. Accurate interpretation of plasma hGH concentration has long been hampered by the fact that hGH is released in pulses over the majority of the day. In addition, conventional hGH assays have not been designed to measure normal concentrations, especially in males as yet.

Normal male hGH levels are 10x lower than normal female concentrations. This is the reason the possible clinical value of fasting hGH levels in males has been unclear to date.

Based on sphingotec's experience in the development of sensitive hGH assays to detect hGH in doping[6], the company has developed the sphingotest® vr-hGH assay, enabling the accurate measurement of even very low hGH concentration in serum and plasma, allowing a threshold at low concentrations that requires a sensitive test.

sphingotest® vr-hGH

6 Bidlingmaier M, Suhr J, Ernst A et al. High-sensitivity chemiluminescence immunoassays for detection of growth hormone doping in sports. Clinical chemistry 2009;55:445-53.

The study population

The medical use of this biomarker has been studied using a subset of the Malmö Diet and Cancer Study (MDC), a general population-based, prospective study[7]. The subset consisted of 4,323 persons (1,778 males; 2,545 females) who did not suffer from prevalent cardiovascular disease at the time of the baseline examination (1991-96). Plasma samples were obtained after overnight fasting and samples were drawn between 7:30am and 9:00am. Archived samples were measured using sphingotest® vr-hGH assay in 2013.

Evidence for the use vr-hGH in the identification of a vascular risk in male subjects

7 Berglund G, Elmstahl S, Janzon L, Larsson SA. The Malmö Diet and Cancer Study. Design and feasibility. Journal of internal medicine 1993;233:45-51.

Clinical characteristics of the study population divided into gender-specific quartiles based on fasting vr-hGH values

	Q1*	Q2*	Q3*	Q4*
Age, mean (SD), years	57.0 (5.9)	57.8 (6.0)	57.9 (6.0)	57.8 (6.0)
Systolic blood pressure, mean (SD), mmHg	143 (19)	142 (19)	141 (20)	141 (19)
Body Mass Index, Mean (SD), kg/m^2	27.1 (4.0)	26.0 (3.8)	25.3 (3.7)	24.7 (3.8)
Antihypertensive therapy, %	17.0	14.2	15.3	15.1
Diabetes Mellitus, %	10.7	7.6	7.3	7.9
LDL-C†, mean (SD), mmol/L	4.30 (0.97)	4.25 (1.00)	4.11 (1.01)	4.01 (0.95)
HDL-C†, mean (SD), mmol/L	1.31 (0.34)	1.37 (0.36)	1.42 (0.37)	1.46 (0.38)
Current smokers, %	21.3	22.7	28.0	33.5
vr-hGH, µg/L, range, males	0.02-0.05	0.06-0.11	0.12-0.33	0.34-23.94
vr-hGH, µg/L, range, females	0.01-0.39	0.40-1.21	1.22-3.14	3.15-40.60

*Quartile 1 (Q1) represents the quartile with the lowest values of fasting vr-hGH. Males and females are divided into the quartiles separately, which makes the male/female ratio similar in the quartiles, but the cut-off values different in the different genders.

†LDL-C, Low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol

The results

Increased fasting vr-hGH level was significantly associated with a higher incidence of coronary artery disease (CAD), stroke, congestive heart failure (CHF), all-cause mortality and cardiovascular mortality in males, independent of the traditional cardiovascular risk factors. The outcome with the strongest independent relationship to baseline fasting vr-hGH was cardiovascular mortality.

Multivariate adjusted Cox proportional hazards models for baseline fasting value of vr-hGH vs incidence of CAD, stroke, congestive heart failure, all-cause mortality and cardiovascular mortality

Event	Events	Gender	HR	95% CI	P
CAD†	397	All	1.11	1.01-1.23	0.04
	247	**Male**	**1.17**	**1.04-1.33**	**0.01**
	150	Female	1.02	0.86-1.21	0.81
Stroke	251	All	1.18	1.04-1.34	0.01
	132	**Male**	**1.21**	**1.02-1.43**	**0.02**
	119	Female	1.16	0.95-1.41	0.15
CHF†	207	All	1.25	1.03-1.52	0.02
	156	**Male**	**1.07**	**0.83-1.39**	**0.59**
	51	Female	1.48	1.08-2.04	0.02
Total mortality	645	All	1.17	1.08-1.26	<0.001
	341	**Male**	**1.25**	**1.13-1.39**	**<0.001**
	304	Female	1.04	0.92-1.18	0.50
CVD† mortality	186	All	1.43	1.24-1.66	<0.001
	105	**Male**	**1.44**	**1.20-1.72**	**<0.001**
	81	Female	1.45	1.12-1.88	0.004

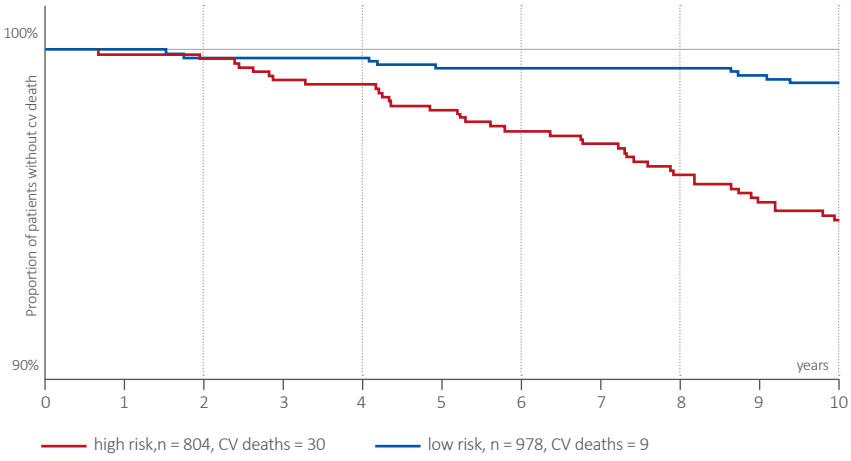
Hazard ratios (HR, 95% CI) are expressed per 1 SD increment of the natural logarithm of vr-hGH. Values of vr-hGH are standardized separately in men and women and this same gender-specific standardization is used in the combined analyses. Variables adjusted for the analysis: age, systolic blood pressure, use of antihypertensive medication, BMI (weight in kilograms divided by height in meters squared), prevalence of diabetes mellitus, current smoking and fasting values of HDL-C and LDL-C. In addition adjusted for sex in the gender combined analyses. In total 4,323 (1,778 males, 2,545 females) individuals available for analysis in all models.

† Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CVD mortality, cardiovascular mortality.

Evidence for the use of vr-hGH in the identification of a vascular risk in male subjects

The Kaplan-Meier plot shows cumulative cardio-vascular mortality for males during 10 years of follow-up below 70pg/ml (blue line) and above 70pg/ml (red line) of the baseline fasting plasma concentration of vr-hGH.

For the risk prediction of adverse cardiac events and mortality in males, this generally results in Relative Risk > 10 on top of known risk factors where vr-hGH associated prediction of cardio-vascular mortality is stronger the earlier the event occurs.



Relative Risk between low and high baseline vr-hGH for different follow-up times

Follow-up time	Baseline vr-hGH < 0.06 ng/ml (Q1)	Baseline vr-hGH >0.34 ng/ml (Q4)	Relative risk Q4/Q1
2.5 years	0 % CVD mortality	1.2% CVD mortality	>15
5 years	0.35% CVD mortality	3.2% CVD mortality	9.1
10 years	0.9% CVD mortality	7.1% CVD mortality	7.9
15 years	2.5% CVD mortality	10.6% CVD mortality	4.2

sphingotec GmbH aims to develop diagnostic methods for prediction, prevention, intervention strategies and early treatment of diseases in the fields of cancer, cardiovascular diseases and kidney function. In order to realize this mission we provide biomarkers indicating susceptibility for a specific disease which enables the monitoring of prevention and intervention strategies. The company was established in 2002 by Dr. Andreas Bergmann who was one of the founders and managers of BRAHMS Aktiengesellschaft where, in addition to several other biomarkers, the sepsis marker Procalcitonin (B·R·A·H·M·S PCT®: www.procalcitonin.com) was developed in his role as Chief Research Officer. This biomarker Procalcitonin created a new diagnostic standard of care supporting patient management in sepsis. sphingotec is located in Hennigsdorf, northwest of Berlin Germany, with its facilities in the Technology Campus one of the largest industrial parks in Berlin and Brandenburg with several companies of the biotechnology branch located there.

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