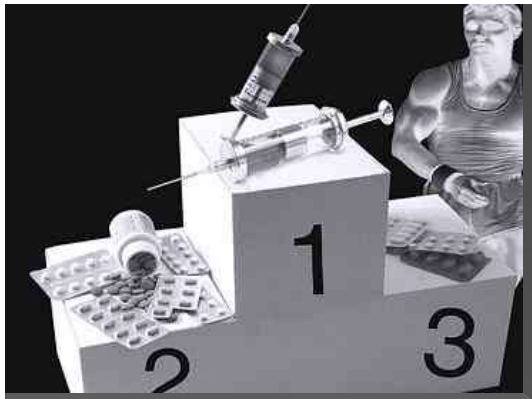
ARISTOTLE UNIVERSITY OF THESSALONIKI
FACULTY OF PHYSICAL EDUCATION & SPORTS SCIENCES
LABORATORY OF SPORTS MEDICINE
DIRECTOR: PROF. E. KOUIDI

EFFECTS OF DOPING SUBSTANCES ON THE CARDIOVASCULAR SYSTEM

Dr. NIKOLAOS A. KOUTLIANOS MD, BSc
Assistant Professor of Athletes' Physical Health Evaluation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TOUR DE DOPING
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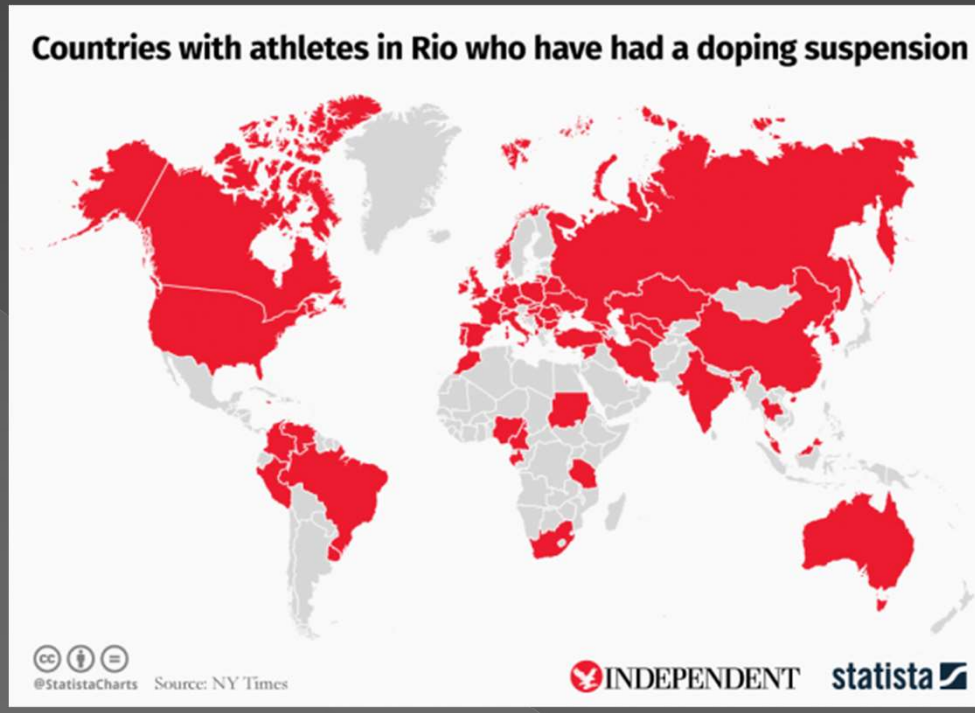
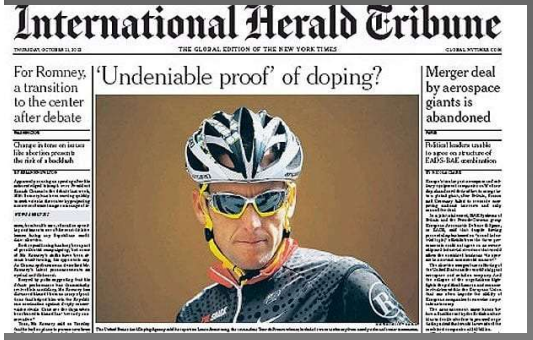
Getty Images
REPORT: RUSSIAN ATHLETES' DOPING STATE-SPONSORED
CNN
Nikkei ▲ 28.52
CNN NEWSROOM


BREAKING
NEWS


Countries with athletes in Rio who have had a doping suspension
@StatistaCharts Source: NY Times
INDEPENDENT
statista


THE DOPING SCANDAL


International Herald Tribune
THE GLOBAL EDITION OF THE NEW YORK TIMES
For Romney, a transition to the center after debate
'Undeniable proof' of doping?
Merger deal by aerospace giants is abandoned

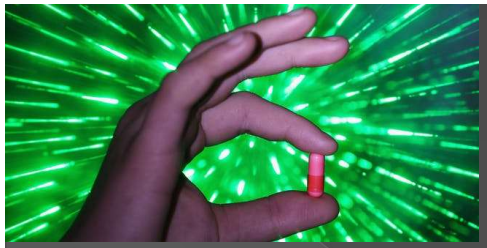

THE SUNDAY TIMES
British doctor claims he doped 150 sports stars
INSIGHT
THE DOPING SCANDAL
PREMIER LEAGUE FOOTBALLERS, AN ENGLAND CRICKETER, BRITISH TOUR DE FRANCE CYCLISTS, A BOXING CHAMPION AND TENNIS PLAYERS ARE AMONG HIS ALLEGED CLIENTS
Pollution alert as heatwave hits UK


THE SUNDAY TIMES
THE DOPING SCANDAL


Le Monde WEEK-END
sport&forme


WM news
SHARAPOVA
DOPING

Tokyo Marathon winner Endeshaw Negesse has become the first Ethiopian named in connection with a failed drugs test following reports that as many as nine athletes from the distance running powerhouse are under investigation.



ERGOGENIC AIDS

SUBSTANCES & METHODS WHICH IMPROVE THE PHYSICAL CAPACITY, HUMAN FUNCTIONS & SPORTS PERFORMANCE

- APPROVED AIDS
- DOPING

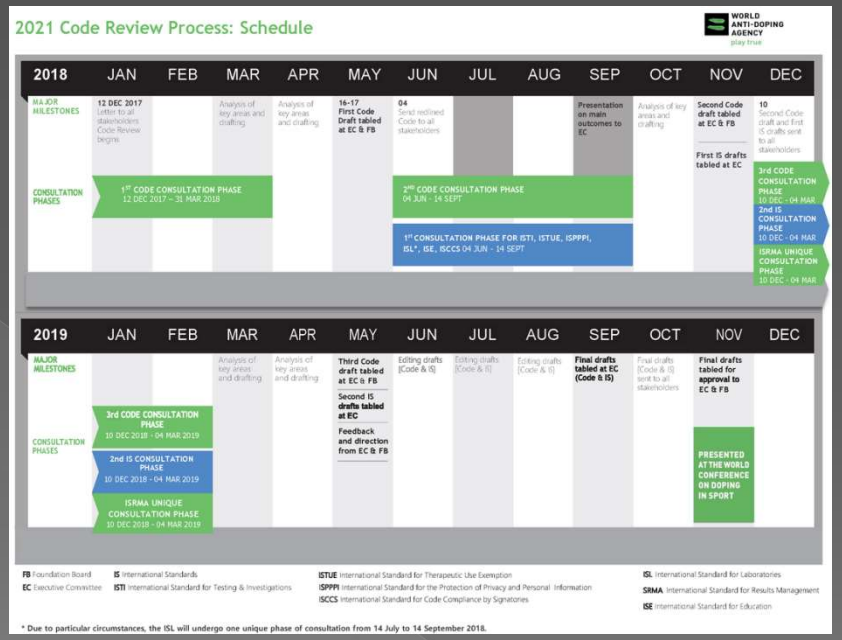
ARTICLE 1 DEFINITION OF DOPING

Doping is defined as the occurrence of one or more of the anti-doping rule violations set forth in Article 2.1 through Article 2.10 of the *Code*.

WORLD ANTI-DOPING CODE

2015

WORLD ANTI-DOPING AGENCY
play true



THE PROHIBITED LIST (2018)

Non-approved substances

Prohibited at all times

Anabolic agents, peptide hormones, growth factors, related substances and mimetics, beta-2 agonists, hormone and metabolic modulators, diuretics and masking agents

Methods at all times

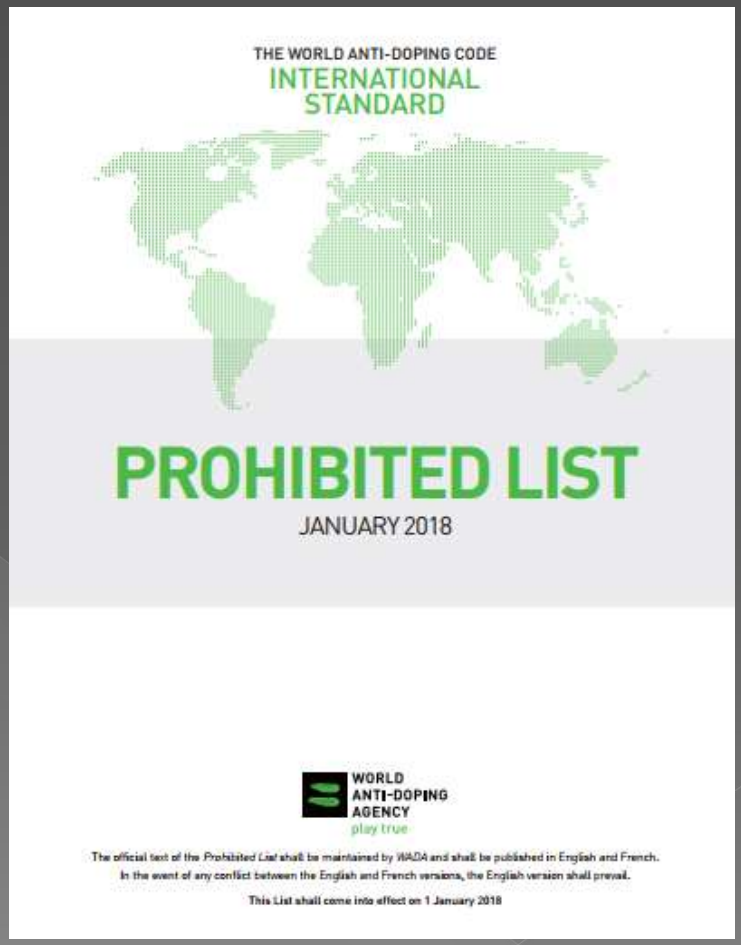
Blood doping, chemical and physical manipulation, gene doping-editing

Prohibited substances in-competition

Stimulants, narcotics, cannabinoids, glucocorticoids

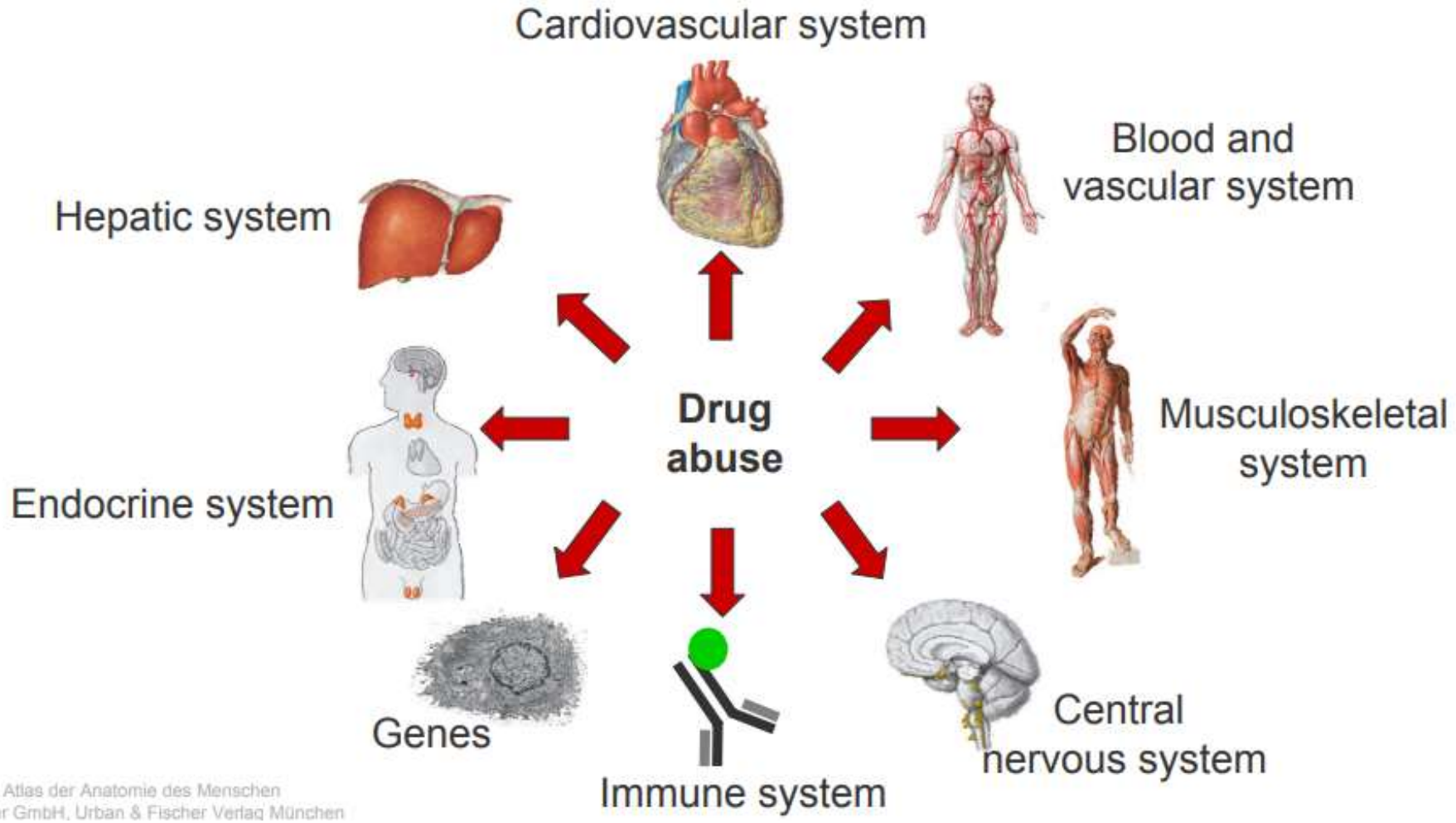
Prohibited substances in particular sports

Beta-blockers



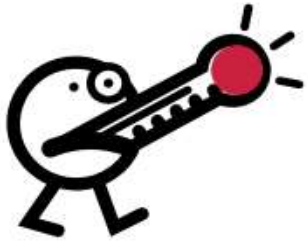
Biomedical Side Effects

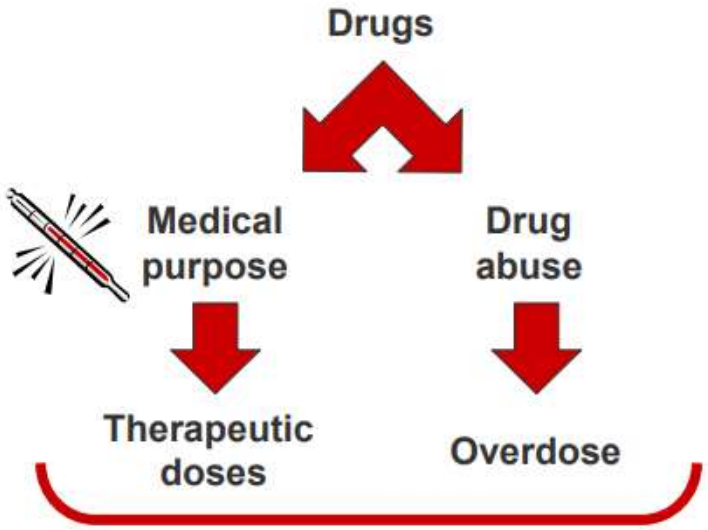
Main organs affected by biomedical side effects

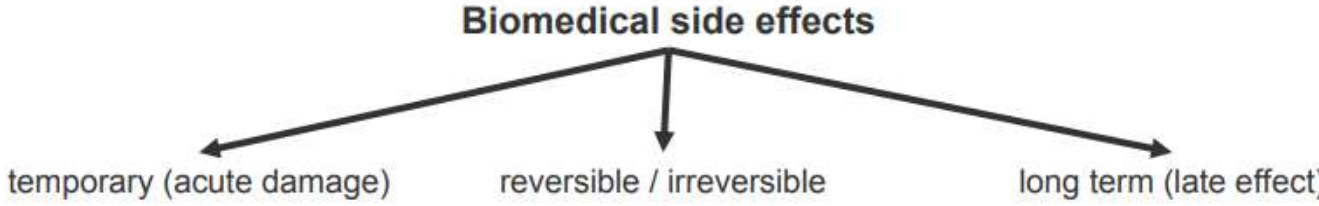


botta: Atlas der Anatomie des Menschen
Elsevier GmbH, Urban & Fischer Verlag München

The dual character of drugs/doping substances







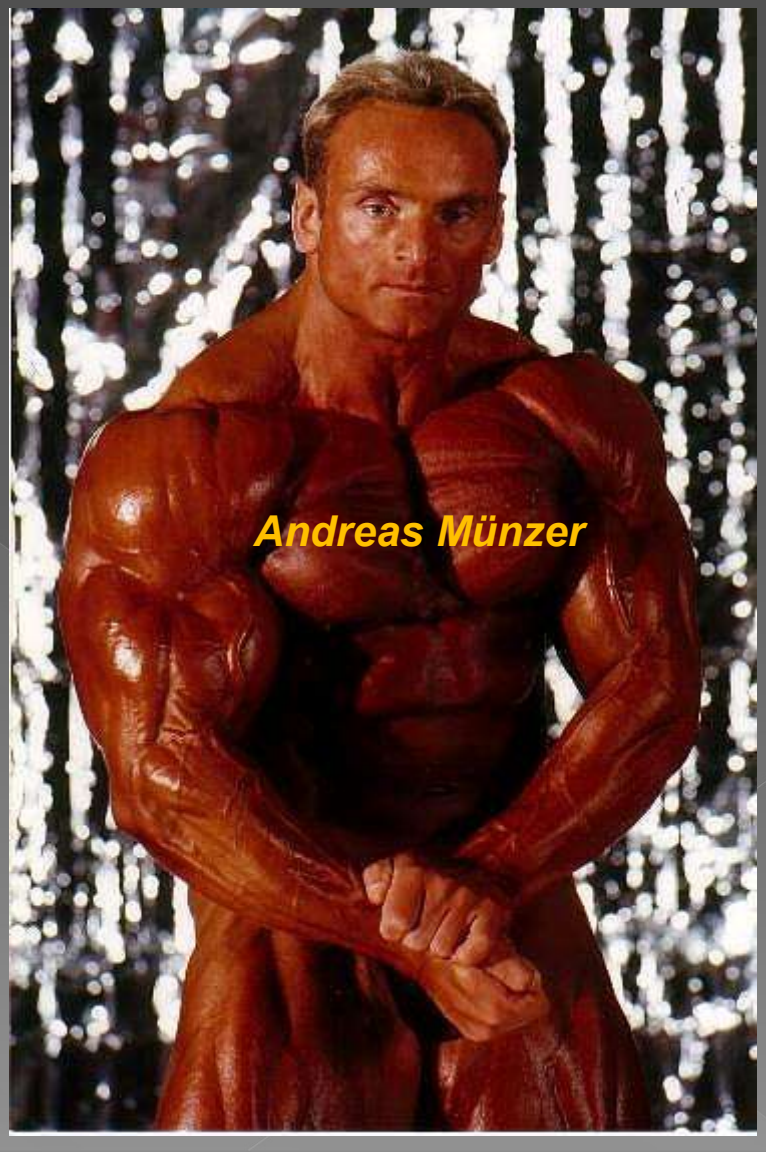
ATHLETE'S DIARY

10-9 weeks before the competition daily:
Ephederine, AN 1, Catagon, Aspirine, Valium, Clenbuterol

8-6 weeks before the competition daily:
2 injects Testoviron a 250mg, 1 inject Parabolan, 30 tabletts Halotestin, 30 tabletts Metandienon, 20IE* STH, 20IE* Insuline,

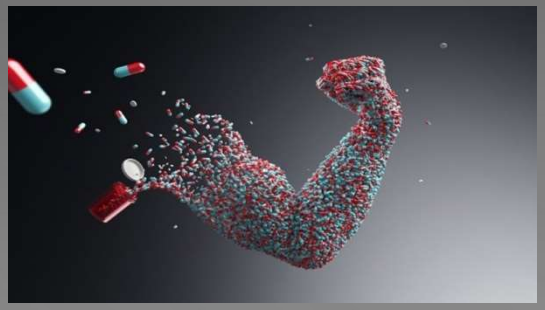
5-3 weeks before the competition daily:
2 injects Parabolan, 2 injects Stromba, 30 tabletts Halotestin, 50 tabletts Stromba, 24IE* STH

2-1 weeks before the competition daily:
2 injects Masteron, 2 injects Stromba, 40 injects Halotestin, 80 tabletts Stromba, 24 IE* STH, Insuline, IGF



Birgit Dressel died due to anaphylactic shock in 1987:

- ✓ **Toxicology report showed 102 different substances in her body**



Biomedical side effects of doping substance abuse…

…on the cardiovascular system

Cardiac side effects induced by		Side Effects
Anabolic androgenic steroids	most effects	Sudden cardiac death
Cocaine, Ephedrine Amphetamines, Alcohol		Arrhythmias
Human growth hormone (hGH)		Myocardial infarction
Beta-2-agonists		Heart failure
Cannabinoids		Hypertension
Glucocorticosteroids		Coronary artery disease
Erythropoietin		Left ventricular hypertrophy
Diuretics		
Narcotics	less effects	

Deligiannis et al. (2006); Eur J Cardiovasc Prev Rehabil, 687-694
Sobotta: Atlas der Anatomie des Menschen
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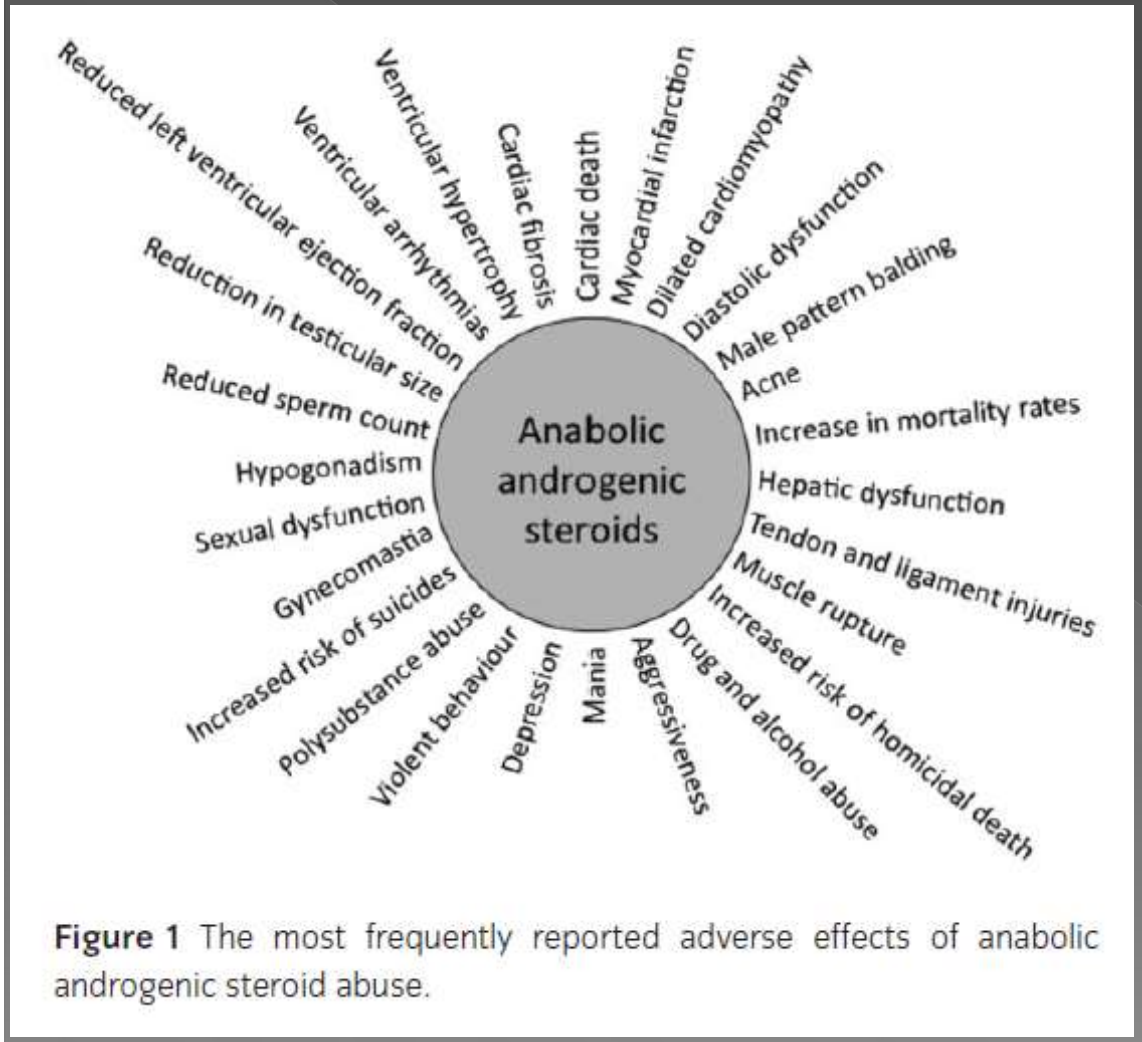


Figure 1 The most frequently reported adverse effects of anabolic androgenic steroid abuse.

Birzniece, Intern Med J, 2015

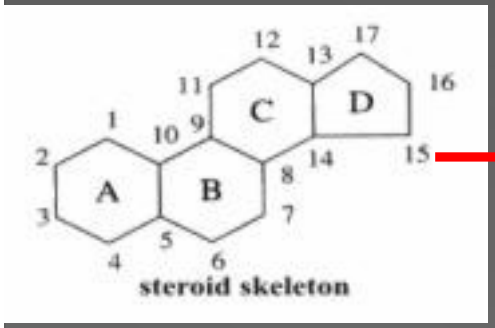
Table 1. Adverse Events Associated With Anabolic-Androgenic Steroid Use[a]

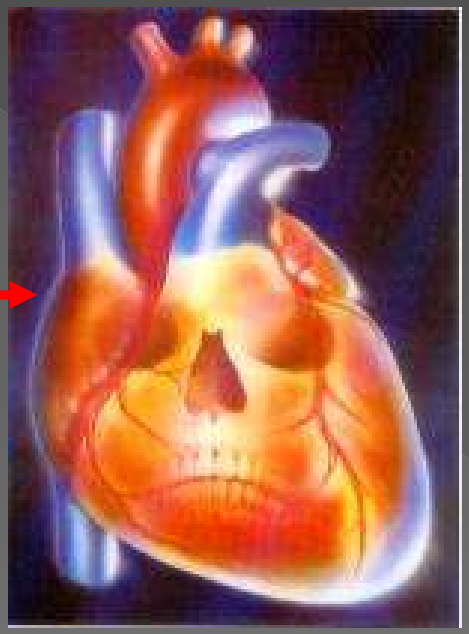
Organ System/Effect	Severity
Cardiovascular	
Dyslipidemia, atherosclerotic disease	++
Cardiomyopathy	++
Cardiac conduction abnormalities	+
Coagulation abnormalities	+
Polycythemia	+
Hypertension	+
Neuroendocrine (males)	
HPT suppression, hypogonadism from AAS withdrawal	++
Gynecomastia	+
Prostatic hypertrophy	+/−
Prostate cancer	+/−
Virilizing effects	
Neuroendocrine (females)	++
Neuropsychiatric	
Major mood disorders: mania, hypomania, depression	++
Aggression, violence	+
AAS dependence	++
Neuronal apoptosis, cognitive deficits	+/−
Hepatic	
Inflammatory and cholestatic effects	+
Peliosis hepatis (rare)	+
Neoplasms (rare)	+
Musculoskeletal	
Premature epiphyseal closure (in adolescents, rare)	+
Tendon rupture	+
Kidney	
Renal failure secondary to rhabdomyolysis	+
Focal segmental glomerulosclerosis	+
Neoplasms (rare)	+/−
Immune	+/−
Immunosuppressive effects	
Dermatologic	
Acne	+
Striae	+

[a] Severity is scored as follows: ++, well-recognized and probably of serious concern; +, well-recognized but either less common or causing less serious morbidity; +/−, possible risks whose relation to AAS use remains poorly understood.

Pope et al., Endocrine Rev, 2014

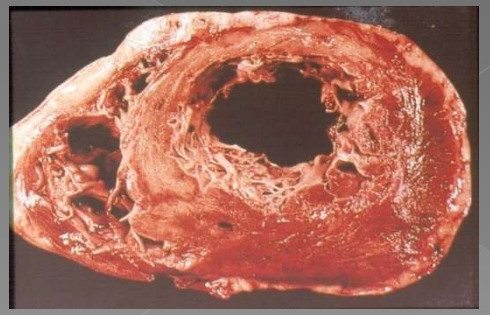
AAS CARDIOVASCULAR SIDE EFFECTS



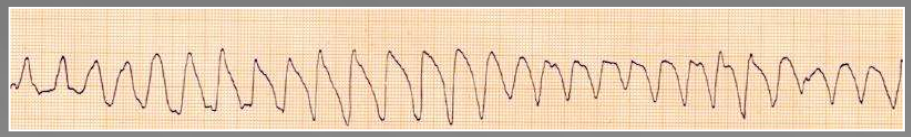


- Altered exercise-induced cardiac adaptations
- Cardiomyopathy
- Myocarditis
- Arterial hypertension
- Coronary atheromatosis
- Arrhythmias
- LV dysfunction

Myocardial infarction



Sudden Cardiac death



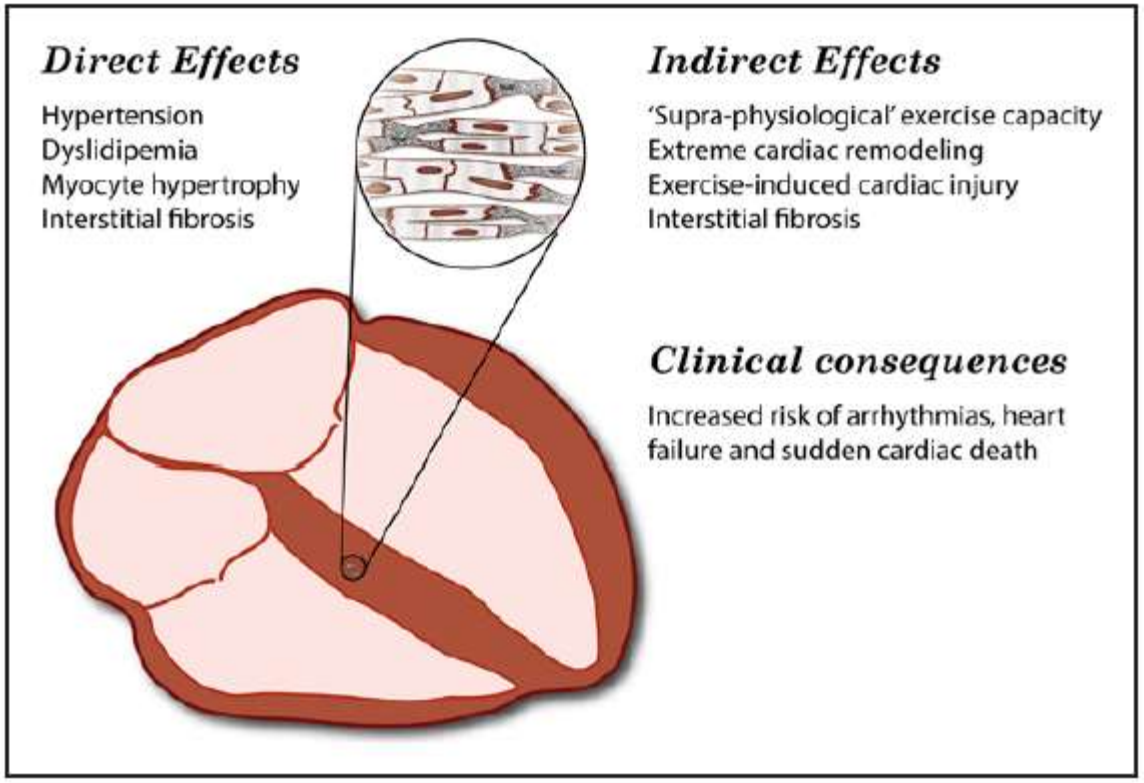


Figure 3. Adverse athletic heart remodeling as a consequence of both direct and indirect effects of performance-enhancing drugs.

La Gerche et al., Circulation, 2017

MECHANISMS OF CARDIOVASCULAR SIDE EFFECTS

Biomedical side effects of anabolic androgenic steroids…

…on the cardiovascular system

Atherogenesis Mechanism

Hepatic triglyceride lipase

⇩

Serum HDL-cholesterol ⇩

Serum LDL-cholesterol ⇧

⇩

Atherosclerotic changes in blood vessels

Tischer et al. (2003): Z Kardiol, p326-331.
Hartgens & Kuipers (2004): Sports Med, p513-554.

MECHANISMS OF CARDIOVASCULAR SIDE EFFECTS

Biomedical side effects of anabolic androgenic steroids…

…on the cardiovascular system

Thrombosis Mechanism

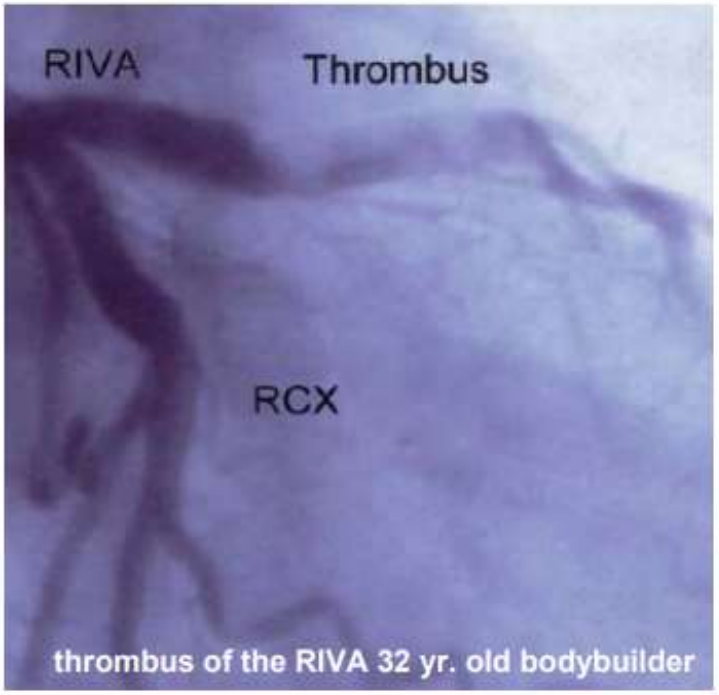
Platelet aggregation ⇧
& Fibrinolytic activity ⇩

⇩

Blood-clot formation ⇧

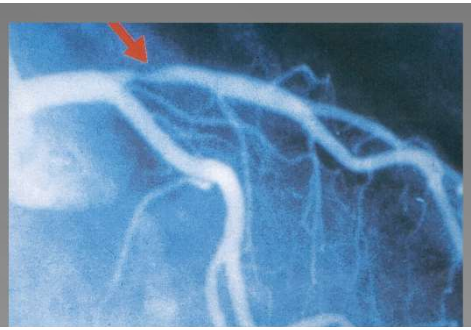
⇩

Cardiovascular risk ⇧



thrombus of the RIVA 32 yr. old bodybuilder

Tischer et al. (2003): Z Kardiol, p326-331.
Hartgens & Kuipers (2004): Sports Med, p513-554.



MECHANISMS OF CARDIOVASCULAR SIDE EFFECTS

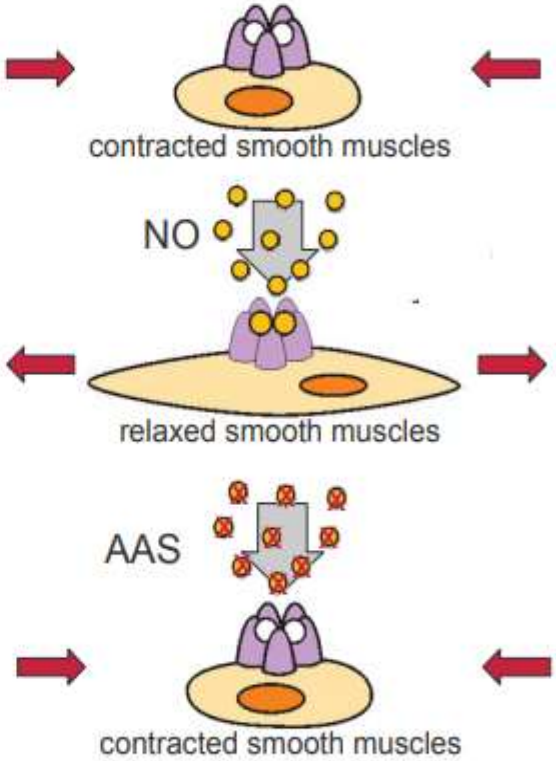
Biomedical side effects of anabolic androgenic steroids…

…on the cardiovascular system

Coronary Artery Vasospasm Mechanism

Nitric oxide (NO)
endothelian-derived relaxing factor
in smooth muscles of arteries
⇨ Vasodilatation

Vasospasm / Vasoconstriction ⇩
by nitric oxide



Hartgens & Kuipers (2004): Sports Med, p513-554.

Müller-Esterl: Biochemie, 2004
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MECHANISMS OF CARDIOVASCULAR SIDE EFFECTS

Biomedical side effects of anabolic androgenic steroids…

…on the cardiovascular system

Direct Cell Death Mechanism

Anabolic androgenic steroids

⇩

Myocardial cell hypertrophy

⇩

Myocardial cell injury

⇩

Myocardial cell death

⇩

Fibrosis

⇩

Ventricular arrhythmias

⇩

Sudden cardiac death

Hartgens & Kuipers (2004); Sports Med. p513-554.

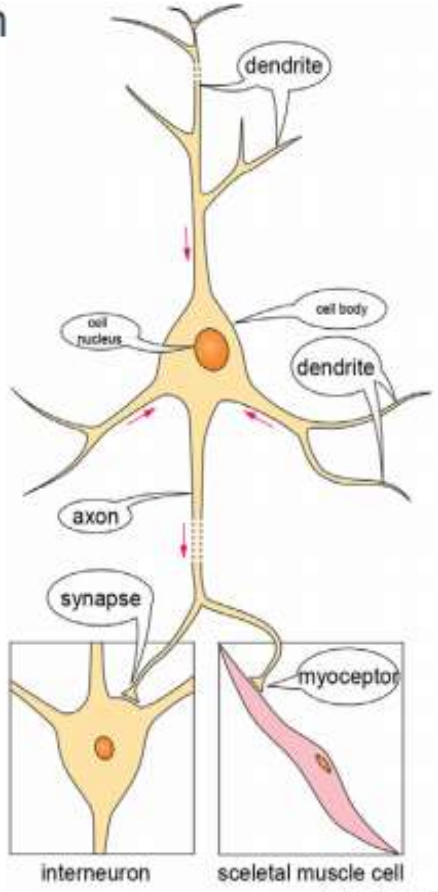
MECHANISMS OF CARDIOVASCULAR SIDE EFFECTS

Biomedical side effects of anabolic androgenic steroids…

…on the cardiovascular system

Degenerative Changes

Degenerative sympathetic neurons leading to arrhythmias



Hartgens & Kuipers (2004): Sports Med, p513-554.

Müller-Esterl: Biochemie, 2004
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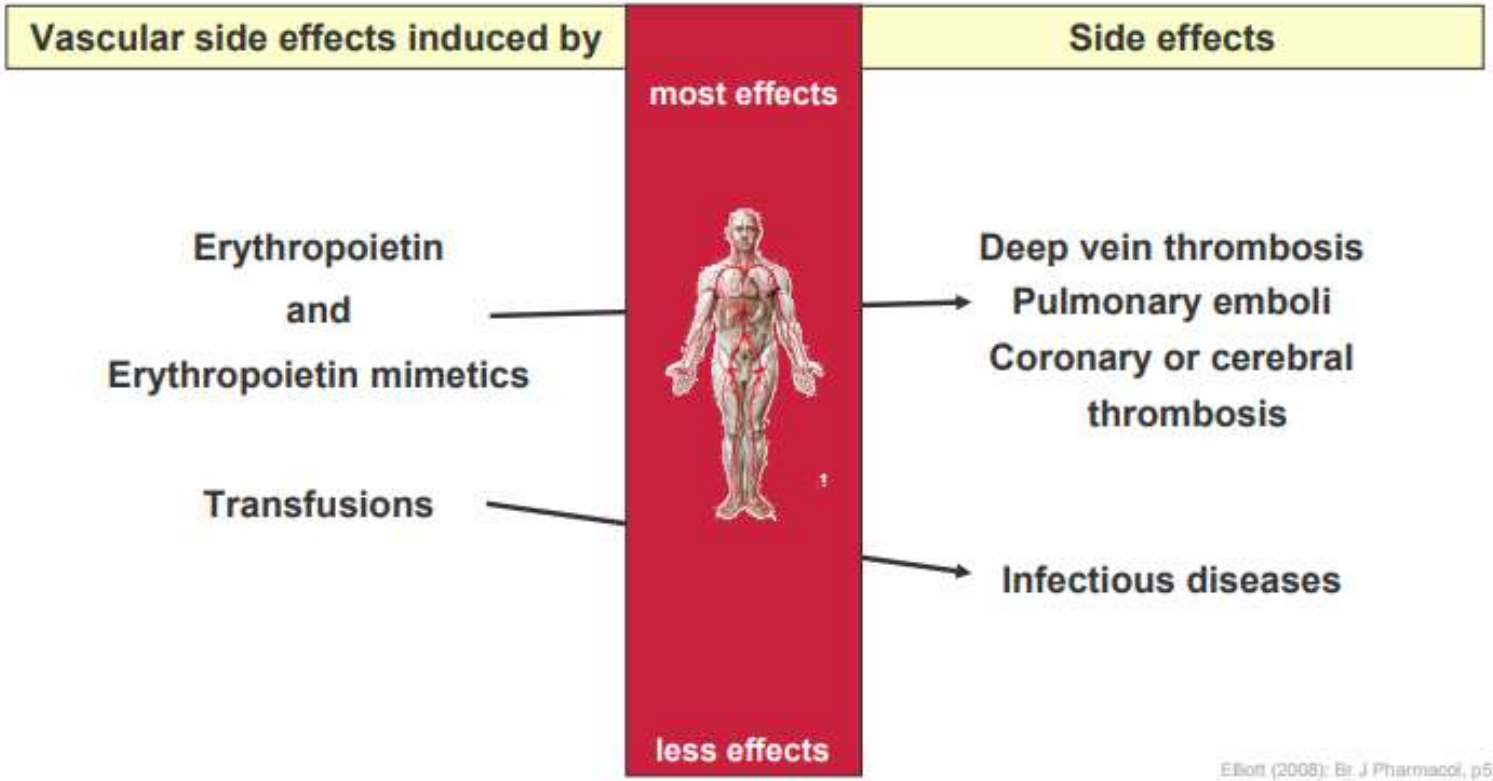
Biomedical side effects of doping substance abuse…

…on the blood & vascular system



Elliott (2008): Br J Pharmacol, p529-541.
Sobotta: Atlas der Anatomie des Menschen
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rHu-EPO SIDE EFFECTS

18 deaths in cycling due to rHu-EPO !

Der Spiegel

10th of June 1991

>50% Hct (rHu-EPO abuse)

Loss of fluids (sweat)

↑ Blood viscosity

↑ Cardiac afterload

Heart failure

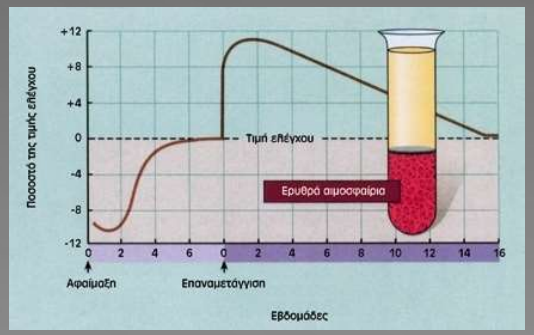
Myocardial infarction

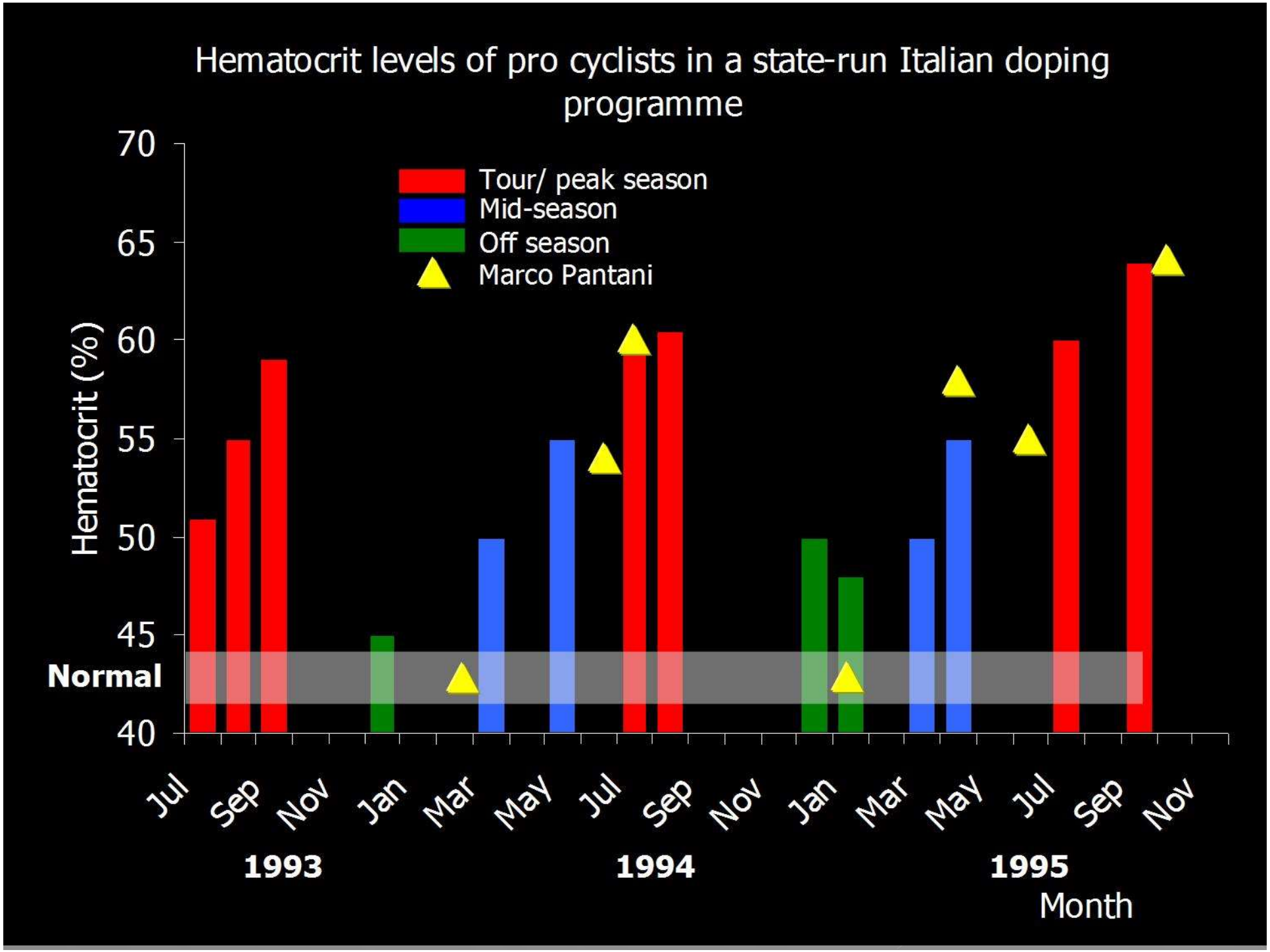
Stroke

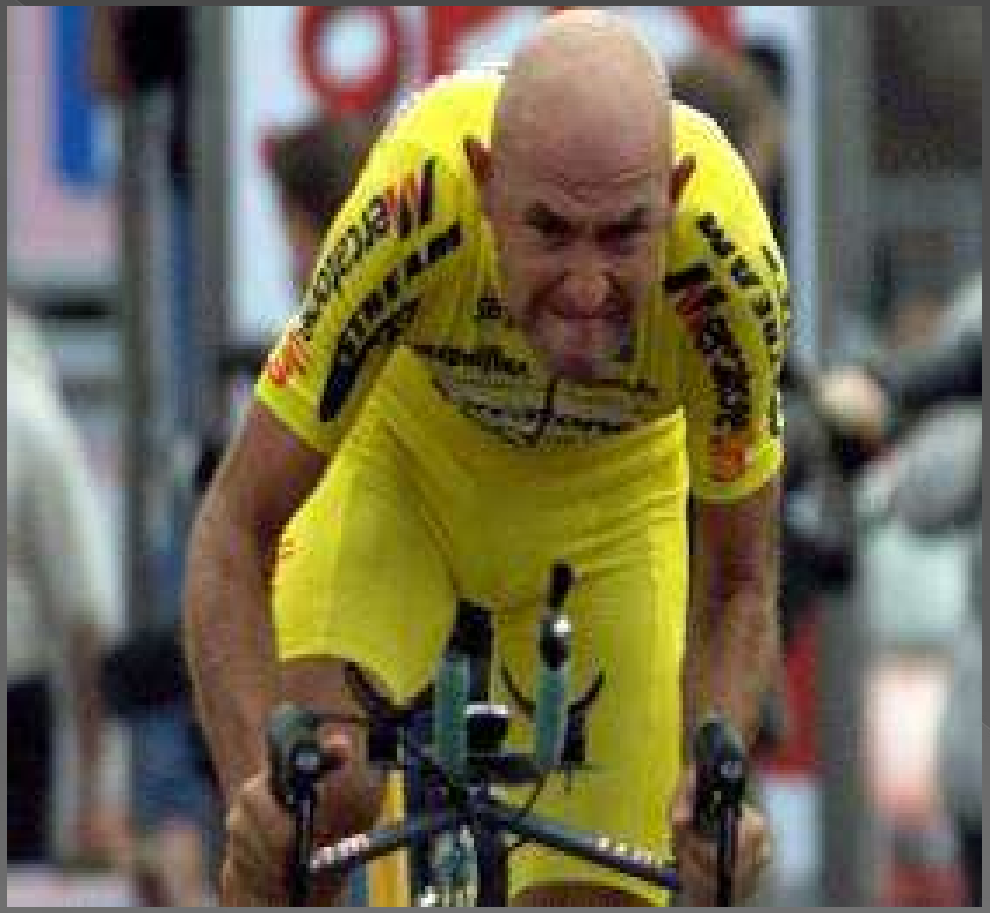
Pulmonary embolism

Arterial hypertension

Thromboembolic episodes




Hematocrit levels of pro cyclists in a state-run Italian doping programme
Tour/ peak season
Mid-season
Off season
Marco Pantani
Hematocrit (%)
70
65
60
55
50
45
40
Normal
Jul
Sep
Nov
Jan
Mar
May
Jul
Sep
Nov
Jan
Mar
May
Jul
Sep
Nov
1993
1994
1995
Month



Marco Pantani † 2004

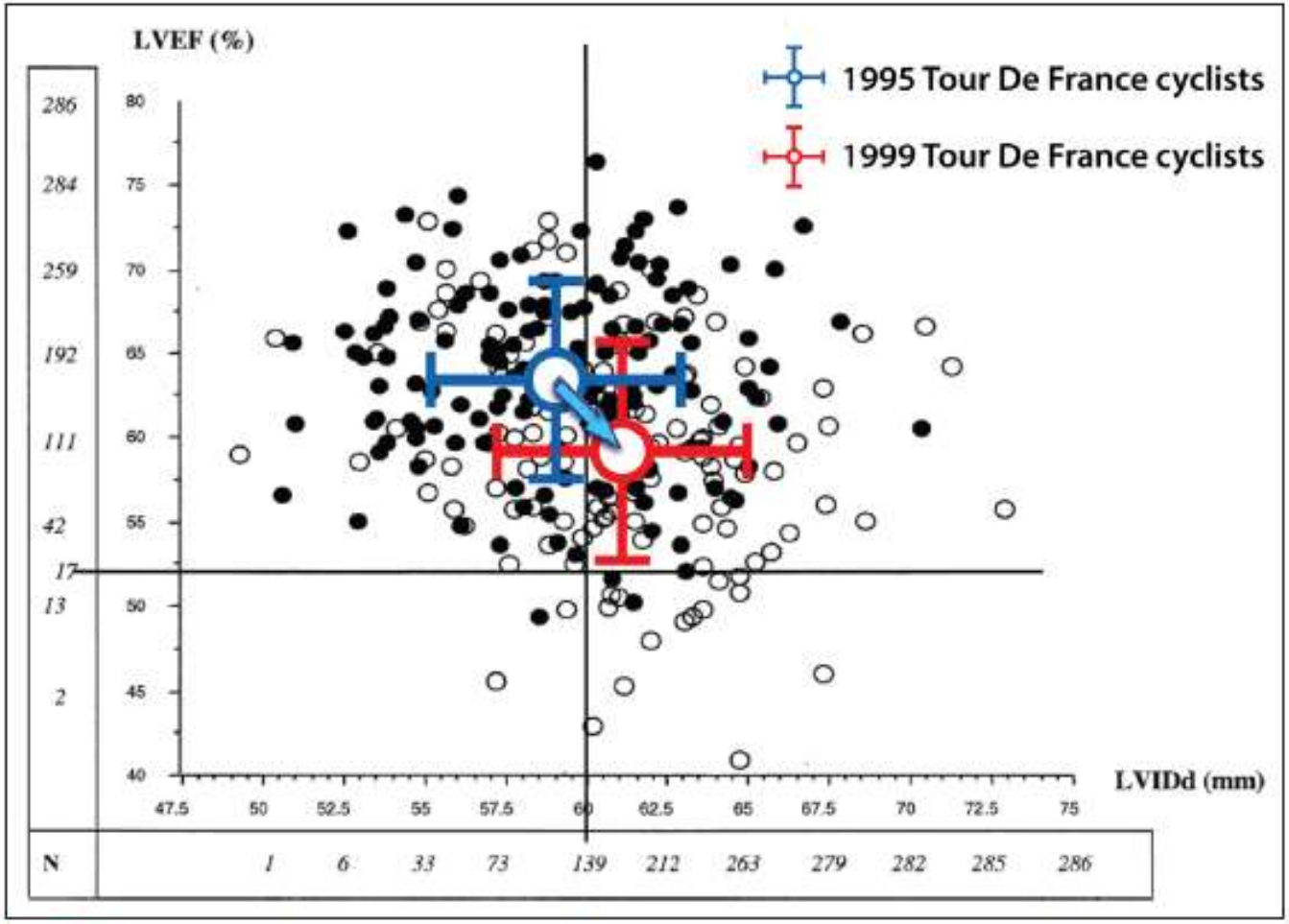


Figure 2. Larger hearts in professional cyclists at the height of erythropoietin use: a causal association?
Adaptation of data from Abergel et al[46] demonstrating that cyclists in the 1999 Tour De France had larger hearts (LVIDd, left ventricular internal diameter) and lower systolic function (LVEF, left ventricular ejection fraction) than cyclists in 1995. One potential explanation is that erythropoietin use is believed to have increased dramatically over this period. Thus, performance-enhancing drugs may facilitate greater exercise capacity and indirectly increase athletic cardiac remodeling. The health consequences of this are not known. Adapted from Abergel et al[46] with permission of the publisher. Copyright ©2004, Elsevier.

Abergel et al., J Am Coll Cardiol, 2004

DIURETICS & SIDE EFFECTS

Loss of water

Loss of electrolytes

- **Arrhythmias**

SUBSTANCES ACTING ON CNS

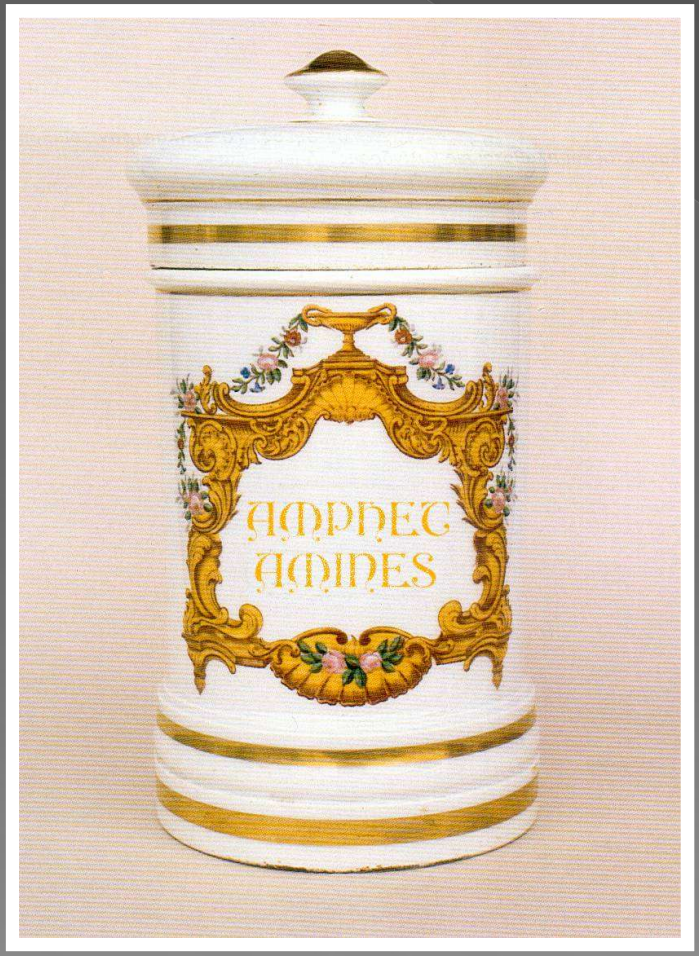
STIMULANTS

- AMPHETAMINES
- CAFFEINE

DEPRESSANTS

- COCAINE
- ANALGESICS (OPIOIDS)

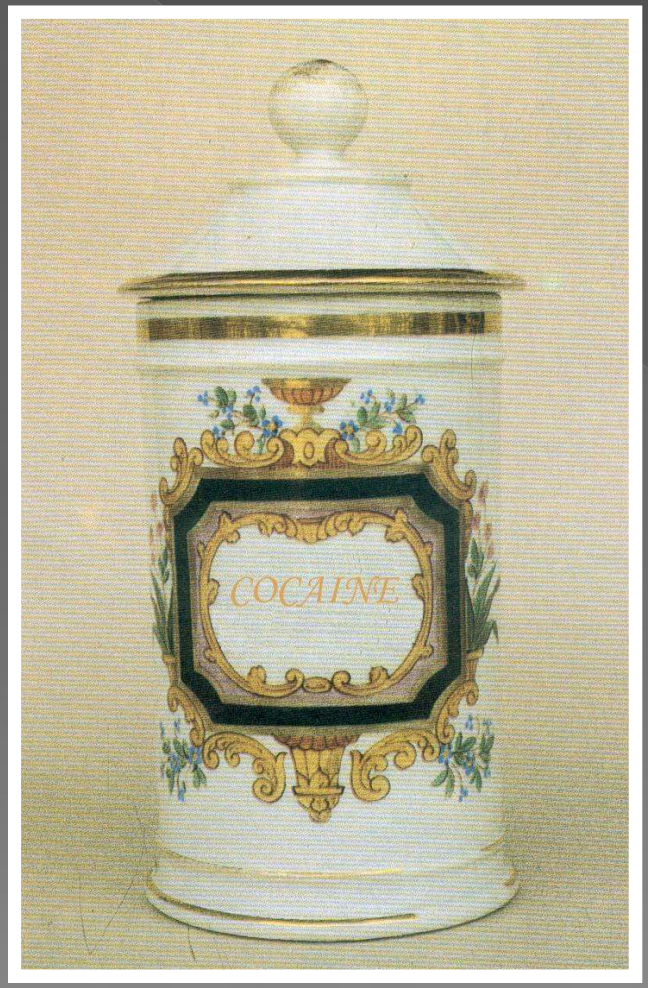
AMPHETAMINES



SIDE EFFECTS

- FATIGUE, DEHYDRATION
- INSOMNIA
- STROKE
- HYPERTENSION
- ARRHYTHMIAS
- CHEST PAIN
- CARDIOMYOPATHY
- HEART FAILURE
- SUDDEN DEATH

COCAINE



COCAINE & CORONARY DISEASE

- ↑ MYOCARDIAL OXYGEN DEMAND
- CORONARY SPASM
- THROMBOGENESIS

OTHER SIDE EFFECTS

- ARRHYTHMIAS
- CONDUCTION DISORDERS
- MYOCARDITIS
- CARDIOMYOPATHY
- ENDOCARDITIS
- RUPTURED AORTIC ANEURYSM
- PULMONARY OEDEMA
- STROKE

COCAINE & SUDDEN CARDIAC DEATH MECHANISM

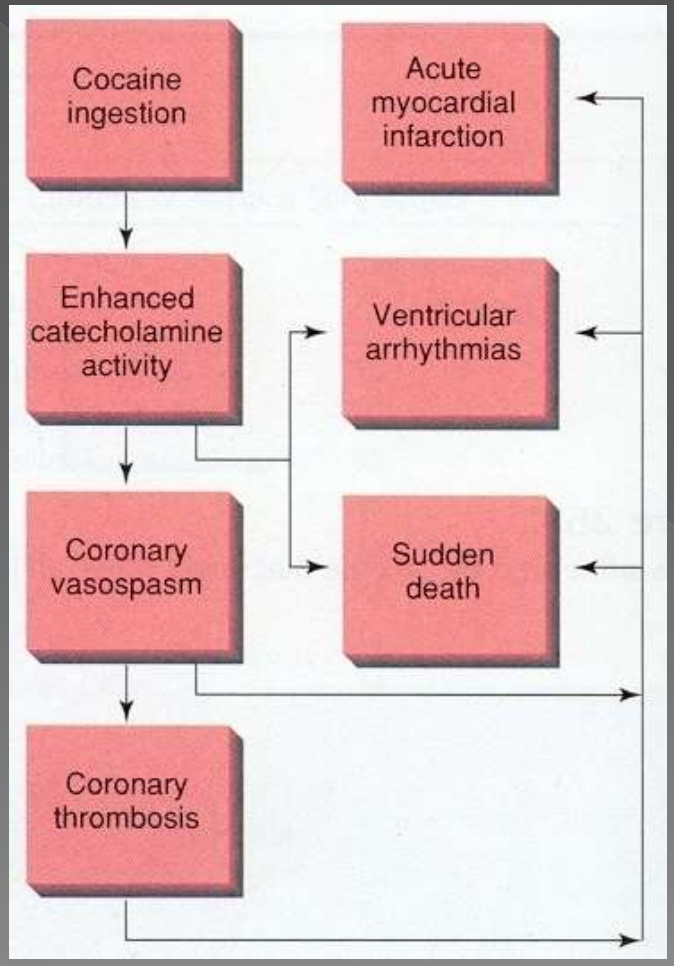


Table 1. Performance-Enhancing Drugs and Potential Cardiovascular Side Effects

Substance Group	Examples	Direct Cardiovascular Side Effects
Oxygen-carrying modulators	Erythropoietin Erythropoietin-stimulating agents Erythropoietin receptor agonists Blood doping Synthetic blood	Thromboembolic events Myocardial infarction Stroke Hypertension
Oxygen dissociation curve modulators	Cobalt RSR13	Cardiomyopathy
Anabolic agents	Human growth hormone, insulin-like growth factor-1 Endogenous anabolic steroids (eg, testosterone) and their metabolites (eg, 5-androstenedione; 7β-hydroxy-dehydroepiandrosterone) and exogenous steroid analogues (eg, stanazolol, nandrolone).	Dyslipidemia Hypertension Pathological cardiac Hypertrophy/cardiac fibrosis Arrhythmias
β_2-Adrenergic receptor antagonists	Clenbuterol	Arrhythmias in animals
Phosphodiesterase type 5 inhibitors	Sildenafil*	Unknown in athletes
Selective androgen receptor modulators	Thymosin beta 4 Andarine Ostarine Multiple "designer peptides"*	Largely unknown
Selective estrogen receptor modulators	Tamoxifen (counteract negative side effects of anabolic agents)	Venous thrombosis, pulmonary embolism
Hormone/metabolic modulators	Meldonium (mildronate) Corticosteroids Insulin and mimetics Thyroxine β-Alanine* Creatine* L-Carnitine*	Hypertension, hyper- or hypoglycemia, dyslipidemia, many agents with untested safety profiles
Amphetamines/stimulants	Methylphenidate, modafinil	Unknown in athletes
Others	Glycerol trinitrate* Tramadol* Opiates* (enables athletes to suppress pain in training and racing) Iron supplementation (especially in combination with altitude or O_2-carrying modulators)* Diuretics (masking agents/making weight) Epitestosterone (masking agent, normalizes testosterone to epitestosterone ratio)	Unknown in athletes

RSR13 indicates right-shifting reagent 13.
*Refers to agents not currently on the World Anti-Doping Agency list of banned substances.

La Gerche et al., Circulation, 2017

Lippincott Williams & Wilkins
a Wolters Kluwer business

EUROPEAN SOCIETY OF CARDIOLOGY

Position Paper

ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes

Asterios Deligiannis[a], Hans Björnstad[b], Francois Carre[c], Hein Heidbüchel[d], Evangelia Kouidi[a], Nicole M. Panhuyzen-Goedkoop[e], Fabio Pigozzi[f], Wilhelm Schänzer[g] and Luc Vanhees[h] on behalf of the ESC Study Group of Sports Cardiology

Table 2 Cardiac side-effects of prohibited substances

	Hyper-tension	Arrhyth-mias	LVH	CAD	MI	HF	SCD
AAS	+	+	+	+	+	+	+
hGH		+	+			+	+
EPO	+					+	
Beta-2 agonists		+			+	+	+
Diuretics		+					
Amphetamines	+	+			+	+	+
Cocaine	+	+		+	+	+	+
Ephedrine	+	+		+	+		+
Narcotics							+
Cannabinoids		+			+		+
Glucocorticosteroids	+			+			
Alcohol	+	+			+	+	+

+ Indicates an effect on a parameter; LVH, left ventricular hypertrophy; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; SCD, sudden cardiac death; AAS, androgenic–anabolic steroids; hGH, human growth hormone; EPO, erythropoietin.

Deligiannis et al., EJCPR, 13: 687-694, 2006

Hellenic J Cardiol 2012; 53: 447-457

Review Article

Cardiovascular Adverse Effects of Doping in Sports

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Table 2. Common cardiovascular complications caused by the most frequently used doping substances.

	AMI	CAD	Cardiomyopathy	Arrhythmias	Hypertension	SCD
AAS	√	√	√	√	√	√
Other anabolic agents (clenbuterol)	√	√	√	√	√	√
hGH			√	√	√	√
EPO	√		√	√	√	√
Beta-2 agonists	√		√	√		√
Diuretics				√		
Amphetamines	√	√	√	√	√	√
Ephedrine	√	√	√	√	√	√
Cocaine	√	√	√	√	√	√
Narcotics				√		√
Cannabinoids	√	√		√	√	√

√ indicates an effect. AMI – acute myocardial infarction; CAD – coronary artery disease; SCD – sudden cardiac death; AAS – anabolic androgenic steroids; hGH – growth hormone; EPO – erythropoietin.

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ORIGINAL ARTICLE

Ventricular androgenic-anabolic steroid-related remodeling: an immunohistochemical study

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inflammatory reactions and the presence of an increased number of M2 macrophages in the areas of fibrotic remodeling confirm that the fibrotic changes in the heart are apoptosis-related and not necrosis-related.

Conclusions In conclusion, the study indicates that, in very young subjects with chronic hypoxia-related alterations of the heart, signs of a heart failure in the other organs and a history of AAS abuse, death can be ascribed to progressive heart failure due to the direct apoptotic cardiac and endothelial changes produced by AAS.

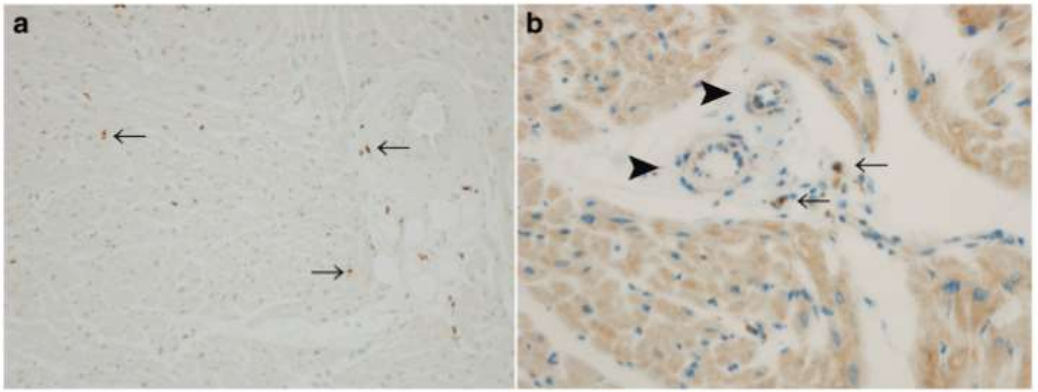

Fig. 3 Heart tissue of the control case. **a** Anti-CD 163-positive M2-type macrophages sparsely in the tissue without forming infiltrates (*arrows*). **b** Caspase 3-negative endothelial cells in two small vessels (*arrowheads*) and positive in few apoptotic myocardocytes (*arrows*) (anti-caspase 3, 20×)

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Circ Heart Fail. 2010 July 1; 3(4): 472–476. doi:10.1161/CIRCHEARTFAILURE.109.931063.

Long Term Anabolic-Androgenic Steroid Use is Associated with Left Ventricular Dysfunction

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Abstract

Background—Although illicit anabolic-androgenic steroid (AAS) use is widespread, the cardiac effects of long-term AAS use remain inadequately characterized. We compared cardiac parameters in weightlifters reporting long-term AAS use to those in otherwise similar weightlifters without prior AAS exposure.

Methods & Results—We performed 2-dimensional, tissue-Doppler, and speckle-tracking echocardiography to assess left ventricular (LV) ejection fraction, LV systolic strain, and conventional indices of diastolic function in long-term AAS users (n=12) and otherwise similar AAS non-users (n=7). AAS users (median [Q1,Q3] cumulative lifetime AAS exposure 468 [169–520] weeks) closely resembled non-users in age, prior duration of weightlifting, and current intensity of weight training. LV structural parameters were similar between the two groups. However, AAS users had significantly lower LV ejection fraction (50.6% [48.4, 53.6] versus 59.1% [58.0, 61.7]; p = 0.003 by Wilcoxon rank sum test, two-tailed); longitudinal strain (16.9% [14.0, 19.0] versus 21.0% [20.2, 22.9]; p = 0.004), and radial strain (38.3 [28.5, 43.7] versus 50.1 [44.3, 61.8]; p = 0.02). Ten of the 12 AAS users showed LV ejection fractions below the accepted limit of normal (≥55%). AAS users also demonstrated decreased diastolic function compared to non-users, as evidenced by a markedly lower E′ velocity (7.4 [6.8, 7.9] versus 9.9 [8.3, 10.5]; p = 0.005) and E/A ratio (0.93 [0.88, 1.39] versus 1.80 [1.48, 2.00]; p = 0.003).

Conclusions—Cardiac dysfunction in long-term AAS users appears more severe than previously reported, and may be sufficient to increase the risk of heart failure.

DOI: 10.1111/echo.13243

Echocardiography

Comparison of Right Ventricle Systolic Function between Long-Term Anabolic–Androgenic Steroid User and Nonuser Bodybuilder Athletes: A Study of Two-Dimensional Speckle Tracking Echocardiography

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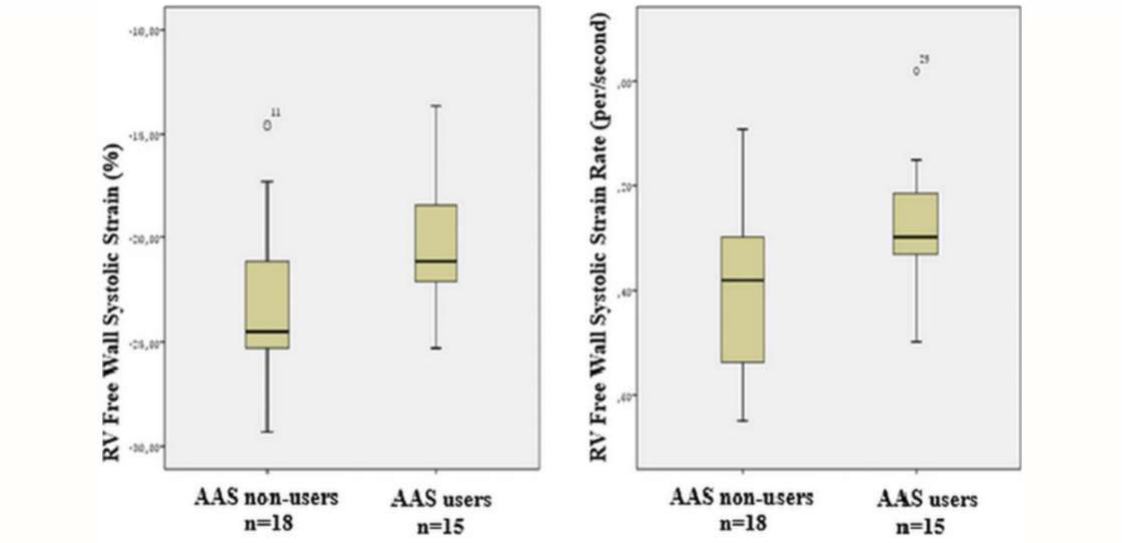

Figure 2. Comparison of peak systolic RV free wall strain and strain rate parameters between AAS user bodybuilders and nonusers.

The International Journal of Cardiovascular Imaging
https://doi.org/10.1007/s10554-018-1370-9

ORIGINAL PAPER

Left atrial myocardial dysfunction after chronic abuse of anabolic androgenic steroids: a speckle tracking echocardiography analysis

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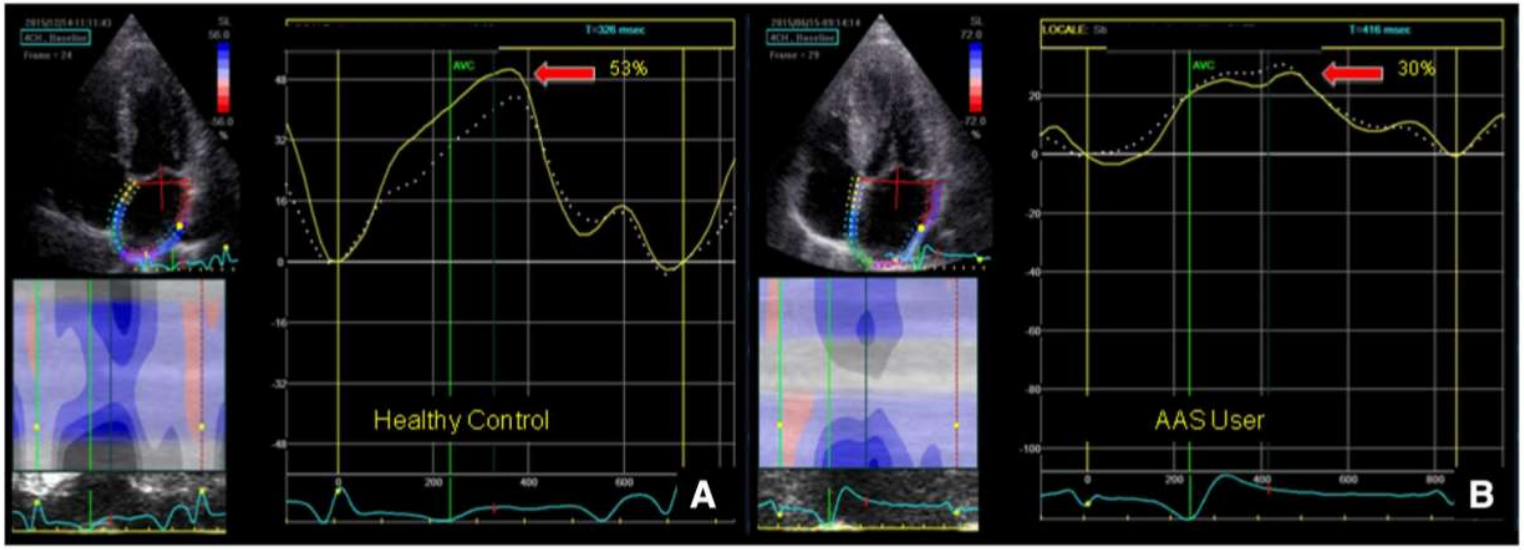

Fig. 1 Left atrial strain curves in a control subject (**a**) and in a power athlete abusing AAS (**b**). Left atrial deformation of lateral wall was significantly impaired (arrows) in the athlete

Case Report

Aortic Dissection in a Healthy Male Athlete: A Unique Case with Comprehensive Literature Review

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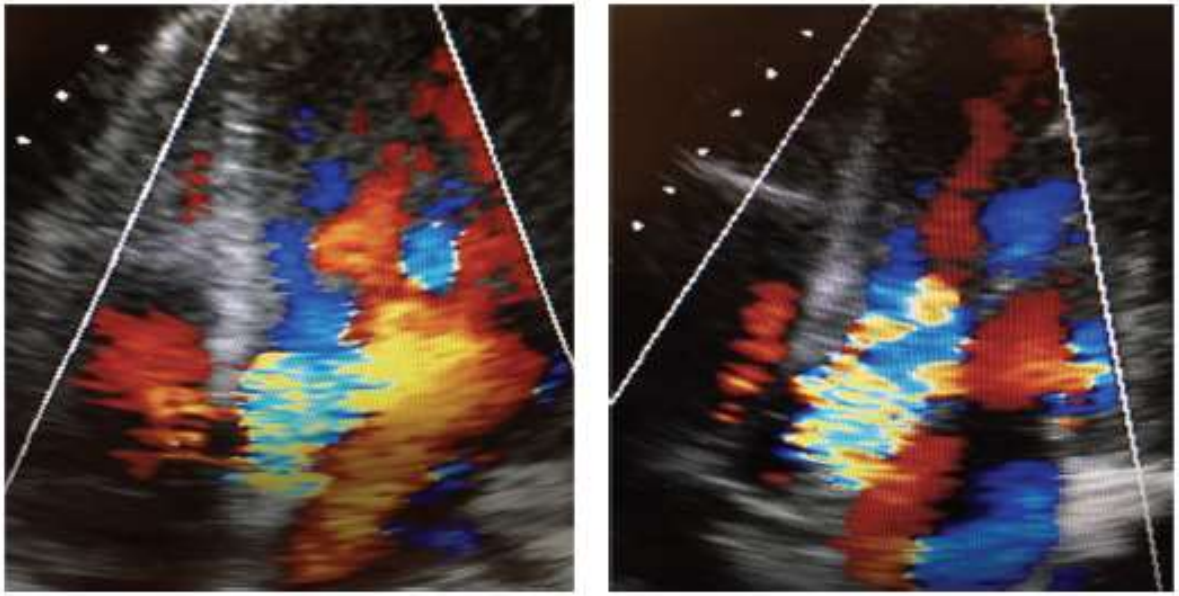
A young otherwise healthy 27-year-old male who has been using anabolic steroids for a long time developed Type I aortic dissection associated with heavy weightlifting. The patient did not have a recent history of trauma to the chest, no history of hypertension, and no illicit drug use. He presented with severe chest pain radiating to back and syncopal event with exertion. Initial vitals were significant for blood pressure of 80/50 mmHg, pulse of 80 beats per minute, respirations of 24 per minute, and oxygen saturation of 92% on room air. Physical exam was significant for elevated jugular venous pressure, muffled heart sounds, and cold extremities with diminished pulses in upper and absent pulses in lower extremities. Bedside echocardiogram showed aortic root dilatation and cardiac tamponade. STAT computed tomography (CT) scan of chest revealed dissection of ascending aorta. Cardiothoracic surgery was consulted and patient underwent successful repair of ascending aorta. Hemodynamic stress of weightlifting can predispose to aortic dissection. Aortic dissection is a rare but often catastrophic condition if not diagnosed and managed acutely. Although rare, aortic dissection needs to be in the differential when a young weightlifter presents with chest pain as a delay in diagnosis may be fatal.

FIGURE 5: CT scan of chest with contrast showing dissection flap in ascending aorta (red arrow).



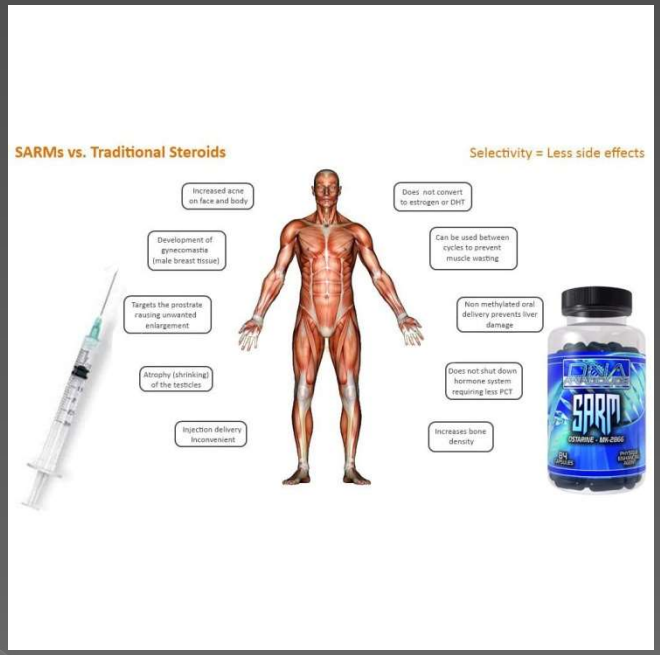
(a) (b)

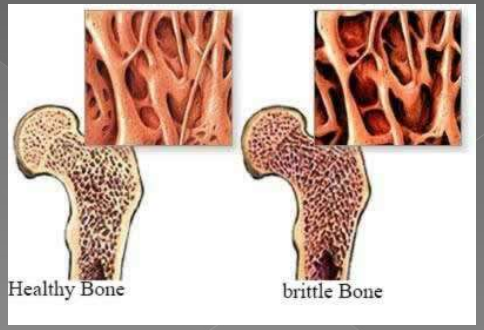
FIGURE 6: Echocardiogram five-chamber view showing severe aortic regurgitation.

Selective Androgen Receptor Modulators (SARMs) & DOPING

* MK-2866 ή GTx-024 (Ostarin)
* LGD-4033 (Ligandrol)
* LGD-3303
* GSX-007 ή δ-4 (Andarin)
* GW-501516 (Cardarin)

✓ **Anabolic-to-androgenic ratios starting at 3:1 and going as high as 90:1**

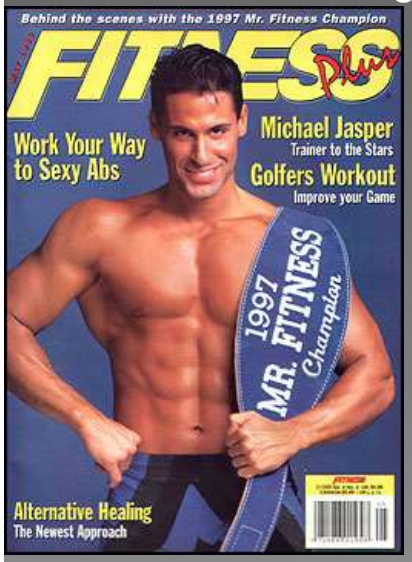


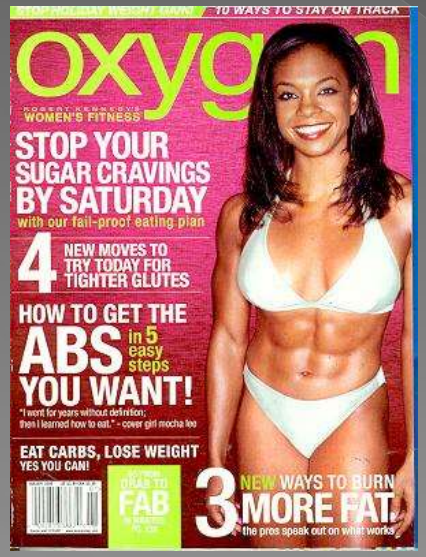


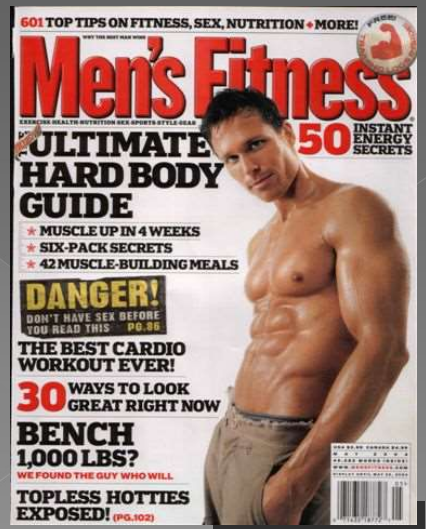
Performance Image Enhancing Drugs (PIEDS)

SARMs and Peptides carry a substantial risk of long term harmful health consequences, which are usually understated by the person promoting their use.

ASADA, November 9th 2017

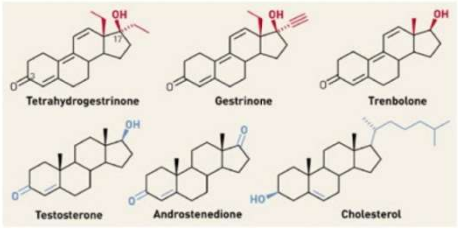






OTHER - DESIGN DRUGS

Tetrahydrogestrinone (THG)



CHEMICAL ANALOGUE OF PROGESTERONE

ANABOLIC ACTION

FIMS Article

Phosphodiesterase Type 5 Inhibitors, Sport and Doping

Luigi Di Luigi, MD[1]; Massimiliano Sansone, MD[2]; Andrea Sansone, MD[2]; Roberta Ceci, PhD[3]; Guglielmo Duranti, PhD[3]; Paolo Borrione, MD[4]; Clara Crescioli, PhD[1]; Paolo Sgrò, MD, PhD[1]; and Stefania Sabatini, BiD[3]

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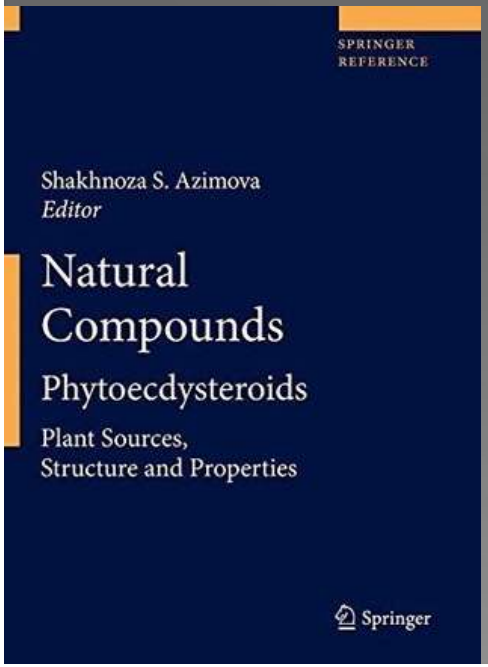
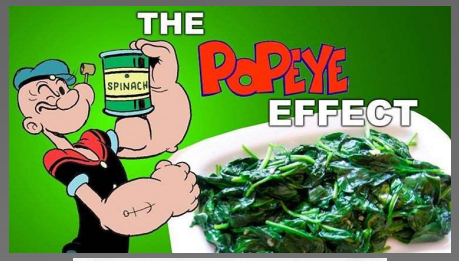
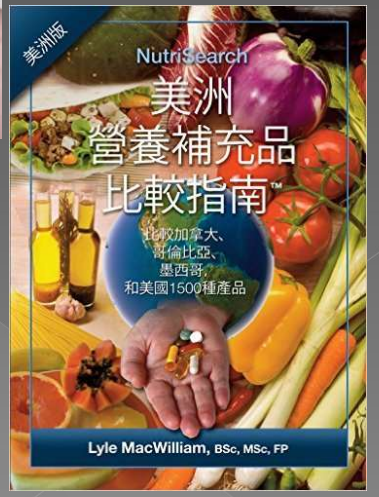


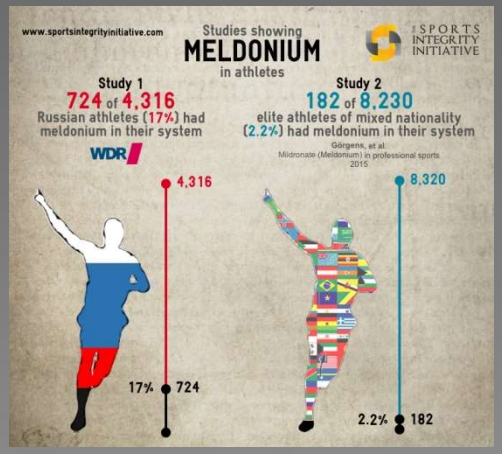




MELDONIUM & DOPING

What is meldonium?

- ✓ **Also known as Mildronate, it is used to treat angina and myocardial infarction**
- ✓ **Manufactured and marketed by Latvian company Grindeks**
- ✓ **Used in Russia and Lithuania, but not approved by food and drug administrations of many countries**

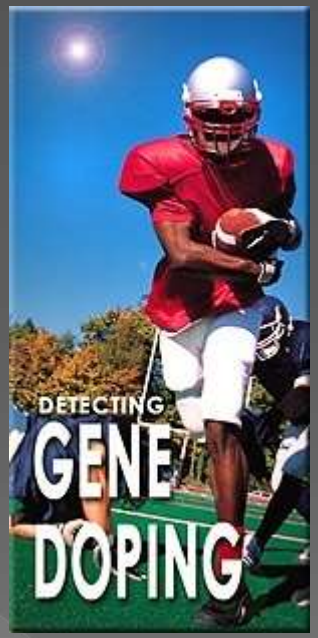


> 500 GENES RELATED TO SPORTS PERFORMANCE

A2M	CaMKIINalpha	DDR2	GJA1	LAMP1	OAS1	S100A13	TRDN	60050_at
ACLY	CAP1	DHRS8	GLS	LAP1B	OLFML2A	S100A4	TREM4	62263_at
ACTA2	CAPN3	DKFZP434B044	GLUL	LASP1	OLFML2B	SCN4B	TRIB1	62480_at
ACTB	CAV1	DKFZp434B1231	GNA12	LDHB	OSRF	SCOTIN	TUBA3	62539_at
ACTC	CAV2	DKFZp434L142	GNAI2	LGALS1	OTUD1	SDPR	TUBB	62594_at
ACTG1	CCDC3	DKFZp564I1922	GNB1	LGALS3	PABPC1	SEMA3C	TXNDC5	63296_at
ACTN1	CCND1	DKFZP564O0823	GNG11	LHFP	PALM2	SERPING1	TYROBP	64064_at
ACTN2	CD164L1	DKFZP566K1924	GPAM	LILRB1	PC326	SERPINH1	UBE2G1	65114_at
ACTN3	CD34	DKFZp761C169	GPNMB	LIM	PCDH18	SESN1	UBE2S	65904_at
ACTN4	CD81	DLC1	GPR124	LNK	PCOLCE2	SESN3	UCP2	67792_r_at
ADAMTS5	CDH5	DMD	GPR34	LOC162073	PDGFRB	SFRP2	UCP3	71786_at
ADAR	CDW92	DNCL1	GPX3	LOC283241	PDK4	SH3BGRL	URB	72674_at
ADD3	CFL1	DPYSL2	GRP58	LOC339924	PDLIM3	SH3BGRL3	USP13	72728_at
AGTRL1	CGI-121	DSTN	GSN	LOC387763	PEA15	SIPA1L2	UTRN	73441_at
AMPD1	CHST1	ECM2	GUCY1A3	LOC388962	PECAM1	SLC20A2	VAT1	74566_at
ANGPTL2	CIDE-3	ECRG4	HBAP1	LOC51668	PFN2	SLC38A1	VDP	75430_r_at
ANKRD1	CKLFSF6	EDIL3	HBB	LOXL1	PHKG1	SLC41A1	VIM	75969_f_at
ANTXR1	CLDN5	EEF1A1	hIAN2	LOXL2	PHLDB2	SMOC2	VWF	76236_r_at
ANXA1	CLIC1	EFHD2	HIPK3	LPL	PLAC9	SNRPN	WSB1	77207_at
ANXA2	CLIC4	EHD2	HLA-B	LUM	PLN	SOX4	YWHAQ	78727_at
ANXA2P3	CLU	EIF4A1	HLA-C	MADH1	PLS3	SOX7	ZAK	79933_at
ANXA5	CMIP	ELOVL5	HLA-DPB1	MAFB	PLSCR4	SPARC	ZC3HAV1	83026_i_at
AOC3	CMYA5	ELTD1	HLA-DRA	MAGED2	PLTP	SPARCL1	ZFP36	85922_r_at
APOE	CNK2	EMCN	HLA-DRB1	MALAT-1	PLVAP	SPIN	ZFP36L2	90557_at
APP	CNN3	EMP3	HLA-F	MARCKS	PODN	SPON2	ZNF145	
ARHGAP1	CNNM3	ENG	HN1	MEOX2	PORIMIN	SPP1	1164_at	
ARHGAP8	COL15A1	ENPP2	HSPC121	MESDC1	PP1057	SPTBN1	1173_g_at	
ARHGDIB	COL1A2	EPS8	HSPC242	MGC1136	PP2135	SSPN	1664_at	
ARPC5	COL3A1	ERG	HSPG2	MGC15606	PPIA	SULT1A1	1882_g_at	
ARRDC3	COL4A1	ETS1	IER5	MGC4083	PPIB	TAGLN	296_at	
ART3	COL4A2	F11R	IFI27	MGC45780	PRCP	TARSH	311_s_at	
ATP2B2	COL5A2	FABP4	IFITM1	MGC45871	PRKAG2	TAZ	35474_s_at	
B2M	COL6A1	FABP5	IFITM3	MGC52010	PRND	TCF7L2	40657_r_at	
BASP1	COL6A2	FADS3	IGF1	MIDORI	PRSS11	TGFBI	41732_at	
BGN	COL6A3	FASN	IGF2	MLF1	PTMA	TGFBR2	44066_s_at	
BMPR2	CORO1C	FBN1	IGFBP2	MRC2	PTPLB	THBS4	44583_at	
BNIP3L	COTL1	FBXL7	IGFBP4	MSN	PTRF	THRSP	44868_s_at	
BOC	COX6A1	FBXO3	IGFBP5	MT1X	PTTG1IP	TIMP1	45660_at	
BRP44L	CPE	FCGR3A	IGFBP7	MYADM	QKI	TIMP2	46653_at	
BTEB1	CRIP1	FER1L3	IGLJ3	MYH11	RAB8B	TIP-1	46898_at	
BTG1	CRIP2	FKBP2	IL17D	MYH9	RAFTLIN	TM4SF1	47482_at	
C10orf104	CSPG2	FKBP5	IQGAP1	MYL6	RAI14	TM4SF3	48069_at	
C10orf58	CTBP2	FLJ10849	ITGB1	MYL9	RAP1B	TMEM16E	48074_at	
C14orf139	CTGF	FLJ14146	ITGB1BP3	MYLK	RBM3	TMSB10	48853_at	
C19orf10	CTNNA1	FLJ20618	ITGB5	MYLK2	RBMS3	TMSB4X	49967_at	
C1QA	CTSO	FLJ23153	ITM2A	MYO1B	RBP1	TNA	50007_at	
C1QG	CXCL12	FLNA	JAM2	NEB	RBP4	TNC	50411_at	
C1QR1	CXCL14	FN1	JPH1	NEXN	RCN1	TncRNA	51939_at	
C1S	CYBRD1	FNDC1	K-ALPHA-1	NGFRAP1	RHOC	TNFAIP3	54668_at	
C20orf3	CYGB	FOS	KCNJ8	NID	RNASE1	Tnfrsf6	54980_at	
C6orf198	D2S448	FOXO3A	KCTD10	NID2	ROD1	TOB2	55328_r_at	
C9orf19	DAB2	FOXP1	KCTD12	NOTCH3	RPL3	TP53INP1	55837_at	
C9orf58	DACH1	FSCN1	KIAA1109	NPC2	RRAD	TPM1	56323_at	
CACNA2D1	DACT1	FXYD6	LAMA4	NR2F2	RSN	TPM2	56543_i_at	
CALD1	DC2	FYN	LAMB1	NRAP	S100A10	TPM3	56600_at	
CALM2	DC-TM4F2	GANAB	LAMC1	NRP1	S100A11	TPM4	59809_f_at	

Timmons et al., 2005

GENE DOPING: THE GREAT THREAT



The use of genes for performance enhancement: doping or therapy? R.S. Oliveira, T.F. Collares, K.R. Smith, T.V. Collares and F.K. Seixas. Braz J Med Biol Res 2011; 44: 1194-1201.

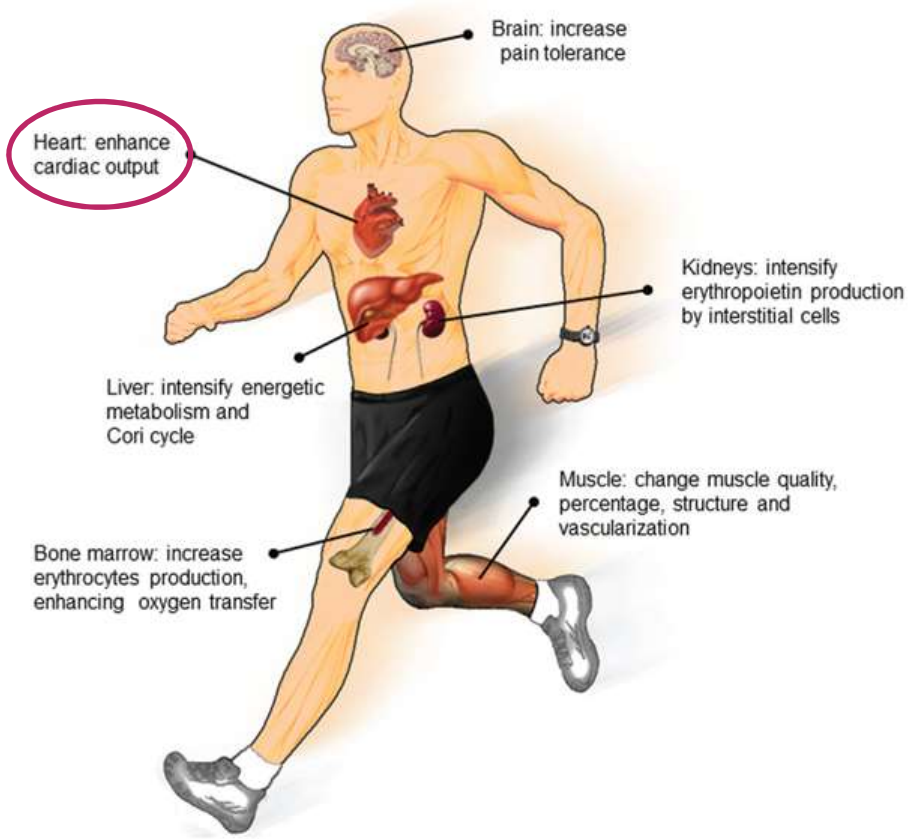


Figure 1. Targeted tissues and organs for gene doping. Main aims of gene doping to enhance sports performance: improvement of pain tolerance (endorphin/enkephalin genes), muscle quality and vascularization (VEGF gene and myostatin antagonists) and erythrocyte number (EPO gene). With more genomic understanding, other organs will be targeted in the future, such as heart and kidneys, to increase cardiac output and EPO production, respectively. VEGF = vascular epithelial growth factor; EPO = erythropoietin.

GENE THERAPY & GENE DOPING
BIOMEDICAL SIDE EFFECTS

- **Lack of regulation in establishing correct levels of gene expression**

- **Gene therapy may lead to unexpected cardiovascular side effects**

TABLE 2. POTENTIAL GENES THAT CAN BE USED IN DOPING, TARGET TISSUES/SYSTEMS AND POTENTIAL RISK TO THE ATHLETE'S HEALTH [29-65].

Potential genes	Target tissue/system	Risks to health	1. Physiological function 2. Expected phenotypic performance
EPO *Locus:* 7q22	Blood system	– Increased blood viscosity, – Difficult laminar blood flow through the vessels, – Severe immune response	1. Increased number of red blood cells and increased blood oxygenation 2. Increased endurance
IGF1/ GH *Locus:* 12q23.2/ 17q22–q24	Endocrine and muscle system	– Intracranial hypertension, – Abnormal vision, – Headache, nausea, vomiting, – Peripheral oedema, – Carpal tunnel syndrome, – Pain in the joints and muscles, – Overgrowth of the cartilage of the nose and jaw, – Cardiomyopathy, – Insulin resistance and diabetes, – Neoplastic disease	1. Excessive growth of bones and tissue mass, muscle hypertrophy and hyperplasia, and stimulation by muscle regeneration (IGF1), – stimulation of glycogenolysis and increased release of glucose from liver, increased lipolysis and reduced lipogenesis, increased protein synthesis (GH) 2. Increased endurance, efficiency, increased muscle mass and strength (IGF1, GH)
HIF-1 *Locus:* 14q23	Blood and immune system	– Increased blood viscosity, – Hypertension – Neoplastic disease	1. Increased number of red blood cells and increased blood oxygenation (indirectly by affecting, among others, EPO gene or genes encoding glycolytic enzymes) 2. Increased muscle strength and endurance
PPARD *Locus:* 6p21.2	Muscular system	– Overexpression of sex hormones, – Colon cancer	1. Acceleration of skeletal muscle cell metabolism, increased insulin sensitivity, increased lipolysis 2. Increased endurance and speed. Probably involved in the control of body weight
MSTN *Locus:* 2q32.2	Muscular system	– Damage of the ligaments, tendons and bones	1. Hypertrophy and hyperplasia of muscle mass 2. Increased muscle mass and strength
ACTN2 and *ACTN3* *Locus:* 1q42–q43 / 11q13.1	Muscular system (actin filaments within the myofibrils of the striated muscle, fast-twitch fibres ACTN3 (type II fibres).	– No data on the negative effects of gene doping using ACTN2 and ACTN3	1. Increased rate of glucose metabolism in response to training (ACTN3), – Compensation for loss of function of ACTN3 gene by ACTN2 gene 2. Increased endurance, muscle strength and speed of muscle; increased efficiency in sprinters
VEGFA *Locus:* 6p12	Vascular endothelium	– Neoplastic disease, – Immune response	1. Induction of new blood vessel formation (angiogenesis) 2. Increased endurance
POMC/ PENK precursors Endorphin/ enkephalins *Locus:* 2p23.3/ 8q23–q24	Central nervous system	– Increased risk of overloading the musculoskeletal system and cardiovascular system, – Stress and increased cardiac workload, – Sudden death	1. Modulation of pain perception threshold 2. Increased endurance
ACE *Locus:* 17q23.3	Skeletal muscle	– Angioedema	1. Adjusting blood pressure by acting on angiotensin II (increase in blood pressure), and participation in the inactivation of bradykinin (decrease in blood pressure), increasing the proportion of slow-twitch muscle fibres (type I) 2. Increased endurance and/or sprint efficiency
PCK1 *Locus:* 20q13.31	Skeletal muscle	No data on the negative effects of gene doping using PCK1 in athletes	1. Adjusting the metabolic processes including gluconeogenesis, involved in the Krebs cycle 2. Increased muscle endurance

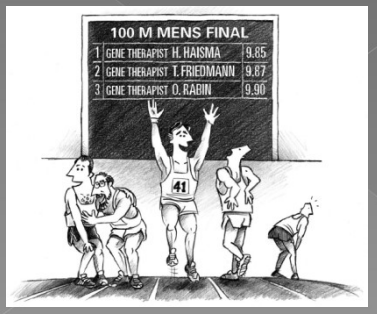
Brzezianska et al., Biol Sport, 2014

Increased Risk of Mutation Genesis

unexpected side effects

Atypical regulation:

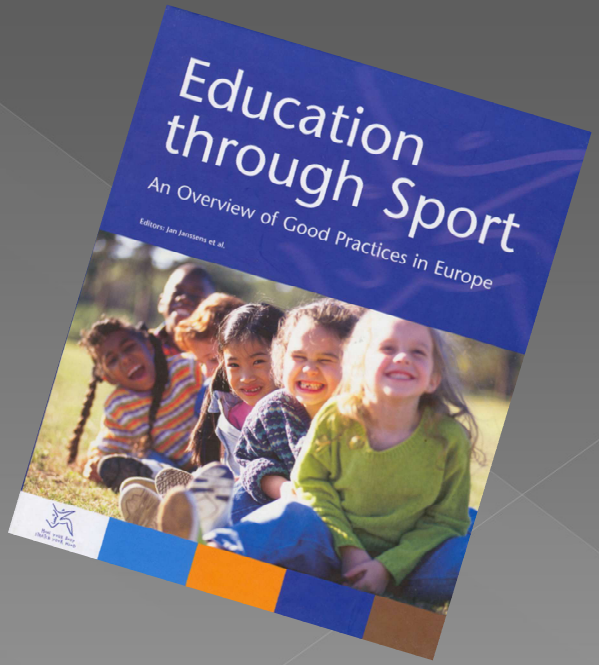
- cell growth
- toxicity due to chronic hyper-expressions of growth factors and cytokines
- malignant cells



FIGHT AGAINST DOPING

MEASURES

PREVENTION

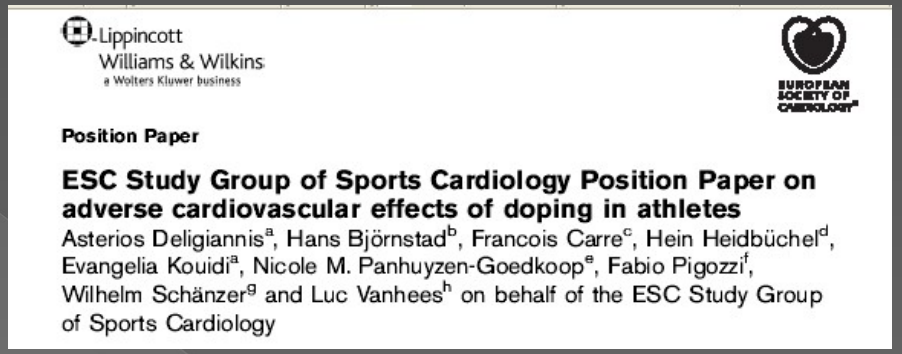


WHAT CAN WE DO?

THE FIGHT AGAINST ABUSE OF ERGOGENIC AIDS IN SPORTS DEMANDS:

INFORMATION

ABOUT USE & ACTION OF ERGOGENIC AIDS



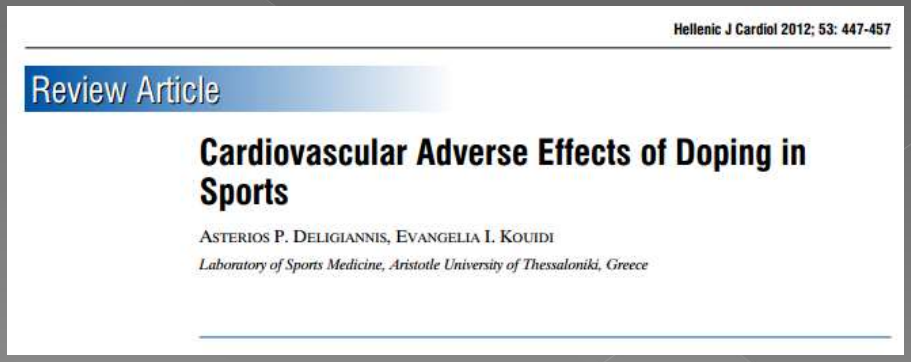
Lippincott Williams & Wilkins
a Wolters Kluwer business

EUROPEAN SOCIETY OF CARDIOLOGY

Position Paper

ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes

Asterios Deligiannis[a], Hans Björnstad[b], Francois Carre[c], Hein Heidbüchel[d], Evangelia Kouidi[a], Nicole M. Panhuyzen-Goedkoop[e], Fabio Pigozzi[f], Wilhelm Schänzer[g] and Luc Vanhees[h] on behalf of the ESC Study Group of Sports Cardiology



Hellenic J Cardiol 2012; 53: 447-457

Review Article

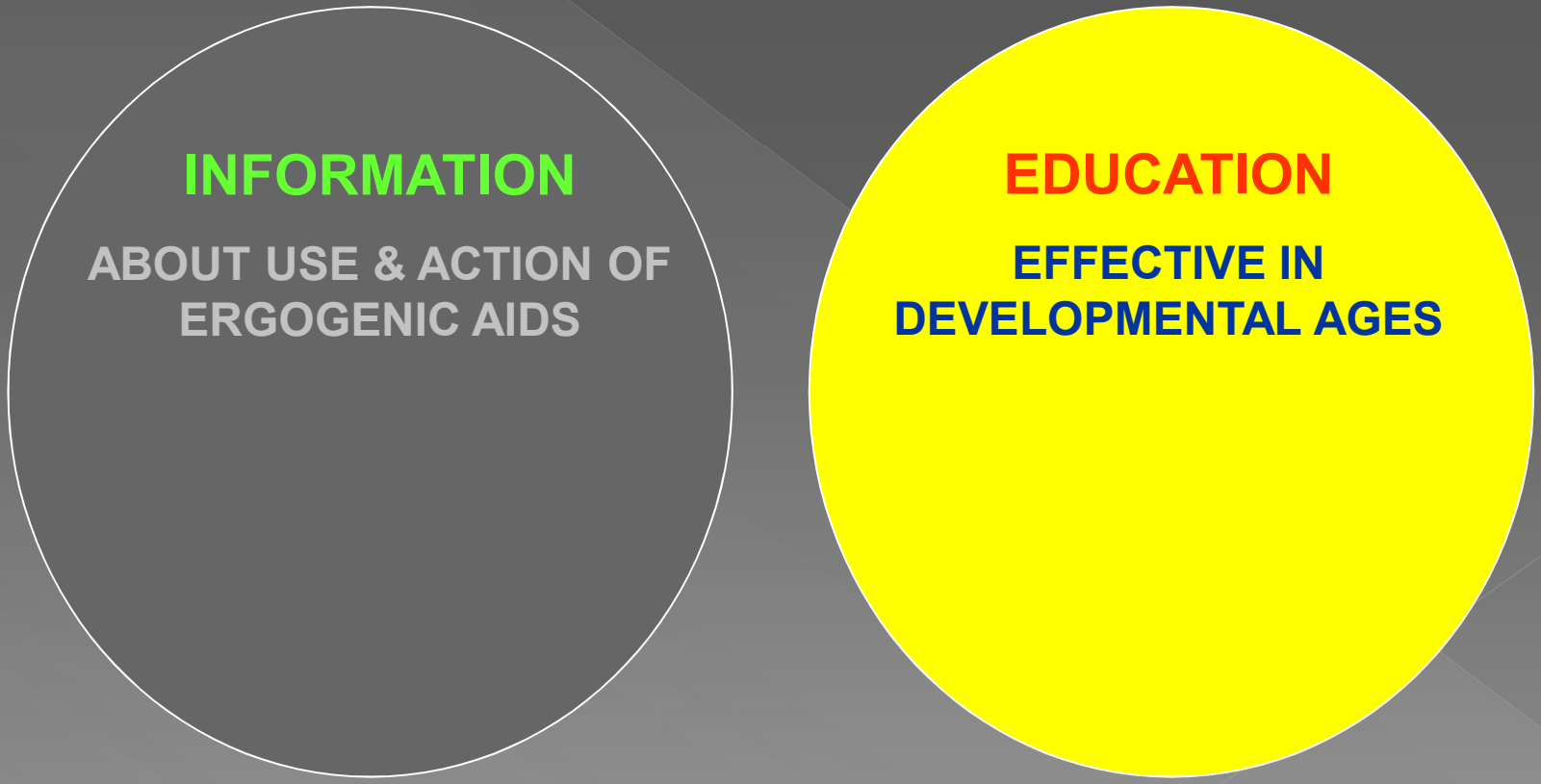
Cardiovascular Adverse Effects of Doping in Sports

ASTERIOS P. DELIGIANNIS, EVANGELIA I. KOUIDI

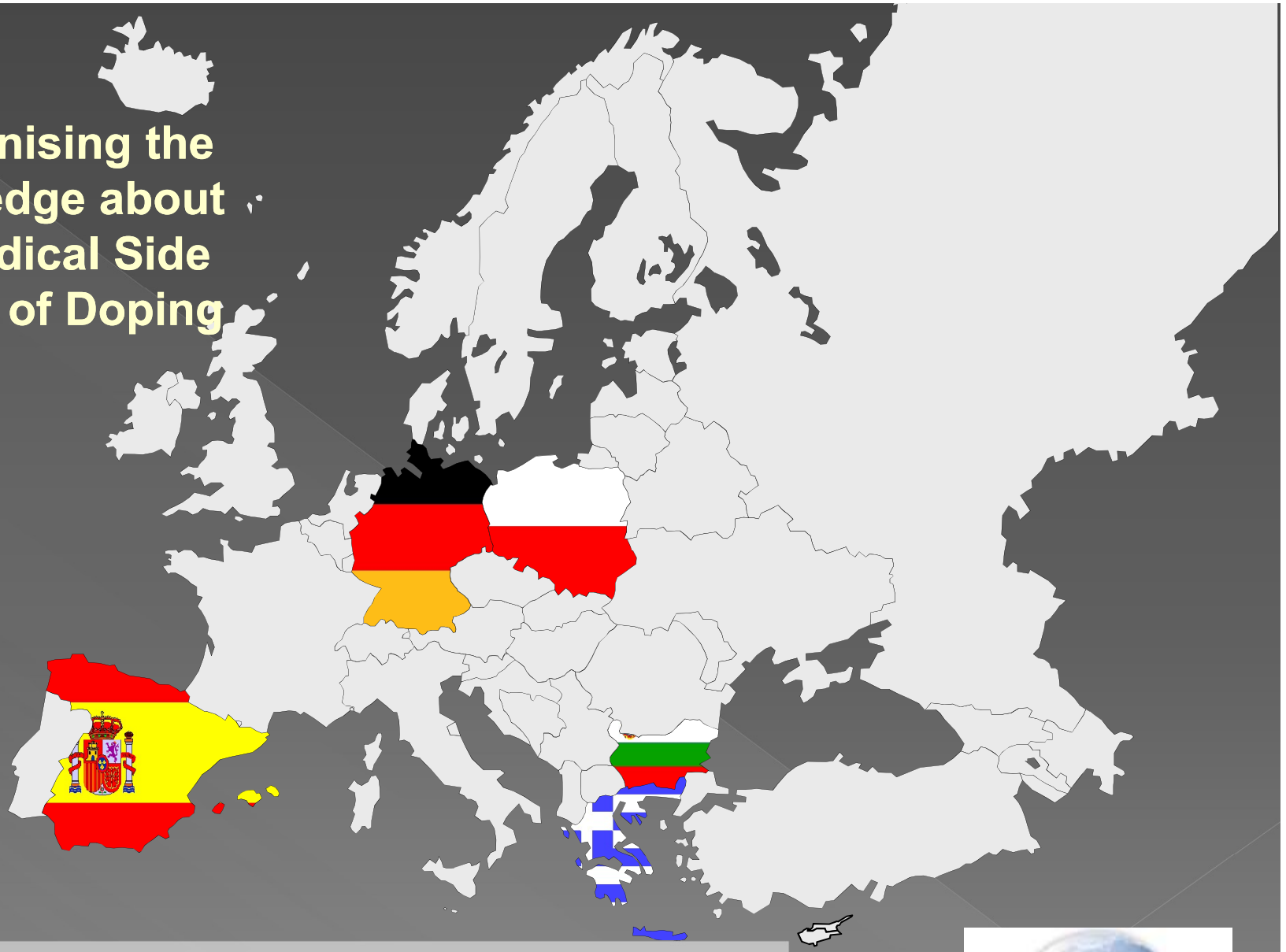
Laboratory of Sports Medicine, Aristotle University of Thessaloniki, Greece

WHAT CAN WE DO?

THE FIGHT AGAINST ABUSE OF ERGOGENIC AIDS IN SPORTS DEMANDS:



Harmonising the Knowledge about Biomedical Side Effects of Doping

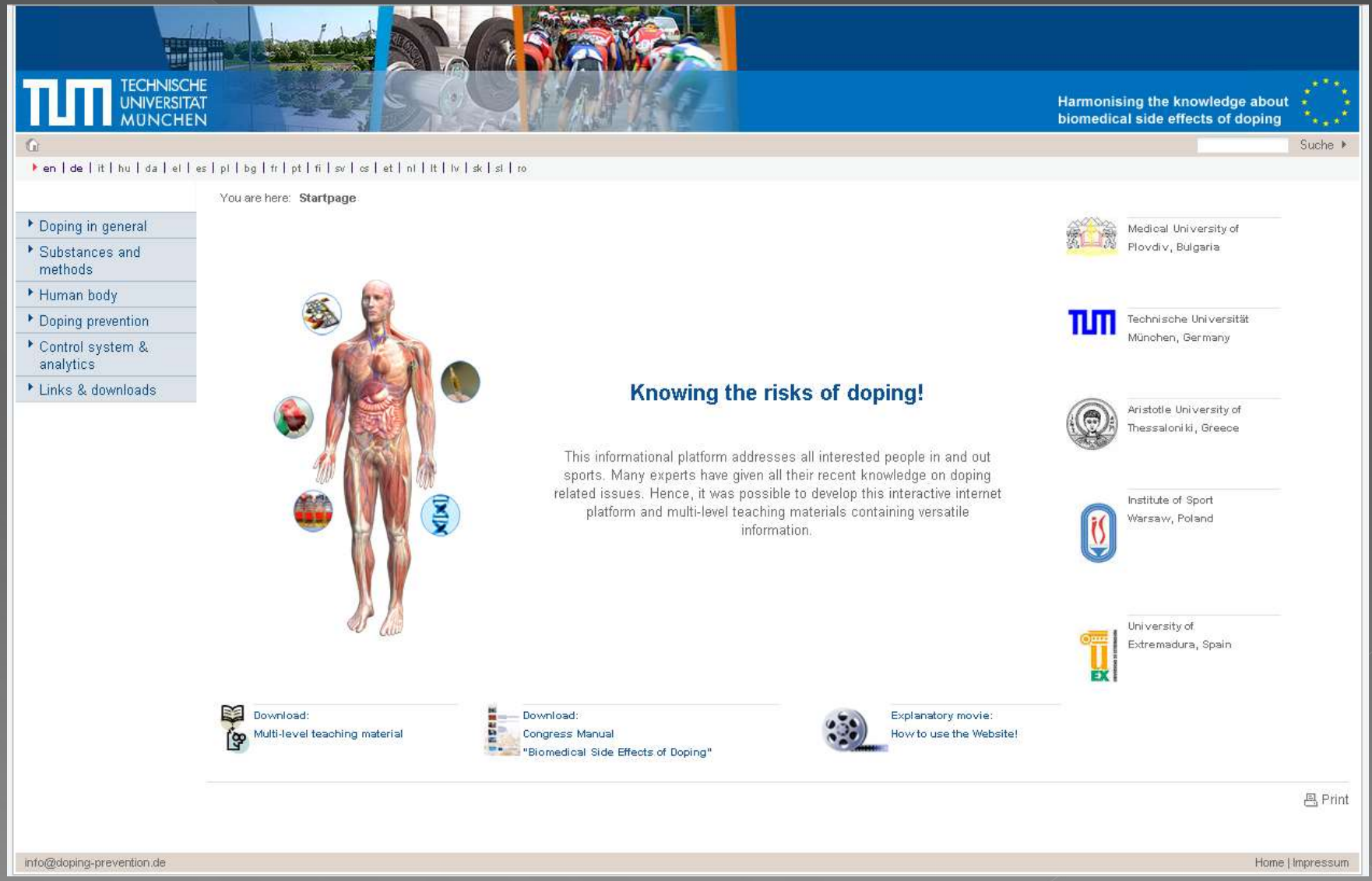


Project Partners

Medical University of Plovdiv, Department of Physiology, Bulgaria
Institute of Sport, Department of Anti-doping Research, Poland
Aristotle University of Thessaloniki, Lab of Sports Medicine, Greece
University of Extremadura, Department of Physiology, Faculty of Science, Spain
Technische Universität München, Institute of Public Health Research, Germany

Doping Prevention

www.doping-prevention.com



Search

- Doping in general
- Substances and methods
- Human body
  - Supporting apparatus and musculoskeletal system
  - Cardiovascular system
  - Respiratory system
  - Gastrointestinal system
  - Liver
  - Reproductive and endocrine system
  - Kidney
  - Electrolyte metabolism
  - Immune system
  - Skin
  - Blood
  - Central nervous system
  - Psychological effects and addiction
- Doping prevention
- Control system & analytics
- Links & downloads

Internet Explorer

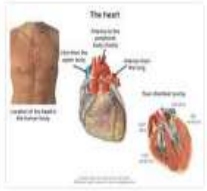
The human heart weighs between 200 to 400 grams and is a little larger than the size of a fist. The heart is located between the lungs, behind and slightly to the left of the sternum. A double-layered membrane (called the pericardium) surrounds the heart like a sac. The heart is the pump responsible for maintaining adequate circulation of oxygenated blood around the vascular network of the body.

It is a four-chamber pump...

- ...with the right side receiving desoxygenated blood from the body at low pressure and pumping it to the lungs (pulmonary circulation) and
- ...the left side receiving oxygenated blood from the lungs and pumping it at a high pressure through the body (systemic circulation).

The upper chambers of the heart are called the left and right atria, and the lower chambers are called the left and the right ventricles. A wall of muscle called the septum separates the left and the right atria and the left and the right ventricles. The left ventricle is the largest and strongest chamber in the heart. The walls of the left ventricle are only about 1 cm thick, but they have enough force to push the blood through the aortic valve. Four types of valves regulate blood flow through the heart. In particular, the tricuspid valve regulates blood flow between the right atrium and the right ventricle. The mitral valve lets oxygenated blood from the lungs pass from the left atrium into the left ventricle. The pulmonary valve controls blood flow from the right ventricle into the pulmonary arteries. The aortic valve opens the way for oxygenated blood to pass from the left ventricle into the aorta.

The heart and the circulatory system make up the cardiovascular system. The heart works as a pump that pushes blood to the organs, tissues, and cells of the body. Blood delivers oxygen and nutrients to every cell and removes carbon dioxide and metabolites. Blood is carried from the heart to the rest of the body through a complex network of arteries, arterioles and capillaries. Blood is returned to the heart through veins.




Crosstalk: › Cardiovascular system

The cardiovascular system is quite often affected by different substances and methods. Within this Crosstalk-Box you can choose the substances and methods with their specific effects on the cardiovascular system.

CROSSTALK

- Anabolic agents
- Hormones and related substances
- Beta-2 agonists
- Hormone antagonists and modulators
- Diuretics and other masking agents
- Stimulants
- Narcotics
- Cannabinoids
- Glucocorticosteroids
- Alcohol
- Beta-blockers
- Enhancement of oxygen transfer
- Chemical and physical manipulation
- Gene doping
- Nutritional supplements

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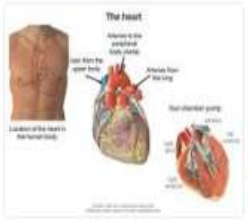
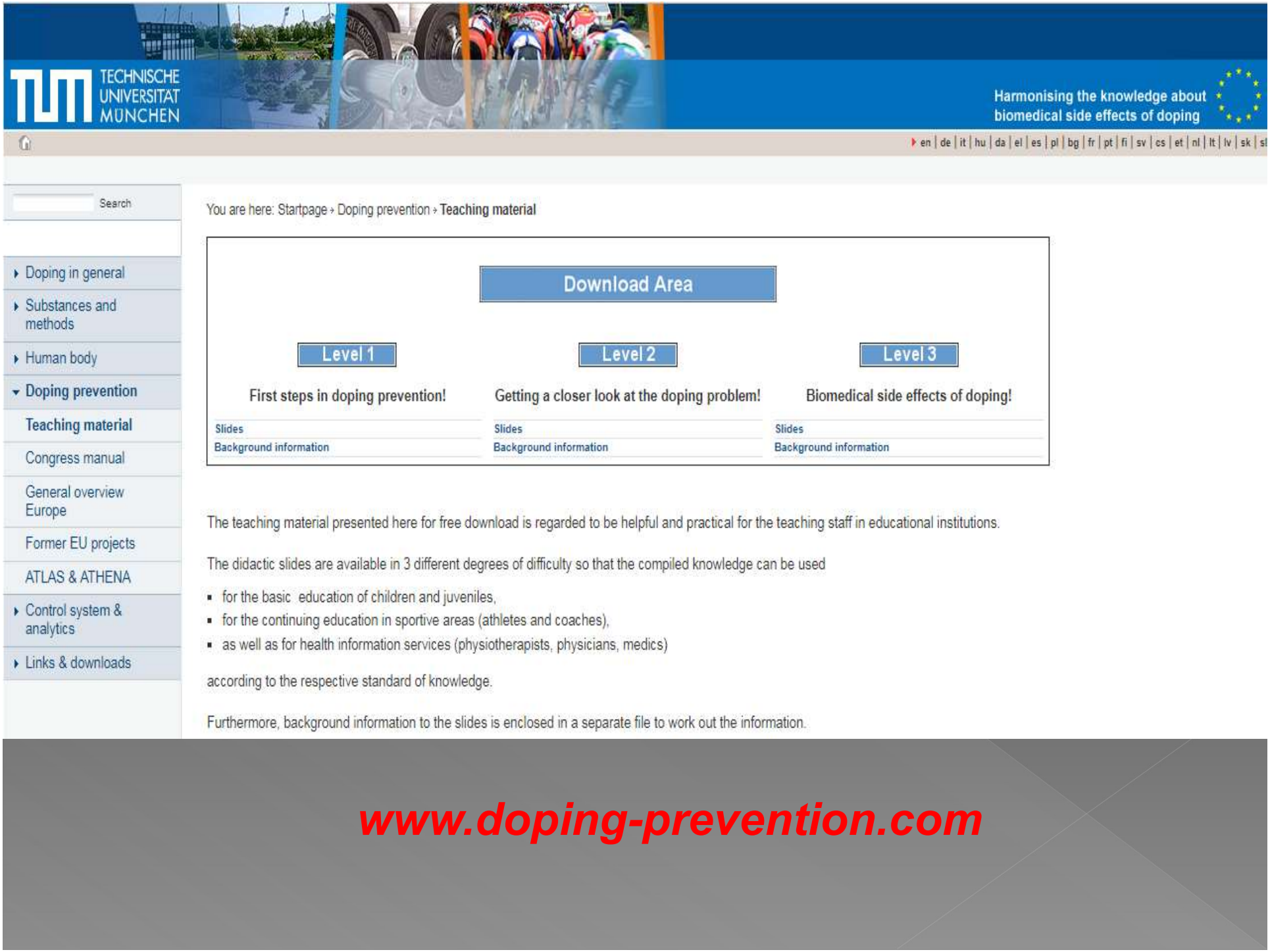


Crosstalk: Cardiovascular system ‹ **Anabolic agents**

The cardiovascular side effects of androgenic-anabolic steroids (AAS) are manifold and unclear, mainly because it is difficult to distinguish the side effects of the drugs used. Myocardial infarction and sudden cardiac death are the most serious complications. Other common cardiovascular disorders are arterial hypertension, heart failure, cardiomyopathy, arrhythmias, thrombosis etc.

Many studies have demonstrated that AAS abuse in combination with resistance training cause concentric hypertrophy of the left ventricular wall. However, not only contractible but also non-contractible elements are increased. Generalized and focal fibrosis and myofibrillar disarray are also found in autopsy of athletes consuming large amounts of AAS. Furthermore, it is reported that AASs use may lead to diastolic dysfunction and to dysrhythmias. AASs are found to affect the cardiac sympathetic nervous system and also electrolyte concentrations, which may lead to atrial or ventricular fibrillation. Sudden cardiac arrest related to adrenergic stress and documented by an extensive myocardial necrosis is also found in young athletes abusing AAS.

Use of AASs is found to lead to a significant decrease in high-density lipoprotein cholesterol and an increase in low-density lipoprotein cholesterol. Decreased fibrinolytic activity and increased clotting factors have also been reported. It is also supported that AAS and particularly androgens may increase either systolic or diastolic blood pressure.


TECHNISCHE UNIVERSITÄT MÜNCHEN
Harmonising the knowledge about biomedical side effects of doping
en | de | it | hu | da | el | es | pl | bg | fr | pt | fi | sv | cs | et | nl | lt | lv | sk | sl
Search
Doping in general
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Human body
Doping prevention
Teaching material
Congress manual
General overview Europe
Former EU projects
ATLAS & ATHENA
Control system & analytics
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for the basic education of children and juveniles,
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as well as for health information services (physiotherapists, physicians, medics)
according to the respective standard of knowledge.
Furthermore, background information to the slides is enclosed in a separate file to work out the information.
www.doping-prevention.com

CONCLUSIONS

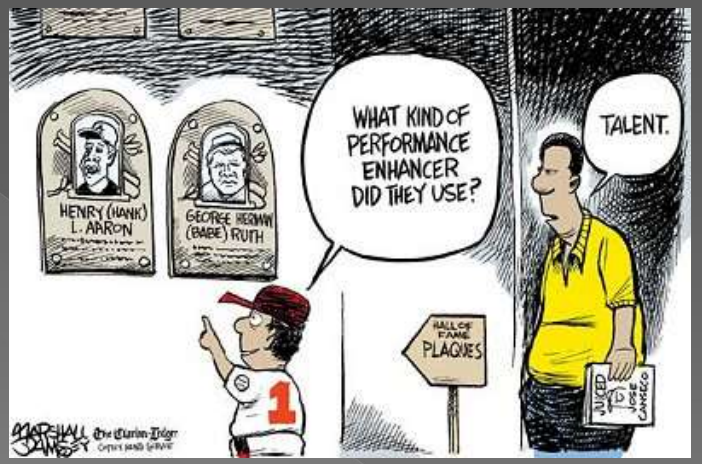
DOPING IN OUR ERA IS LIKE A WAR WITH NO END

THE USE OF NON-APPROVED SUBSTANCES IS ASSOCIATED TO A LARGE NUMBER OF MODERATE TO SEVERE CARDIOVASCULAR SIDE EFFECTS

RESEARCH & EDUCATION ARE THE MOST POWERFUL WEAPONS FOR AN EFFECTIVE FIGHT AGAINST DOPING IN SPORTS

Useful links

- ✓ **EU Project** (www.doping-prevention.com)
- ✓ **UKAD** (www.ukad.org.uk)
- ✓ **SPORTS MEDICINE LAB AUTH** (http://spmedlab.phed.auth.gr)
- ✓ **WADA** (www.wada-ama.org)
- ✓ **IAAF** (www.iaaf.org)
- ✓ **Council of Europe** (www.coe.int)
- ✓ **ANADO** (www.anado.org)



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