Moderne antiischämische Therapie der KHK

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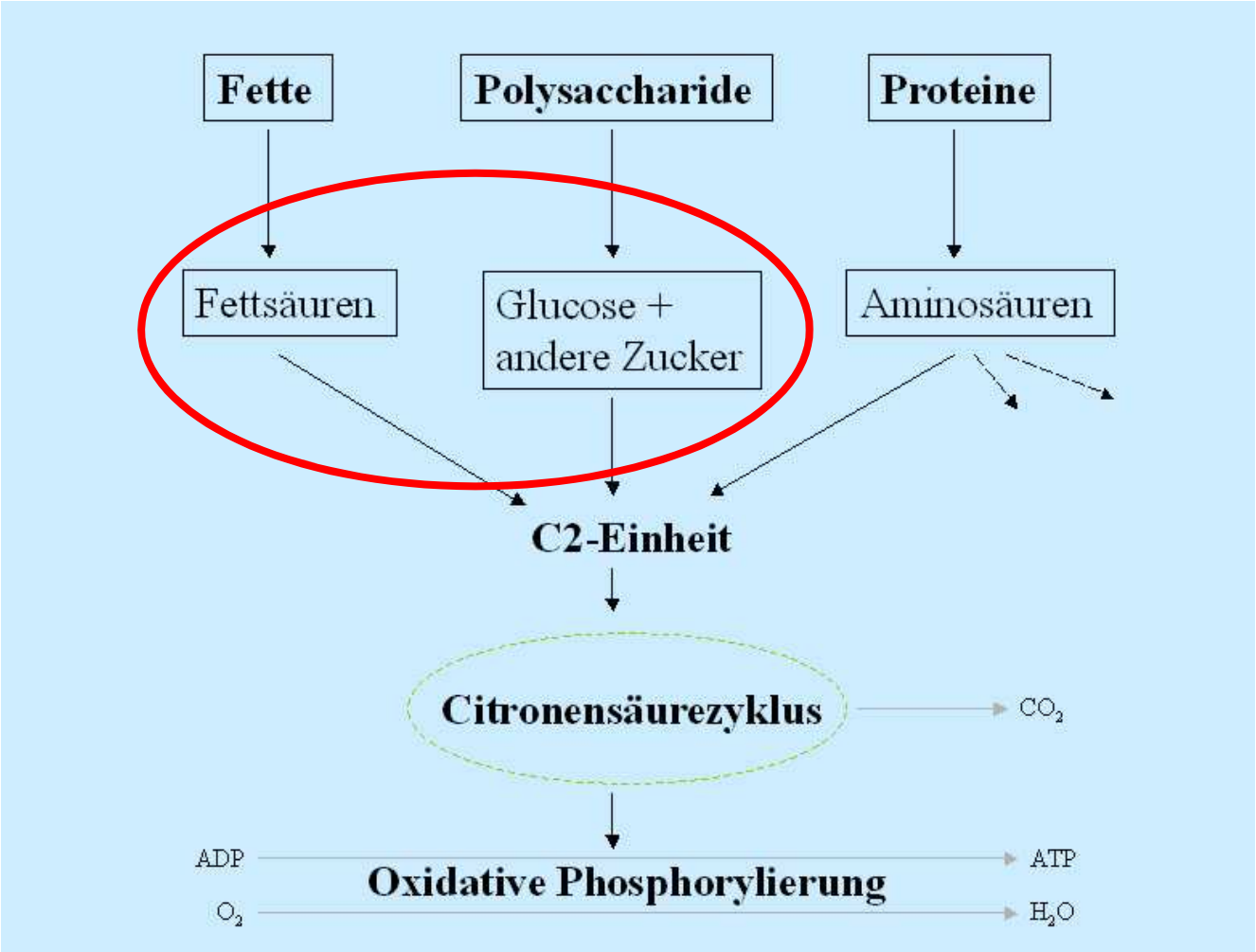
WUNDER HERZ

- Ein Motor mit 0,003 PS
- Hebt pro Tag 40 Tonnen 1 Meter hoch
- 613 200 Stunden Dauerbetrieb/70 Jahre
- 10 000 Liter/Tag; 4 Millionen Liter/Jahr
- Etwa 3 000 000 000 Schläge /70 Jahre

Energiegewinnung des Herzens



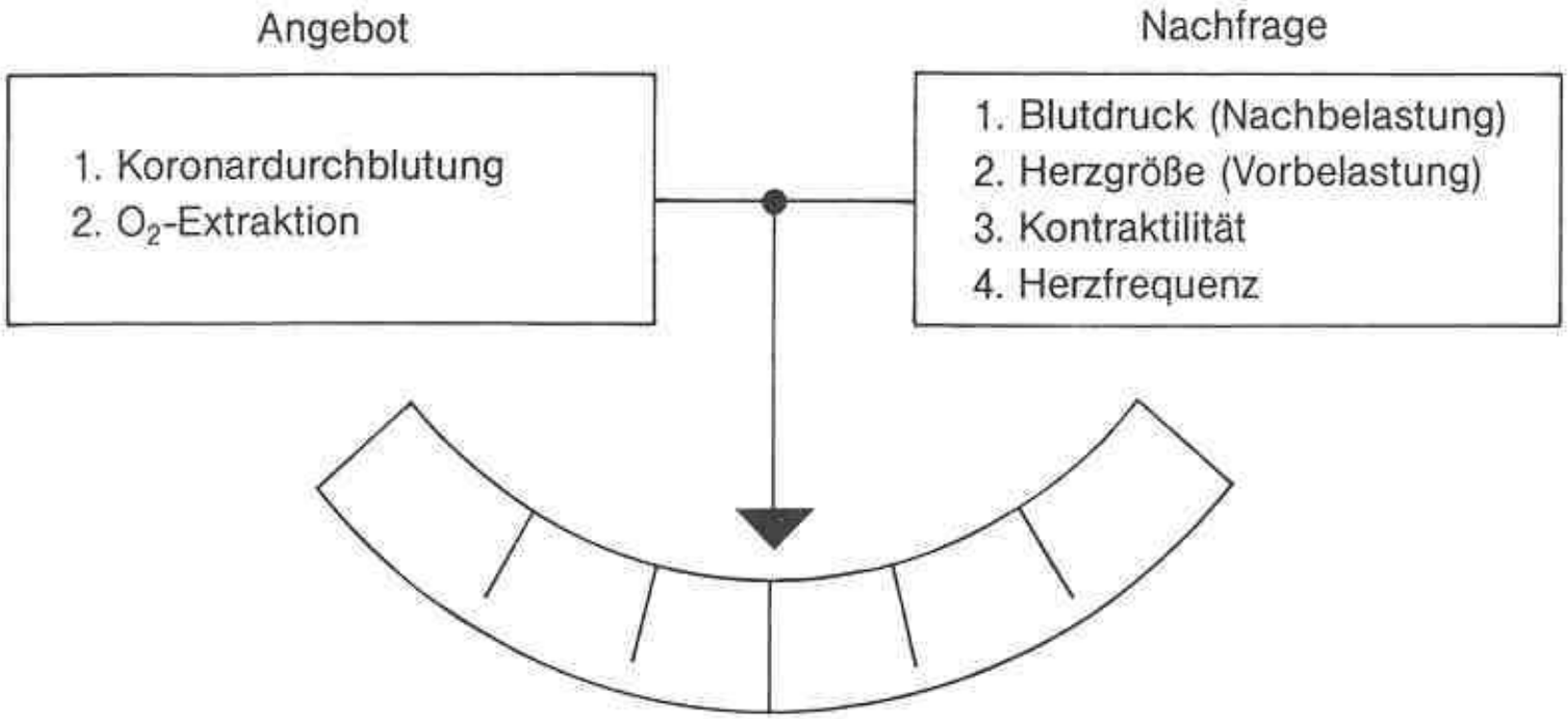
Woran sterben wir im Jahre 2020 ?

Global Burden of Disease Study

1990		2020
1. Ischämische Herzkrankheit	6.3	1. Ischämische Herzkrankheiten
2. Zerebrovaskuläre Krankheit	4.4	2. Zerebrovaskuläre Krankheit
3 untere Atemwegsinfektionen	4.3	3. COPD
4. Durchfallerkrankungen	2.9	4. Verkehrsunfälle
5. Perinatale Erkrankungen	2.4	5. Atemwegskarzinome
6. COPD	2.2	6. Untere Atemwegsinfektionen
7. Tuberkulose (ohne AIDS)	2.0	7. Tuberkulose
8. Masern	1.0	8. Krieg
9. Verkehrsunfälle	0.9	9. Durchfallerkrankungen
10.Atemwegskarzinome	0.9	10. HIV

Lancet 1997;349:1436-42

SAUERSTOFFGLEICHGEWICHT

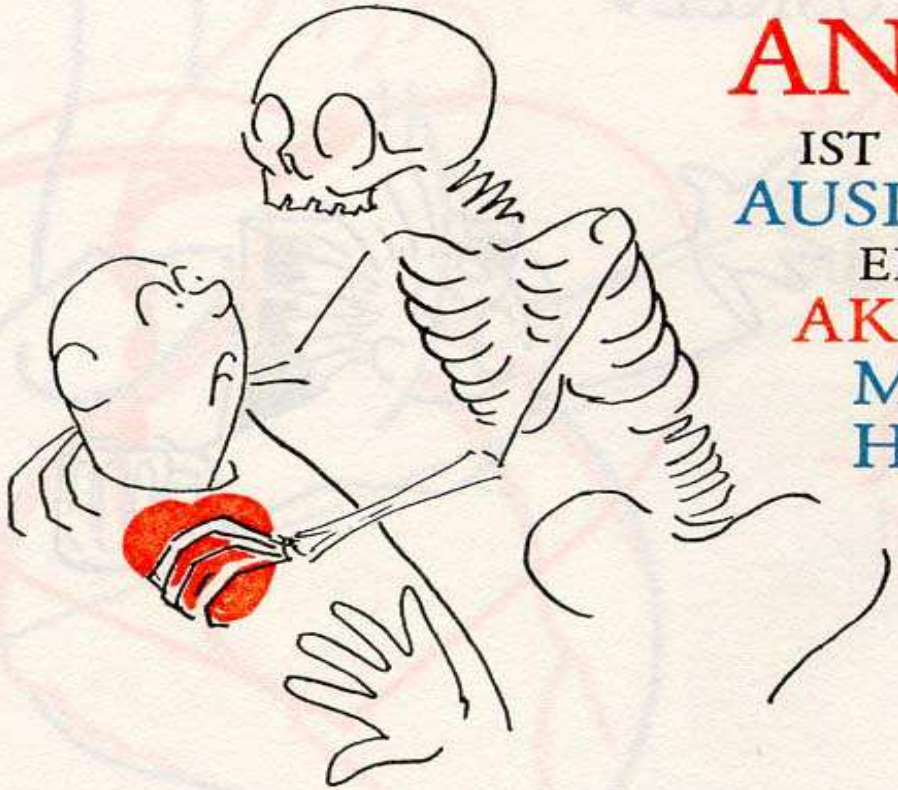


Koronarinsuffizienz

Koronarinsuffizienz = ein Mißverhältnis zwischen Sauerstoffangebot und Sauerstoff-bedarf (regional oder generalisiert)

DER

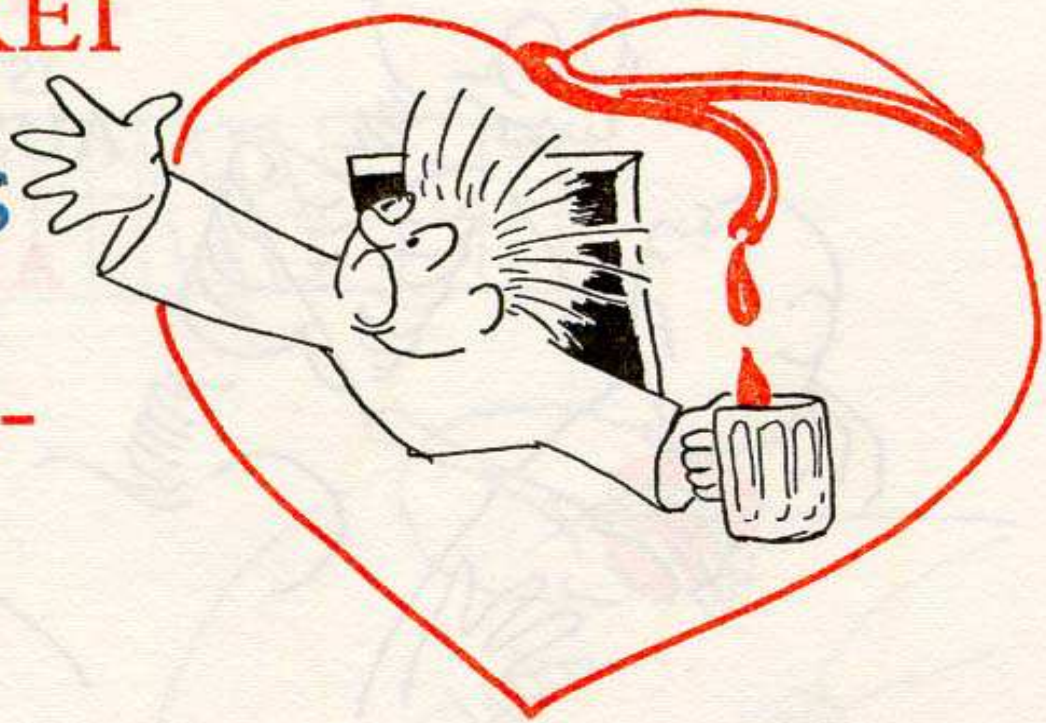
ANGINA-PECTORIS-ANFALL



IST DER
AUSDRUCK
EINES
AKUTEN
MISSVER-
HÄLTNISSES
ZWISCHEN

SAUERSTOFFBEDARF
UND
SAUERSTOFFANGEBOT
IM HERZMUSKEL **

DER SCHREI
DES
HERZENS
NACH
SAUER-
STOFF



ISCHÄMIEKASKADE

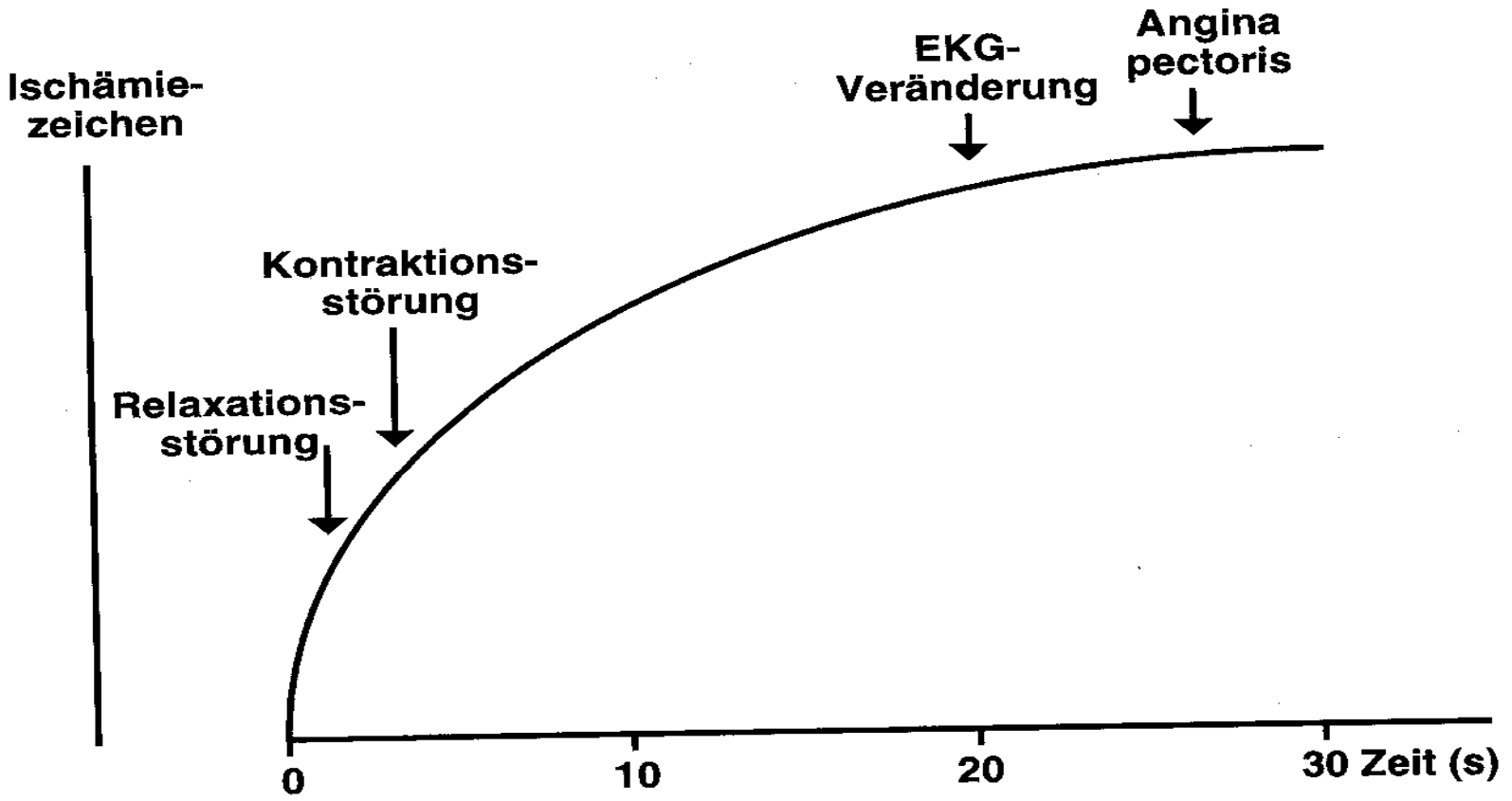
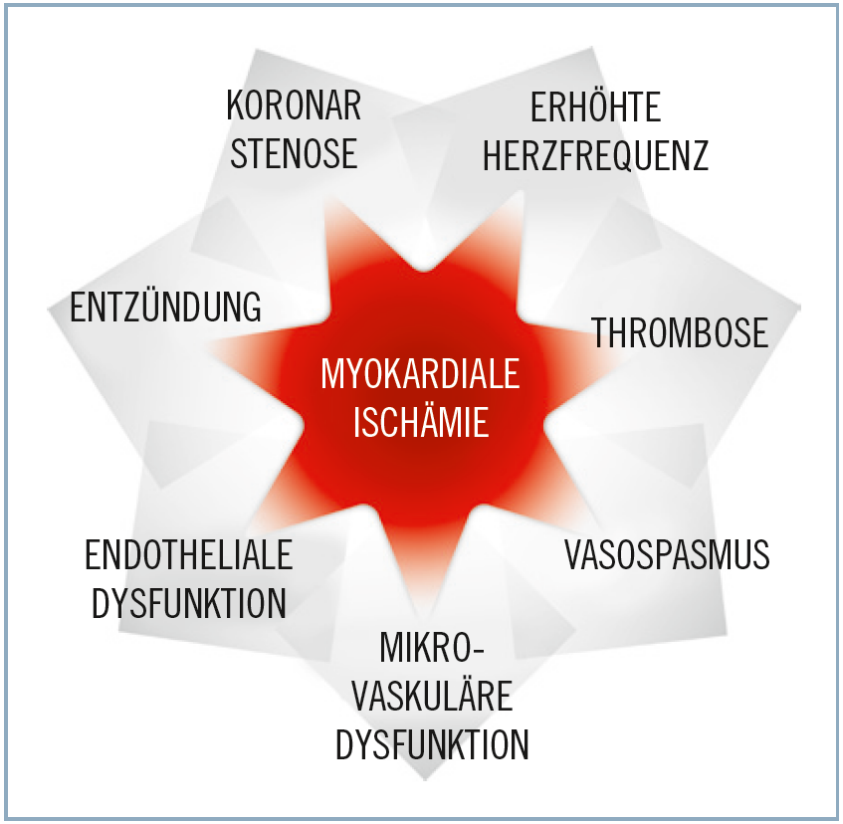


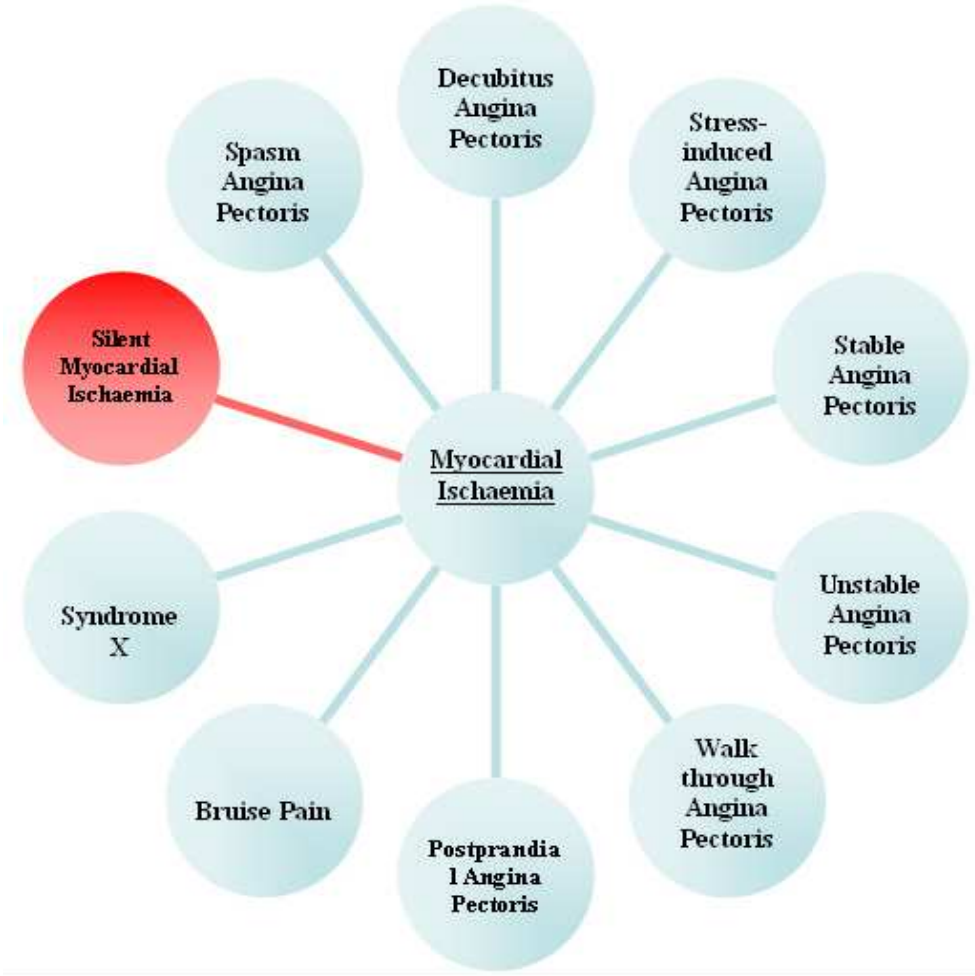
Abb. 3 ▲ **Ischämiekaskade. Zeitliche Abfolge des Auftretens von Ischämiezeichen nach Koronarokklusion im Rahmen einer Ballondilatation**

Myokardiale Ischämie ist eine multifaktorielle Erkrankung…



Zipes DP, et al., eds. Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005. Crea F, et al. Chronic Ischaemic Heart Disease. In: Camm AJ, Lüscher TF, Serryus PW, eds. The ESC Textbook of Cardiovascular Medicine. Oxford, UK: Blackwell Publishing Ltd; 2006:391-424. Stanley et al 1997, Cardiovasc Res. 1997; 33:243-257

Klinische Erscheinungsbilder der Myocardischämie



STUMME ISCHÄMIE

- Auftreten:

bei Gesunden, mittleren Alters	3 %
nach Infarkt	20 %
Anginapatienten	50 %

2/3 der ischämischen Zustände ohne Symptome der Angina pectoris ! (Frauen und Hypertoniker)
Letalität gleich hoch zwischen:
symptomatisch – asymptomatisch

Angina pectoris – Epidemiologie Österreich

Trotz leitliniengerechter Therapie

→ **100 000 Pat. symptomatisch**, weil

- antianginöse First-Line-Therapie nicht ausreichend,

  oder

- nicht vertragen

Steg et al. 2012, CLARIFY Register / State of the Art, Angina Pectoris, Österreichische Ärztezeitung, 10 , 25. Mai 2009

MEDIKAMENTÖSE THERAPIE

Die 8 Säulen der symptomatischen Therapie bei stabiler Angina pectoris

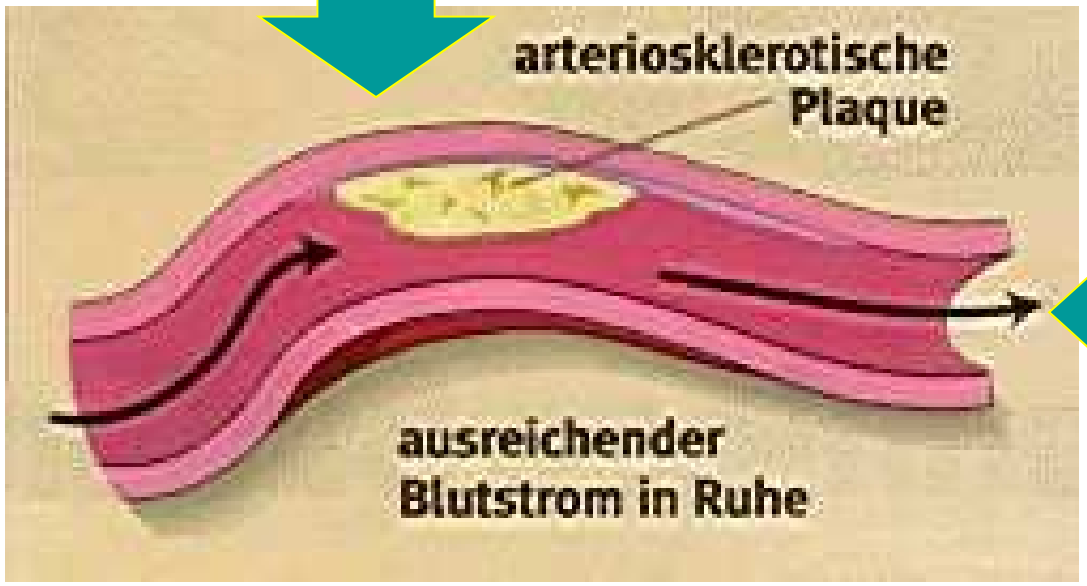
- 1. Nitrate / Molsidomin
- 2. ß-Blocker
- 3. Kalziumantagonisten
- 4. *Katp* Kanal Öffner (Nicorandil)
- 5. *Kif* Kanal Blocker (Ivabradin)
- 6. Metabolische und andere Modulatoren (Ranolazin, Trimetazidin (Vastarel)
- 7. Altbewährte Mittel

Pharmakologische Therapie

Prognose verbessernde Medikamente

Symptome verbessernde Medikamente

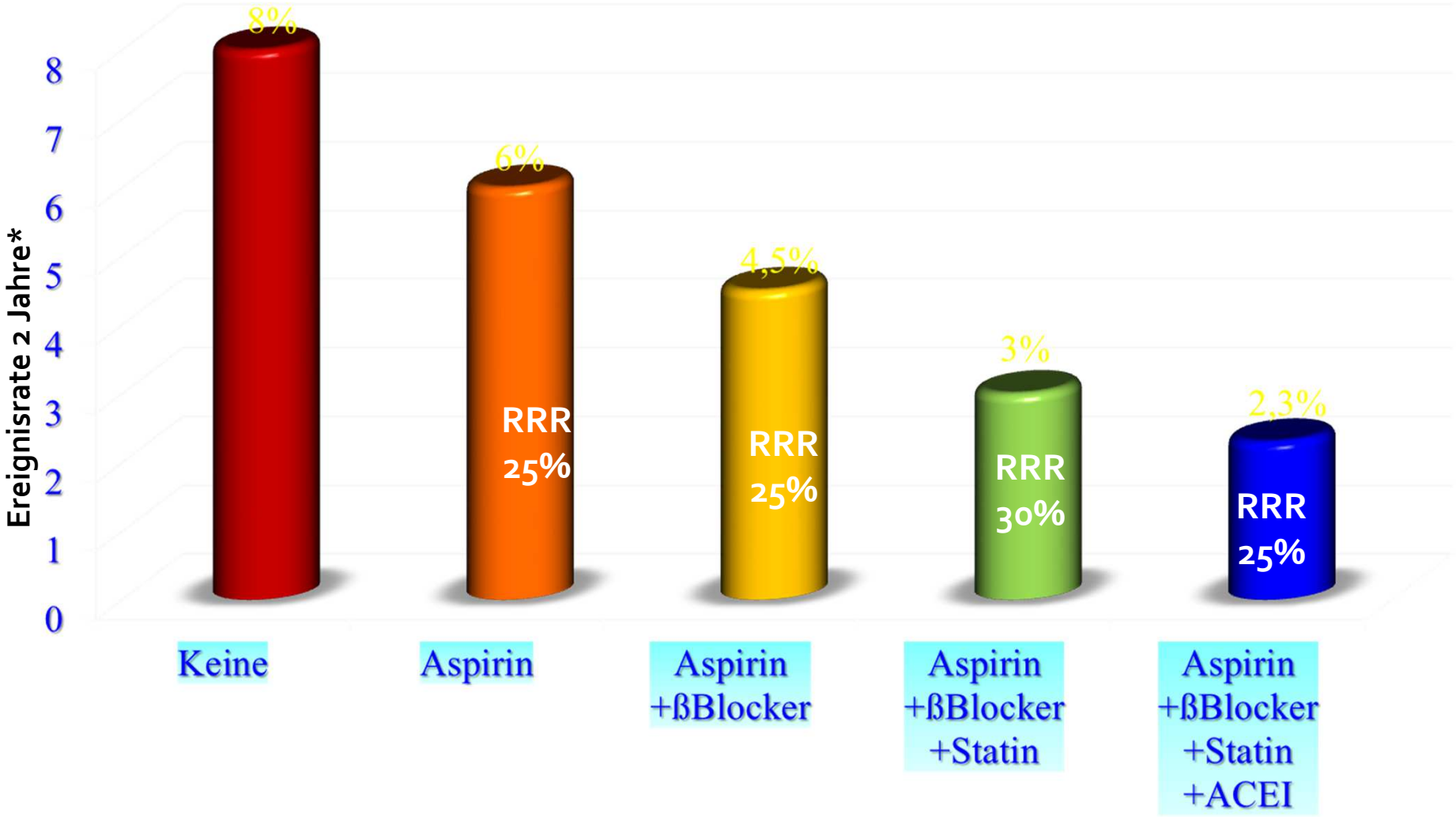
Aspirin, Plavix
ACE-Hemmer
Statine



ß-Blocker
Ca Blocker

Nitrate
Nicorandil

Prognose verbessernde Medikamente



*CV✞, AMI, Apoplex

Yusuf, Lancet 2002; 360: 2

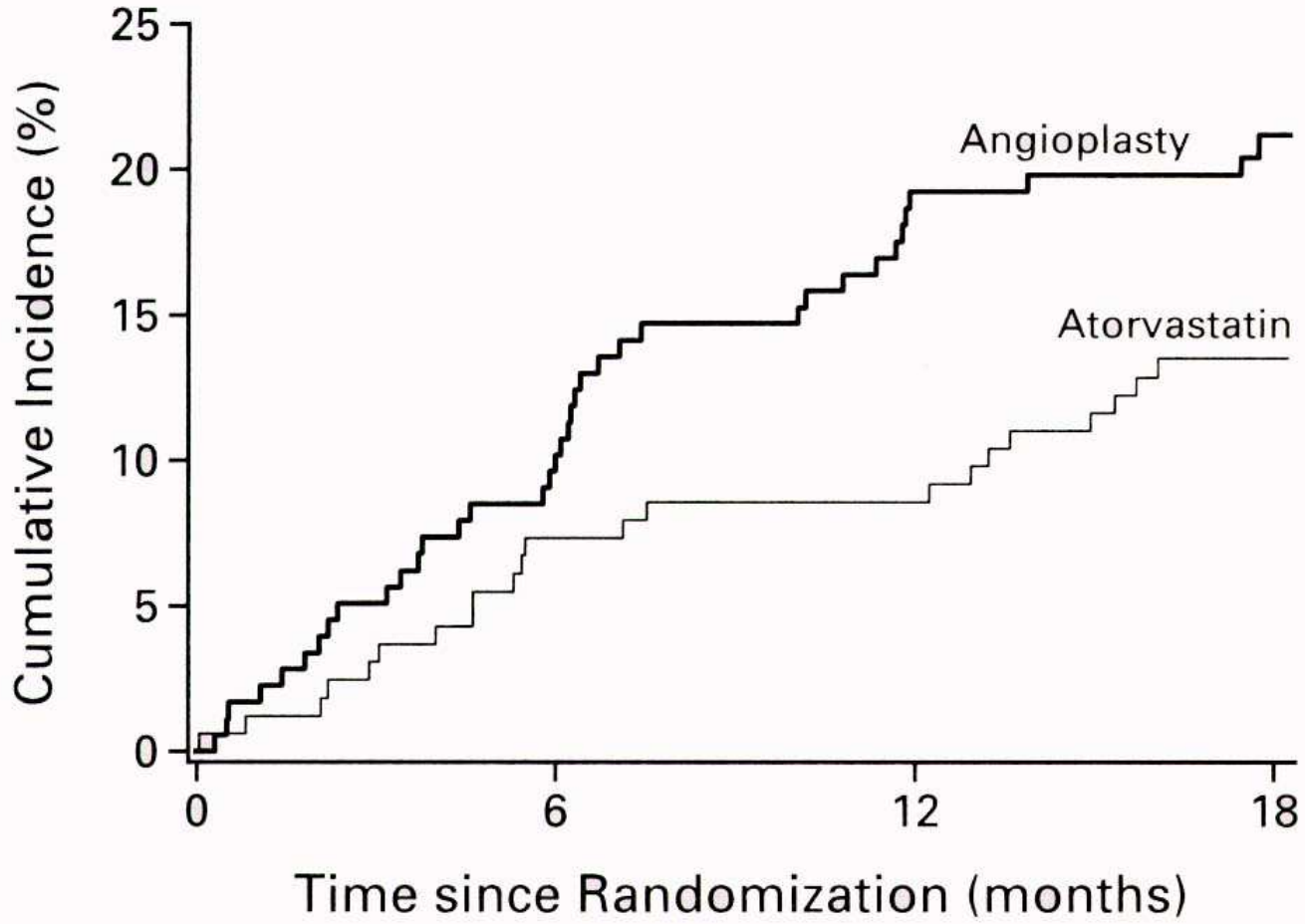


Figure 2. Cumulative Incidence of First Ischemic Events.

The time to an ischemic event was significantly longer in the atorvastatin group (P=0.03), and the risk reduction was 36 percent (95 percent confidence interval, 5 to 67 percent).

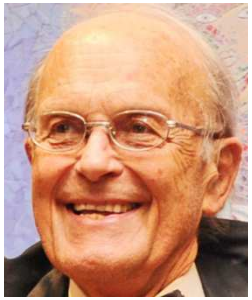
So gut wie ASS, Statin und RR-Senker

PRODUKT (tägliche Menge)	RISIKOREDUKTION in %
Mandeln (68g)	12,5
Knoblauch (2,7g)	25,0
Obst/Gemüse (400g)	21,0
Bitterschokolade (100g)	21,0
Wein (150ml)	32,0
Fisch (4x/Wo 114g)	14,0

BMJ 2004;329:1447ff

Unterschiedliche Therapieansätze

"The heart is more than a pump. It is also an organ that needs energy from metabolism."



Prof. Lionel Opie

Director Emeritus of the Hatter Institute for Cardiovascular Research at the University of Cape Town

Opie L. Lancet.1999;353:768-769.

Metabolismus/Metabolomics wird in den kommenden Jahren weltweit die Hauptzielrichtung in der nicht-intervetionellen kardiovaskulären Forschung sein.

Metabolische Modulatoren

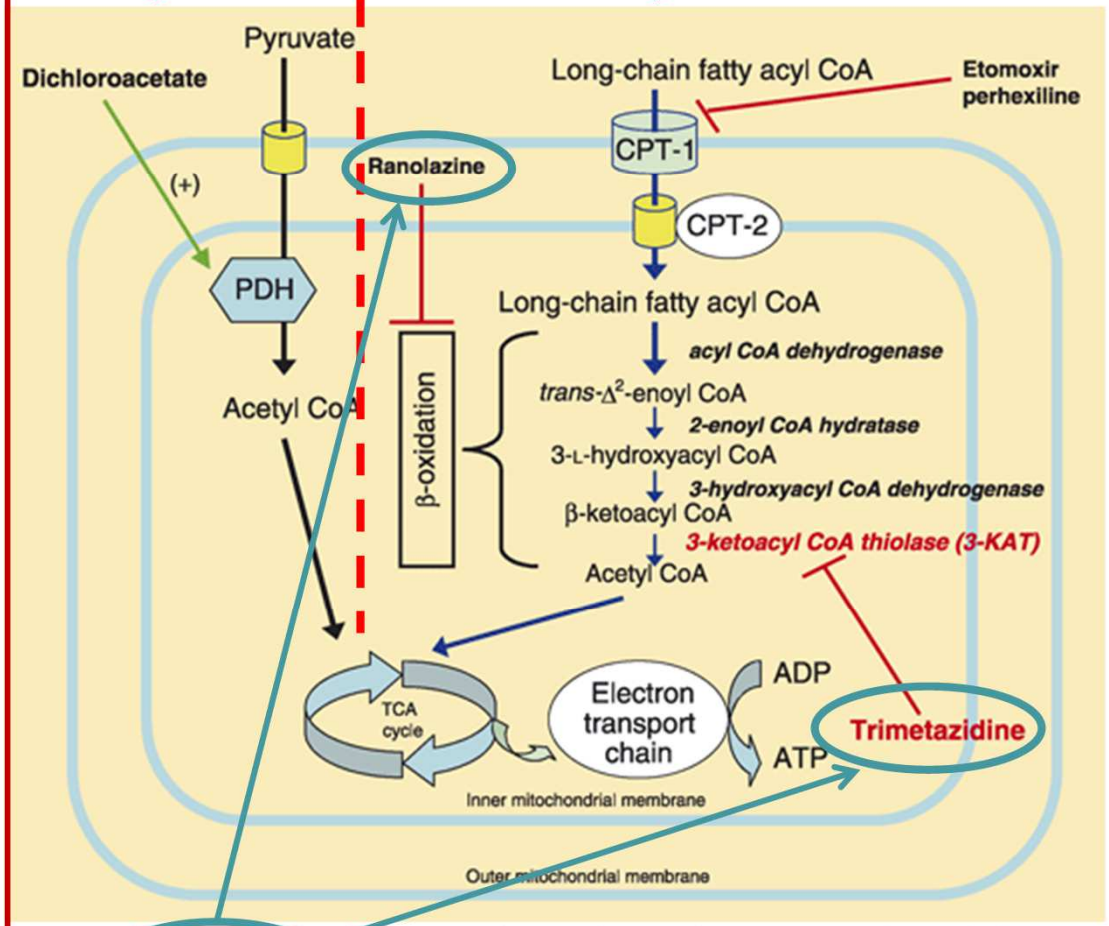
1. **Direkte Hemmer der ß-Oxidation**
   Trimetazidine (Vastarel)
   Ranolazine (Hemmt auch Ca/Na; Ranexa)

2. **Hemmer der Carnitin - Palmitoyl - Transferase im Fettsäurestoffwechsel**
   Perhexilin
   Etoxomir
   Oxfenicin

Targets im ischämischen Metabolismus

Förderung des glycolytischen Pathways

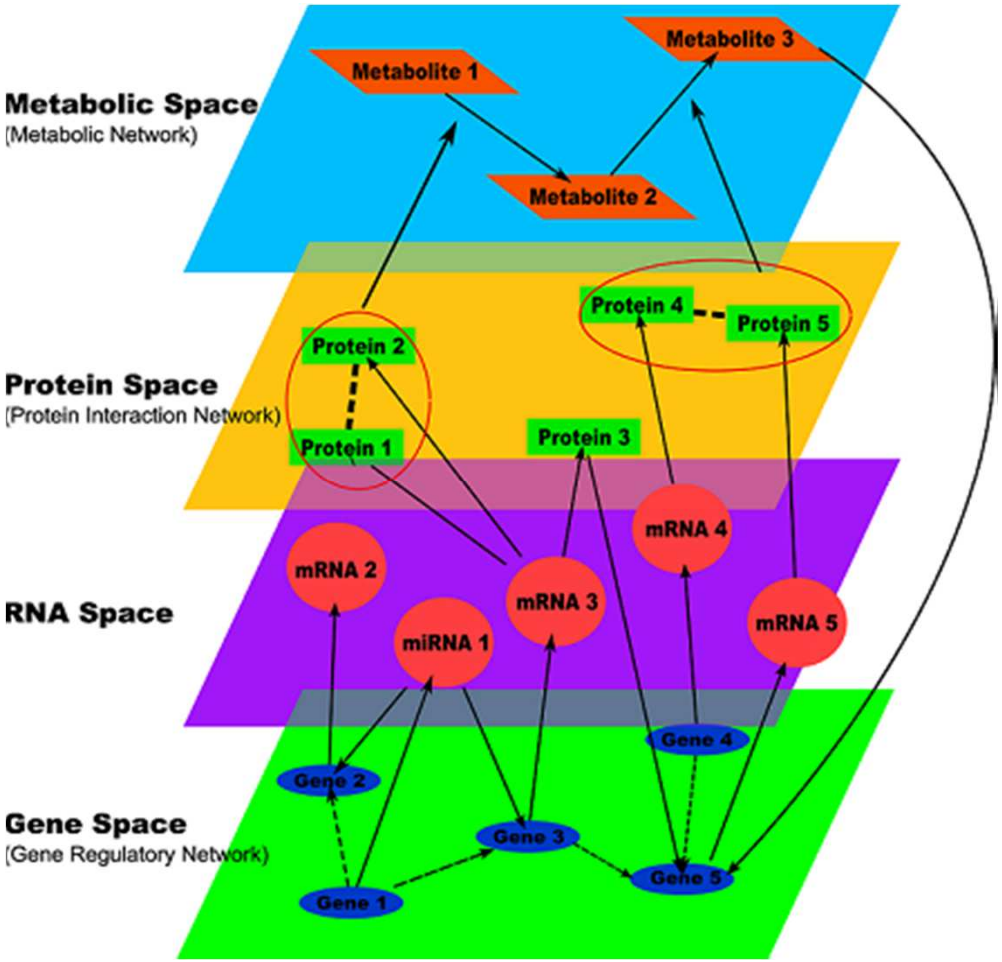
Hemmung des Fettsäure-metabolismus



Im Handel

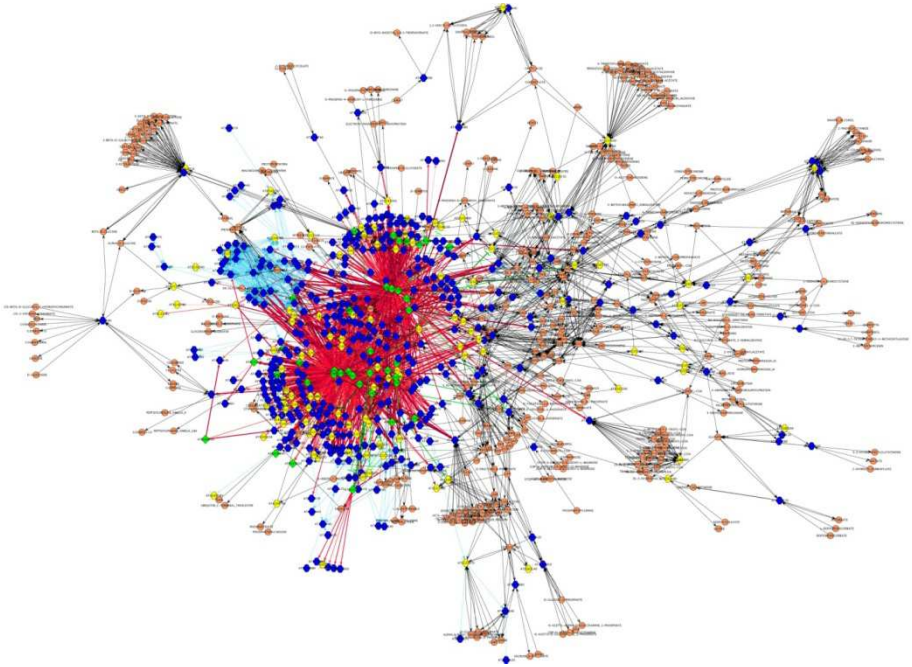
- Usher and Lopaschuk, Heart and Metabolism 2006; 32

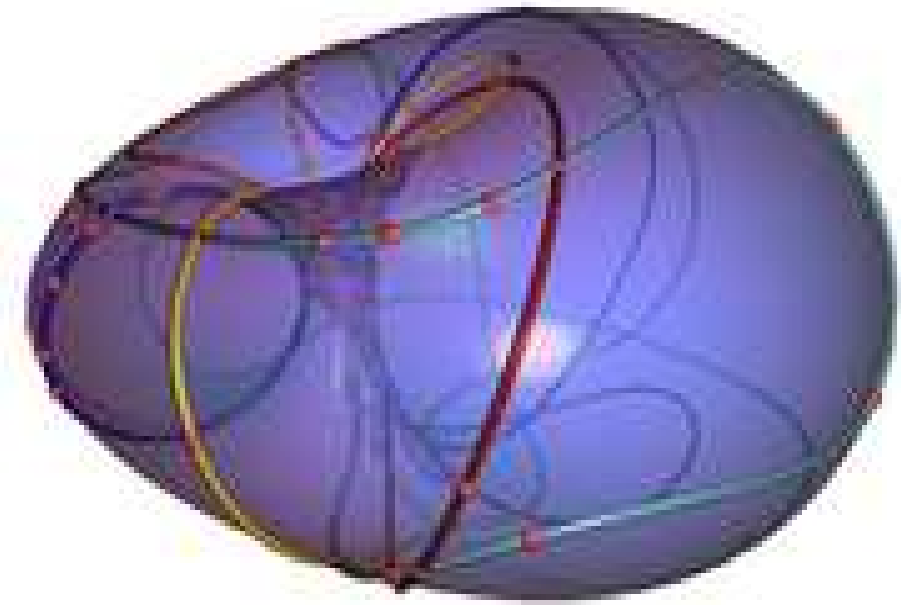
Genomics, Transcriptomics, Proteomics und Metabolomics des ischämischen Herzens



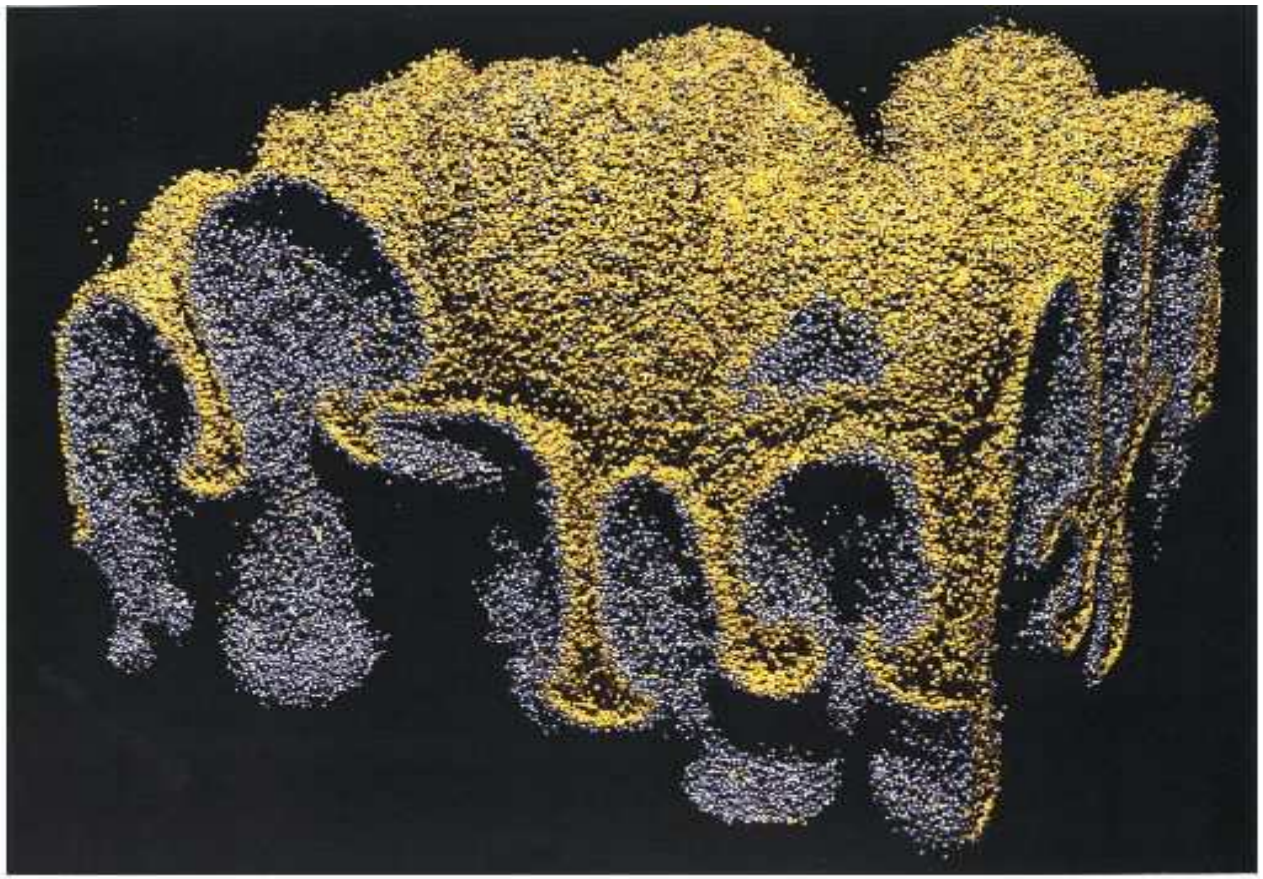
Zahllose retro- und anterograde Mechanismen steuern den ischämischen Metabolismus auf mehreren Ebenen

Gegenwärtiger Kenntnisstand: Molekulare Veränderungen am ischämischen Herzen



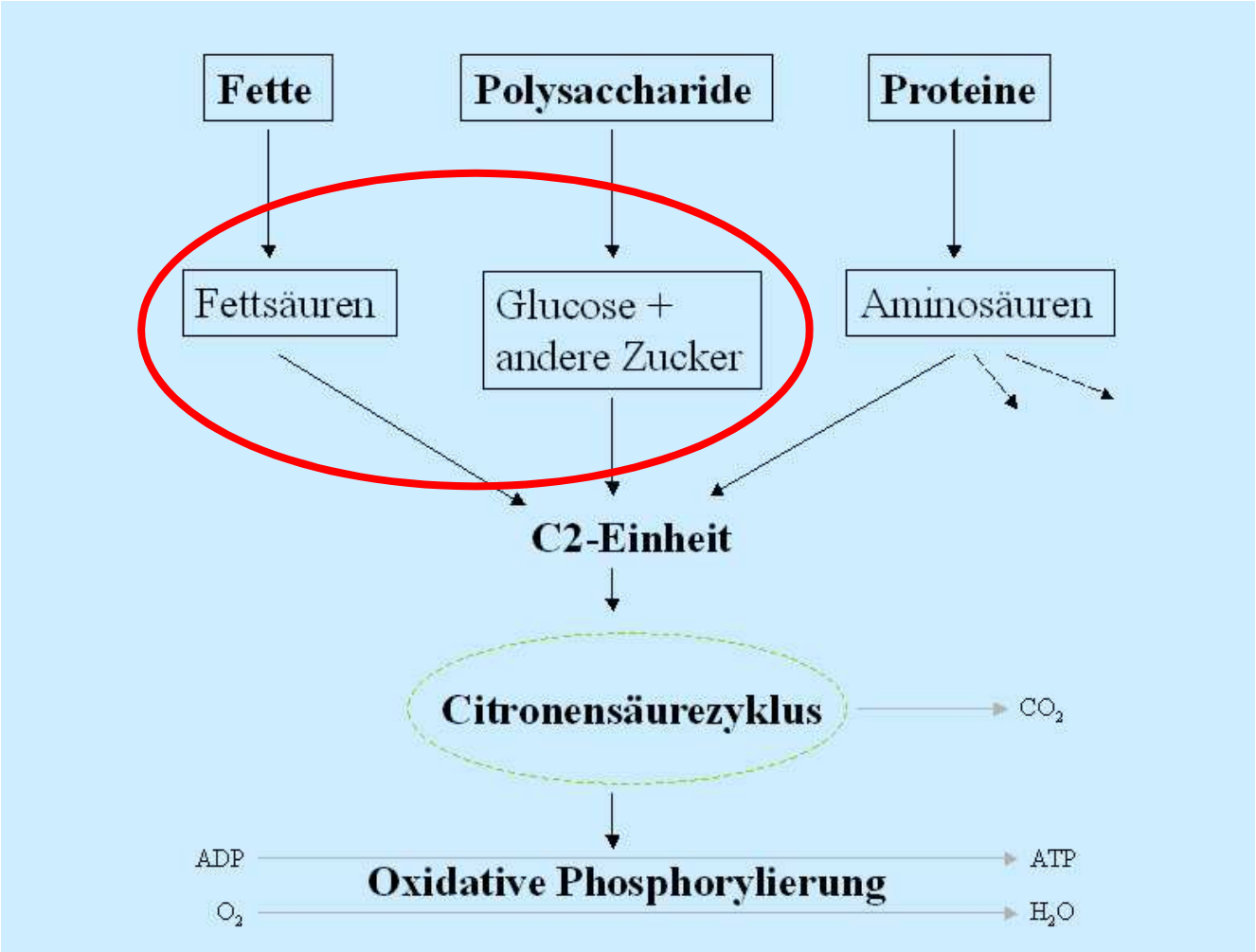


Molekulare metabolische Netzwerke im Bereich eines Mitochondriums



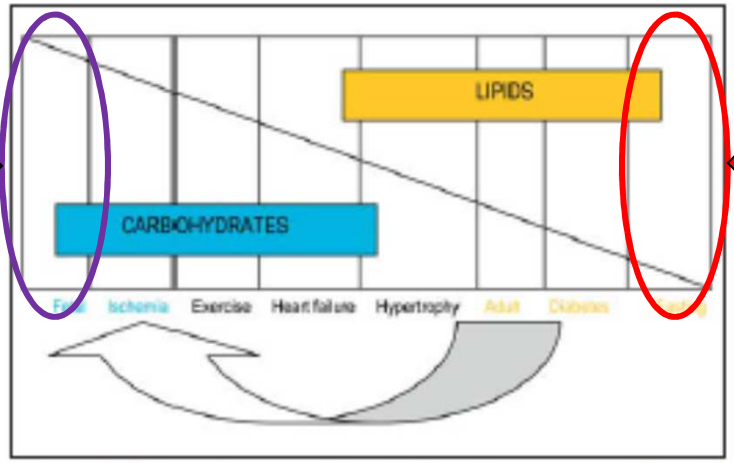
- Jeder Punkt symbolisiert ein molekulares Netzwerk. Man vermutet, daß es ca. 500 000 verschiedene molekulare Netzwerke gibt, welche mit dem zellulären Metabolismus verbunden sind
  - D. Noble Oxford, 2006; Stelling et al 2006, Nature 420, 190-193

Es ist einfacher, den kardialen Metabolismus über seine *Substrate* zu verstehen, als über seine molekularen Netzwerke



Phänotypische Plastizität des myokardialen Metabolismus aus Sicht der Substrate

Fetaler Stoffwechsel, Mischblutcyanose, Dauerhypoxie, Hypoxietoleranz durch Bevorzugung von Glucose als Substrat



Erwachsenenstoffwechsel, vorwiegend Fettsäuren, ausreichend O2 im Blut vorhanden

Figure 6. Plasticity of myocardial metabolism: during exercise, hypoxia/ischemia etc myocardial cells prefer glucose as a substrate. Both fasting and diabetes shift the metabolic substrates to the fatty acid site [29, 33].

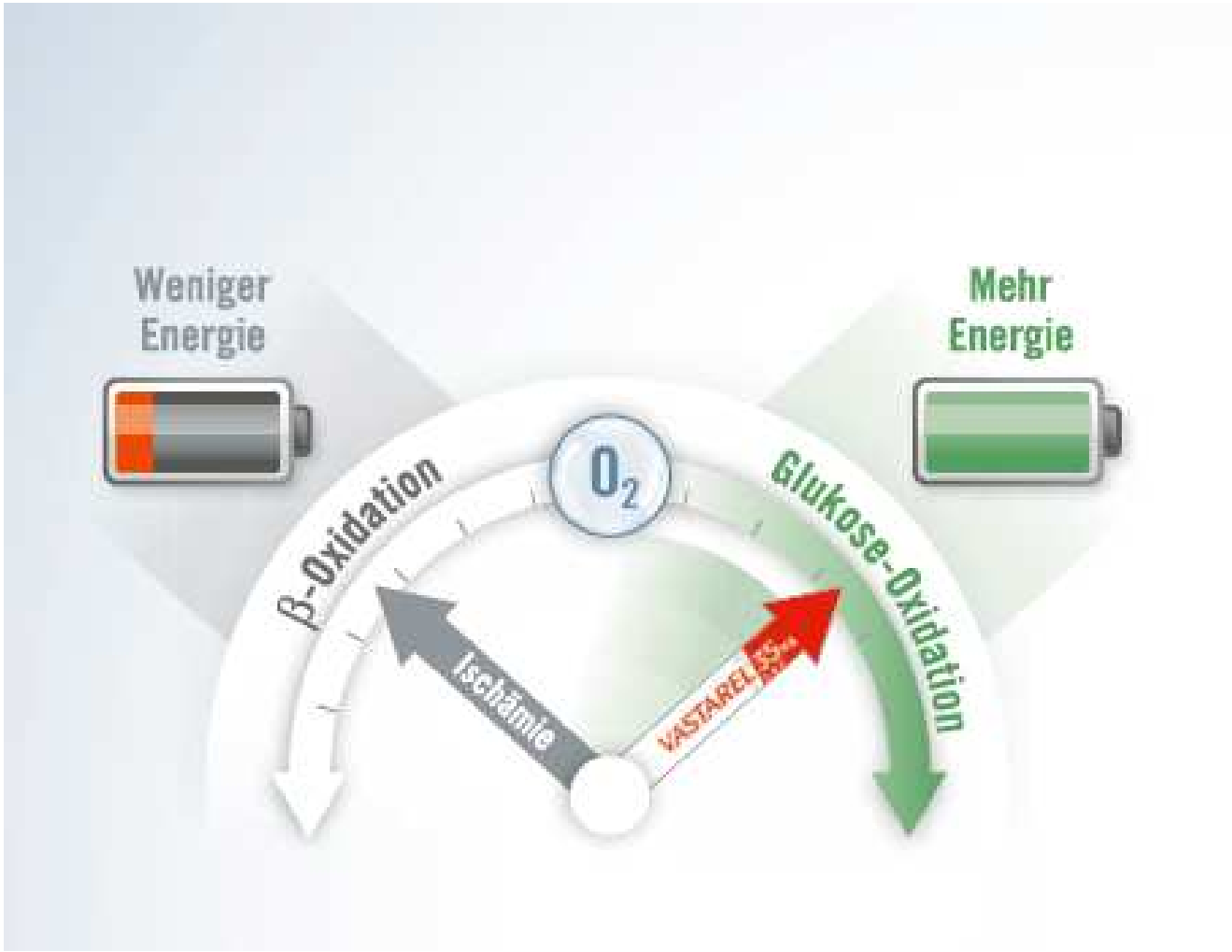
- Das Herz ist in der Lage, verschiedenste Substrate zu verstoffwechseln. Während in Ruhe, bei Diabetes mellitus und unter Fasten vor allem Fettsäuren als Substrat dienen, benützt das Herz unter Hypoxie/Ischämie zunehmend Kohlehydrate um seinen Energiebedarf zu decken und bewegt sich somit zum fetalen Phänotypus zurück.
  - Gasser R. et al.: JCBC 2006

Targets im ischämischen Metabolismus

Hemmung des Fettsäuremetabolismus:

- Die Carnitine Palmityl Transferase (CPT-1) ist ein Schlüsselmolekül für die Aufnahme von Fettsäure in die Mitochondrien zur Oxidation. Die Hemmung von CPT-1 durch Etoximir oder Perhexilin hemmt somit den Fetsäuremetabolismus und verschiebt das Gelichgewicht zum Glucosemetablismus, was während Ischämie günstiger ist.
  - » Lee et al, Circulation 2005; Schmidt-Schweda et al, Clin Scie 2000
- Die Fettsäureoxidation kann auch direkt gehemmt werden (Trimetazidine, Ranolazin) „Direct inhibition of fatty acid oxidation represents another approach to optimizing cardiac energetics".
  - » Fragasso, Int J Clin Pract 2007; El-Kady, Am J Cardiovasc Drugs 2005

Targets im ischämischen Metabolismus



Ranolazin (Ranexa)

- **<u>Wirkmechanismus:</u>**
  - Hemmung der myocardialen ß-Oxidation
  - Na-Kanalblockade mit Reduktion von Nai und über Na/Ca Exchanger Reduktion von Cai
  - In Folge Reduktion des O2-Verbrauches über Kontraktilität
  - Ähnliche Wirkung wie Ca-Antagonisten

  Möglicherweise auch gegen diastolische Steiffigkeit, diastolische Herzinsuffizienz (?)…viel beforscht, wenig klinische Relevanz

Schlüsselstudie: CARISA (add on zu normaler antianginöser Therapie)

Trimetazidine (Vastarel)

Mechanismus	Grundprinzip	Wirkung
Vermindert Fettsäureoxydation	Shift vom Erwachsenen Phänotyp zum embryonalen Phänotyp des Stoffwechsels	Erhöht Glucoseverbrauch Verstärkt die Glycolyse Erhöht die Pyruvatoxidation
Führt Fettsäuren der Zellmembran zu		ATP Produktion erhöht O2consumtion vermindert Reduziert den Laktatanfall Vermindert H+accumulation Reduziert die intrazelluläre Acidose Vermindert Calcium Overload Reduziert den Anfall freier Radikale Reduziert Zellschäden
Erhöht die Effinzienz des Herzmuskels Erhöht das Überleben von Cardiomyocyten während Ischämie		

2013 ESC Guidelines on the Management of Stable Coronary Artery Disease

- 7.1.3.3.6 **Trimetazidine** is an anti-ischaemic metabolic modulator,312 with similar anti-anginal efficacy to propranolol in doses of 20 mg thrice daily. The heart rate and rate × pressure product at rest and at peak exercise remained unchanged in the trimetazidine group, thus showing a **non-mechanical anti-ischaemic action**.
- Trimetazidine (35 mg twice daily) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the EMA in June 2012,315 and remains **contra-indicated in Parkinson's disease and motion disorders** [such as tremor (shaking), muscle rigidity and walking disorders and restless leg syndrome].
- In diabetic persons, trimetazidine improved HbA1c and glycaemia, while increasing forearm glucose uptake.316

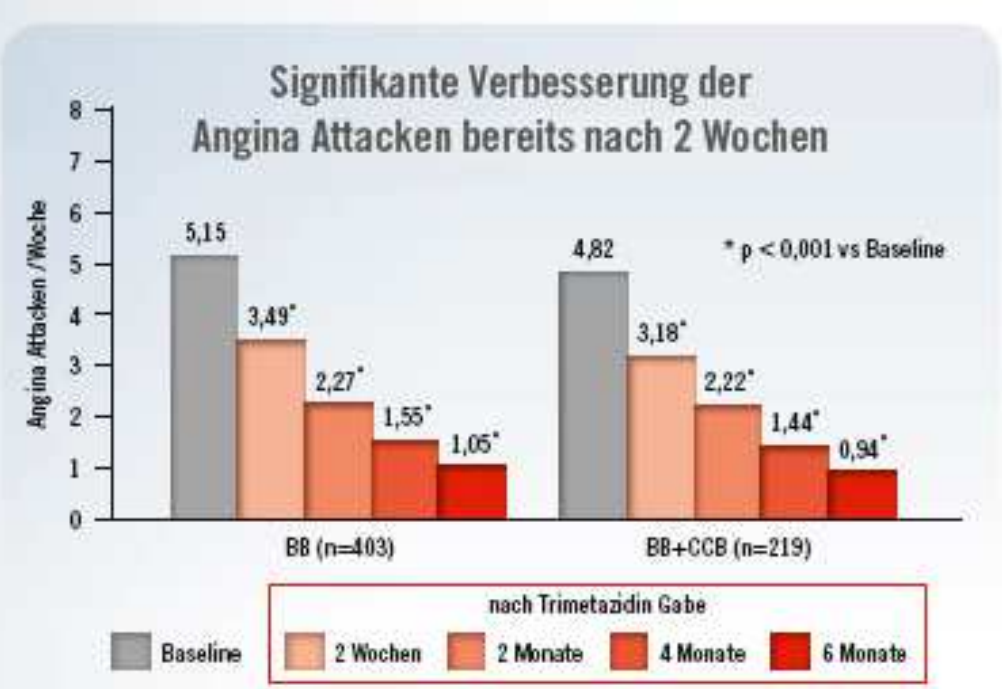
Trimethazidin erhöht die Hypoxietoleranz

Trimetazidine Effekte auf hämodynamische Faktoren

-

Class of drug	Oxygen Supply	Oxygen Demand			
	Coronary blood flow	Heart rate	Arterial pressure (after load)	Venous return (preload)	Myocardial contractility
Beta-Blockers	No effect	↓↓	↓	No effect	↓
Ca^{2}+-antagonists Dihydropyridines	↑↑	↑ (Reflex)	↓↓	↓	↓
Ca^{2}+-antagonists Diltiazem	↑	↓	↓	↓	↓
Long-acting nitrates	↑	↑ (Reflex)	↓	↓↓	No effect
Trimetazidine	No effect	No effect	No effect	No effect	No effect

Angina Attacken

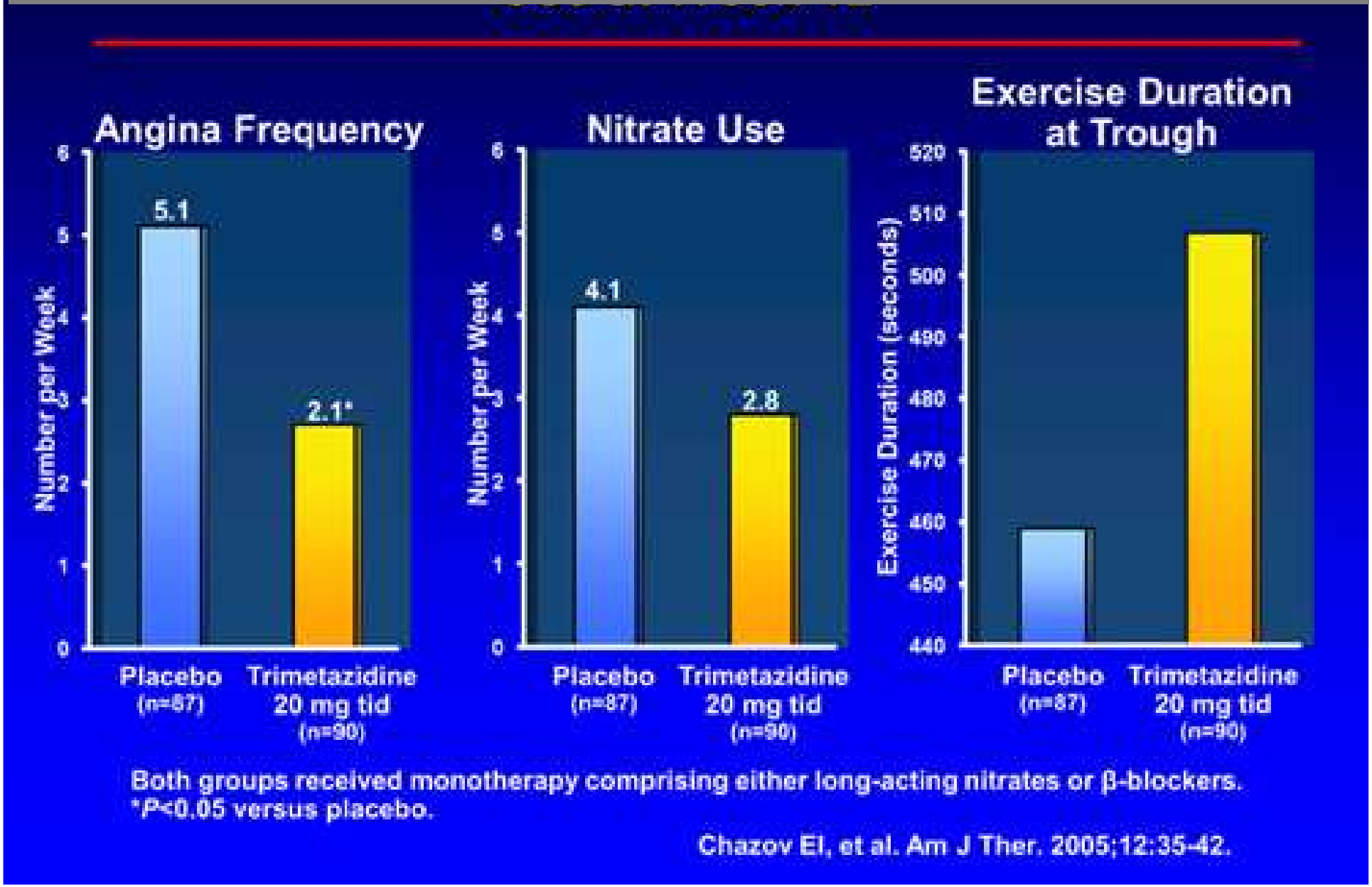


Reduktion der Angina Attacken um 80% nach 6 Monaten

„Die direkte Kombination von Trimetazidine mit ß-Blockern ist der schnelle und effizienteste Weg, Angina-Entlastung zu erreichen."[16]

(Glezer M et al., 2017)

TACT Studie: Trimetazidin (Vastarel) bei stabiler AP:
Verringerung der Anfallshäufigkeit und des Nitratverbrauches sowie zu einer Erhöung der **Leistungsdauer** in der Ergometrie



2013 ESC Guidelines on the Management of Stable Coronary Artery Disease

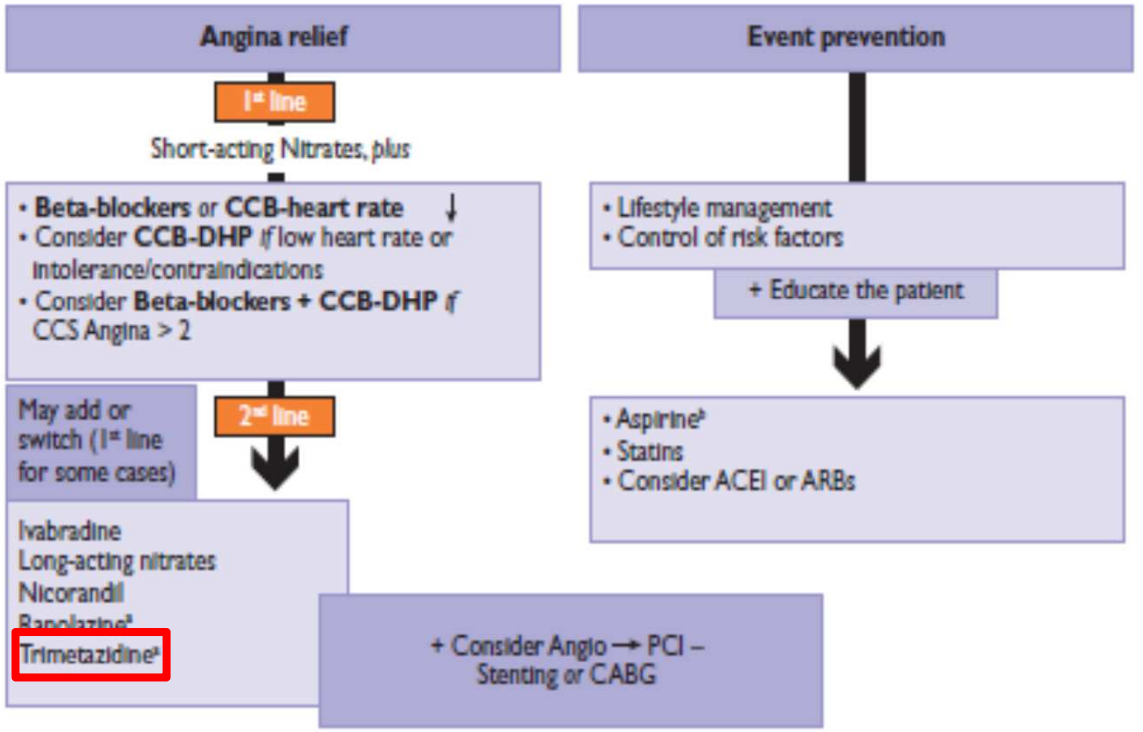
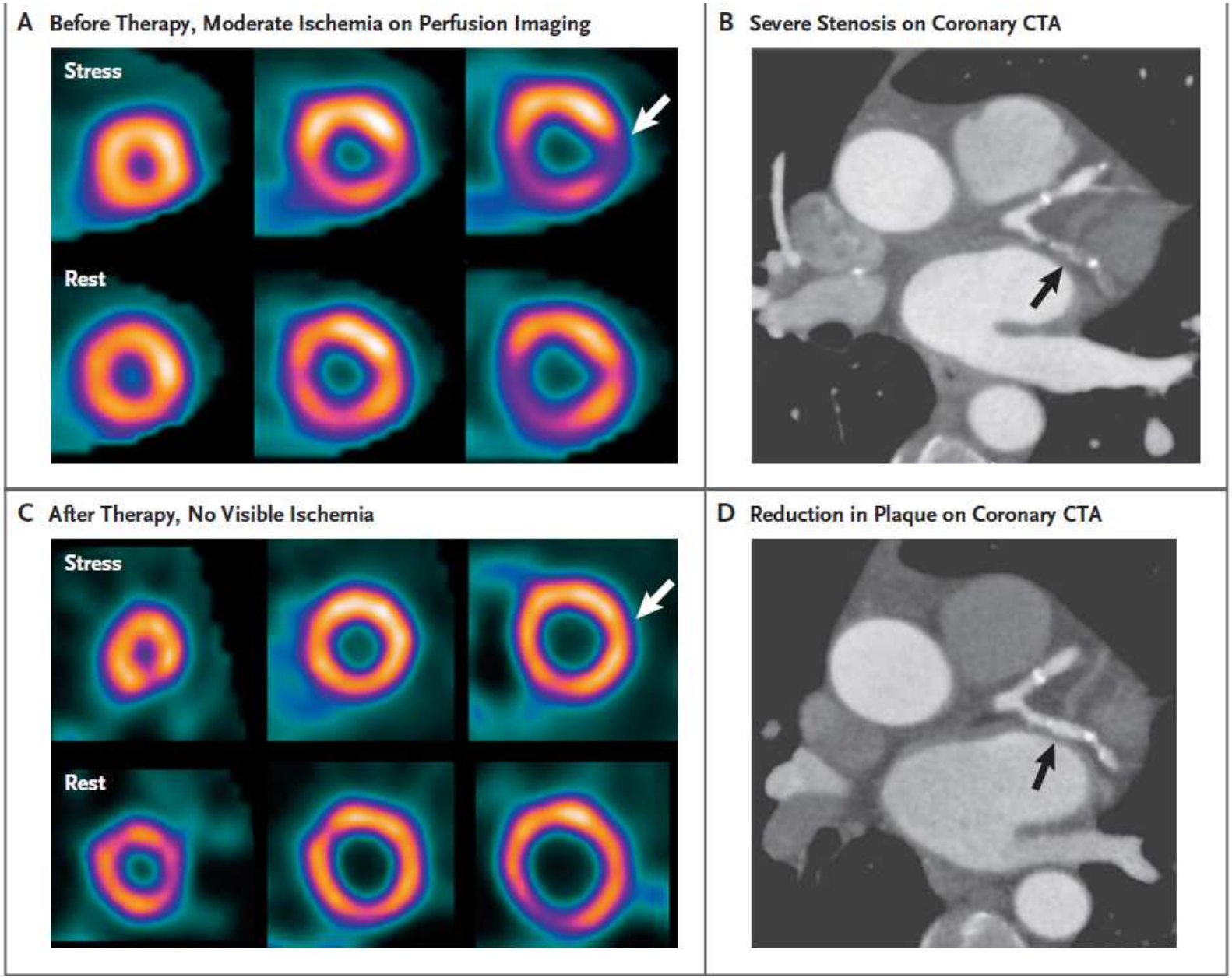


Figure 4 Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.

[a]Data for diabetics.

[b]if intolerance, consider clopidogrel



NEJM April 6, 2017

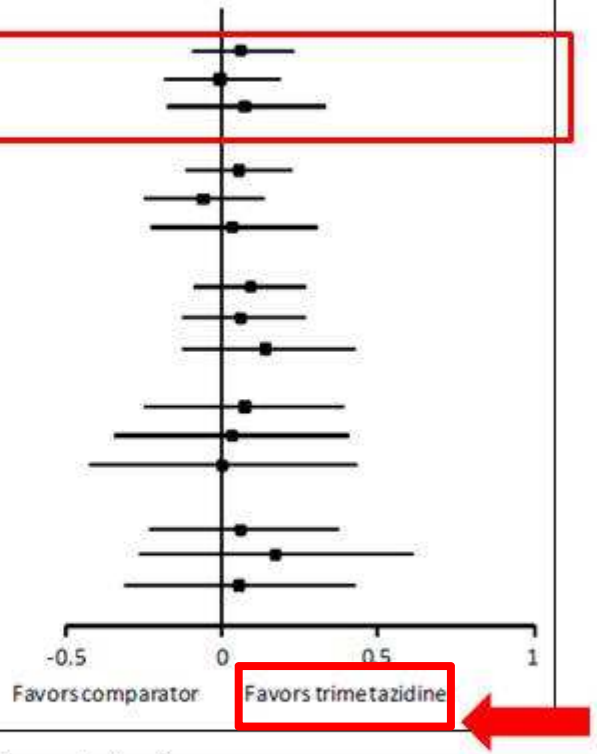
Metaanalyse Trimetazidine: eine der bestuntersuchten antianginösen Substanzen

- For the first time, a meta-analysis allows a comparison of the efficacy trimetazidine (Vastarel) with all therapeutic alternatives.
- It pooled 218 randomized, controlled, single- or double-blind clinical trials assessing the treatment of stable angina pectoris or stable ischemic disease.
  One treatment arm had to include a non-heart-rate-lowering antianginal agent. It could be given as a monotherapy or as a combination therapy. Trials needed to assess exercise tolerance and/or clinical criteria. The average treatment duration was 4 weeks.
- The meta-analysis enrolled 20 000 patients. Antianginal agent subgroups included in the analysis were dihdropyridines, long-acting nitrates, nicorandil, and ranolazine.

Comparison of efficacy: results

- Exercise tolerance

	Trials	N	Effect [95% CI] size	Transposition into seconds
Antianginal agents TED	158	13791	0.06 [-0.10 ; 0.23]	7 [-12 ; 28]
Antianginal agents T1	117	12440	-0.01 [-0.19 ; 0.18]	-1 [-23 ; 22]
Antianginal agents TOA	105	10905	0.07 [-0.18 ; 0.33]	8 [-22 ; 40]
Dihydropyridines TED	170	15744	0.05 [-0.12 ; 0.22]	6 [-14 ; 26]
Dihydropyridines T1	126	13598	-0.06 [-0.25 ; 0.13]	-7 [-30 ; 16]
Dihydropyridines TOA	111	11652	0.03 [-0.23 ; 0.30]	4 [-28 ; 36]
Longacting nitrates TED	170	15744	0.09 [-0.09 ; 0.26]	11 [-11 ; 31]
Longacting nitrates T1	126	13598	0.06 [-0.13 ; 0.26]	7 [-16 ; 31]
Longacting nitrates TOA	111	11652	0.14 [-0.13 ; 0.42]	17 [-16 ; 50]
Nicorandil TED	170	15744	0.07 [-0.25 ; 0.39]	8 [-30 ; 47]
Nicorandil T1	126	13598	0.03 [-0.35 ; 0.40]	4 [-42 ; 48]
Nicorandil TOA	111	11652	0.00 [-0.43 ; 0.43]	0 [-52 ; 52]
Ranolazine TED	11	3791	0.06 [-0.24 ; 0.37]	7 [-29 ; 44]
Ranolazine T1	13	3861	0.17 [-0.27 ; 0.61]	20 [-32 ; 73]
Ranolazine TOA	6	3576	0.05 [-0.32 ; 0.42]	6 [-38 ; 50]



TED = total exercice duration ; T1 = time to 1-mm ST segment depression ; TOA = time to onset of angina.

Trimetazidin ist gleich oder besser als andere anti-anginöse Medikamente

Danchin N, Marzilli M. Efficacy Comparison of Trimetazidine with Therapeutic Alternatives in Stable Angina Pectoris : A Network Meta-Analysis. *Cardiology*. 2011. Published online 26 June 2011.

Tabelle 1: Empfehlungen für die Behandlung der stabilen Angina pectoris mit symptomatischer (NYHA-Klasse II–IV) Herzinsuffizienz mit reduzierter Auswurffraktion. Aus [1] mit freundlicher Genehmigung der Oxford University Press.

Recommendations	Class[a]	Level[b]
Step 1		
A beta-blocker (in an evidence-based dose or maximum tolerated) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment (reducing the risk of HF hospitalization and the risk of premature death).	I	A
Step 2: on top of beta-blocker or if a beta-blocker is not tolerated		
Ivabradine should be considered as an anti-anginal drug in suitable HFrEF patients (sinus rhythm and HR ≥70 bpm) as per recommended HFrEF management.	IIa	B
Step 3: For additional angina symptom relief – except from any combination not recommended		
A short-acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, safe in HF).	IIa	A
A long acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, not extensively studied in HF).	IIa	B
Trimetazidine may be considered when angina persists despite treatment with a beta-blocker (or alternative) to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	A
Amlodipine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effectve anti-anginal treatment, safe in HF).	IIb	B
Nicorandil may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C
Ranolazine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C
Step 4: Myocardial revascularization		
Myocardial revascularization is recommended when angina persists despite treatment with anti-angina drugs.	I	A
Alternatives to myocardial revascularization: combination of ≥ 3 antisnginal drugs (from those listed above) may be considered when angina persists despite treatment with beta-blocker, ivabradine and an extra anti-angina drug (excluding the combinations not recommended below).	IIb	C
The following are NOT recommended:		
(1) Combination of any of ivabradine, ranolazine, and nicorandil because of unknown safety.	III	C
(2) Combination of nicorandil and a nitrate (because of lack of additional eficacy).	III	C
Diltiazem and verapamil are not recommended because of their negative inotropic action and risk of worsening HF.	III	C

bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association.
[a] Class of recommendation; [b] Level of evidence.

Major studies with trimetazidine use in CHF patients

Authors	Year	Materials and methods	Results
Gao et al. [53]	2011	17 randomized studies from the period between 1966 and May 2010; 955 CHF patients	In comparison with placebo, the use of trimetazidine results in: · **Increased exercise tolerance** (WMD 30.26 s, $p < 0.01$), · **Reduced NYHA class** (WMD 0.41, $p < 0.01$), · **Improved LVEF** in ischaemic HF (WMD 7.37 %, $p < 0.01$) and non-ischaemic HF patients (WMD 8.72 %, $p < 0.01$), · **Reduced rate of cardiovascular events and hospitalizations** (RR 0.42, 95 % CI 0.30–0.58, $p < 0.00001$), · **Reduced overall mortality** (RR 0.29, 95 % CI 0.17–0.49, $p < 0.00001$)
Zhang et al. [54]	2012	16 randomized studies; 884 CHF patients	Trimetazidine treatment results in: · **Improved ejection fraction** (WMD 6.46 %, $p < 0.0001$), · **Increased exercise tolerance** (WMD 63.75 s, $p < 0.0001$), · **Reduced NYHA class** (WMD −0.57, $p = 0.0003$), · Decreased LVESV (WMD −6.67 mm; $p < 0.0001$) and LVEDV (WMD −6.05 mm, $p < 0.0001$), · Lowered BNP levels (WMD −203.40 pg/mL, $p = 0.0002$), · **Reduced rate of cardiovascular hospitalization** (RR 0.43, $p = 0.03$) Trimetazidine continues to have **no effect on overall mortality** (RR 0.47, $p = 0.27$)
Fragasso et al. [55]	2013	A multicentre retrospective study; 669 CHF patients, including 362 patients receiving trimetazidine. Follow-up period: 38.76 ± 15.66 months in the trimetazidine group and 40.17 ± 15.53 months in conventional therapy alone group	Addition of trimetazidine in comparison with the conventional treatment alone is associated with: · **Reduced rate of cardiovascular hospitalization** (adjusted HR 0.524, 95 % CI 0.352–0.781, $p = 0.001$), · **Reduced cardiovascular mortality** (HR 0.072, 95 % CI 0.019–0.268, $p = 0.0001$), · **Reduced overall mortality** (HR 0.102, 95 % CI 0.046–0.227, $p = 0.0001$)

BNP brain natriuretic peptide, *CHF* cardiovascular heart disease, *HF* heart failure,
LVEDV left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *NYHA* New York Heart Association, *WMD* weighted mean difference

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- Trimetazidine has been shown to exert some beneficial effect as an add-on to beta-blockers in patients with HF and angina.[400-406] There are data suggesting that it may improve NYHA functional capacity, exercise duration and LV function in patients with heart failure with reduced ejection fraction.[402-406]
- The safety of other anti-anginal agents in heart failure with reduced ejection fraction, such as ranolazine, is uncertain, while other drugs, specifically diltiazem and verapamil, are thought to be unsafe in patients with HFrEF (although they may be used in HFpEF).[214] Dihydropyridine CCBs may all increase sympathetic tone, and their safety in HFrEF [except amlodipine[215] and felodipine[216]] and HFpEF is uncertain.

DW NEWS Top Stories 2014

Doping: Ukraine's Lisogor becomes third athlete to fail doping test at Sochi Games

Ukrainian nordic skier Marina Lisogor tested positive for the anti-anginal substance trimetazidine, the Ukrainian Olympic Committee said on Saturday.

Trimetazidine is classified as a "specified stimulant" on the World Anti-Doping Agency's prohibited list. As such, it is considered more susceptible to inadvertent use and can carry reduced penalities.

Take Home Message

Vastarel (Trimetazidin) ist gleichwertig oder besser als andere Arzneimittel in der Behandlung von stabiler Angina pectoris

Für Vastarel (Trimetazidin) gibt es seit 1968 klinische Erfahrungen in der Behandlung stabilen AP

Vastarel eignet sich auch zur Behandlung der chronischen ischämischen Herzinsuffizienz

Vastarel (Trimetazidin) wurde in die Guidelines der ESC zur Behandlung der stabilen Angina pectoris *und* der chronischen Herzinsuffizienz aufgenommen.

„Haben Sie noch Fragen?"