New translational perspectives in cardiovascular medicine

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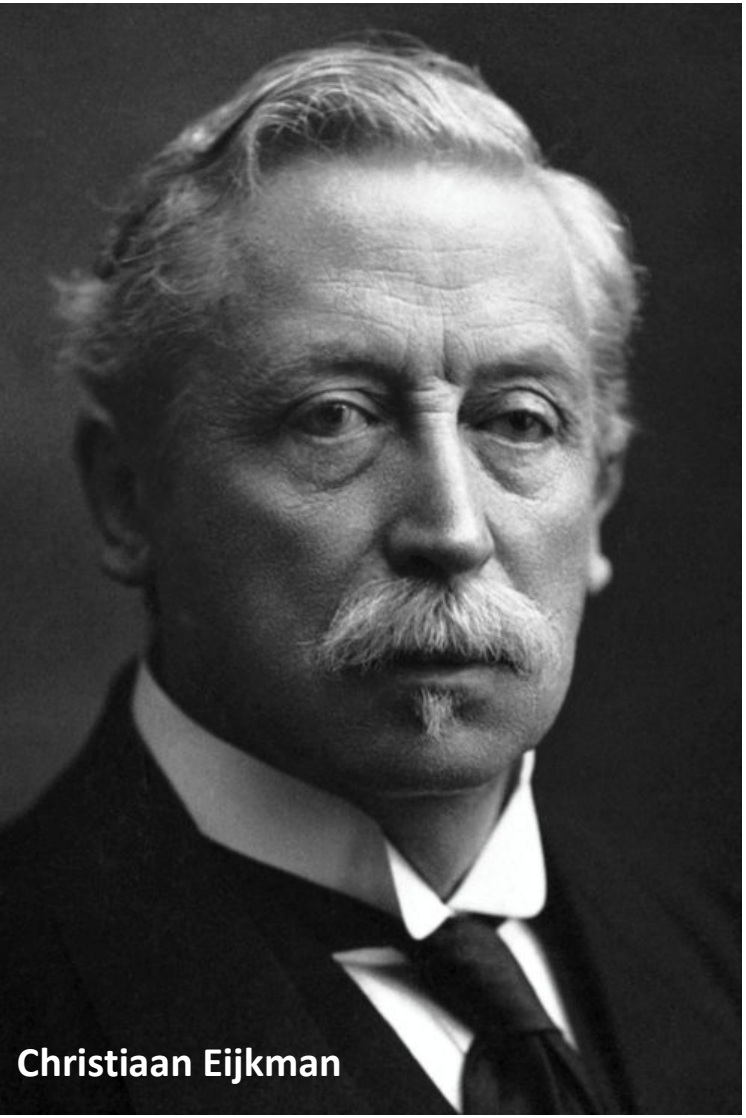
What do we learn today?

Beriberiis a relatively common disease in Asia, sailors and prisoners.

1873: a Dutch naval doctor observed that European crew members had significantly fewer cases of beriberi than sailors recruited from the East Indies. When the amount of white rice in the diet of the East Indies sailors was decreased, the rate of beriberi came down.

Beriberi was believed to have been caused by some toxin or infectious agent in the white rice. Kanehiro Takaki, a Japanese naval doctor, was the first to report beriberi as a nutritional deficiency. His reports were based on the fact that the incidence of beriberi reduced in Japanese sailors when they were given additional meat, dry milk, and vegetables.

What do we learn today?



Christiaan Eijkman

In 1875, after taking his preliminary examinations, Eijkman became a student at the Military Medical School of the University of Amsterdam, where he was trained as a medical officer for the Netherlands Indies Army, passing through all his examinations with honours.

Christiaan Eijkman was appointed as Director of the “Dokter Djawa School” (Javanese Medical School) in 1888. Eijkman was also Director of the “Geneeskundig Laboratorium” (Medical Laboratory) from January 15, 1888 to March 4, 1896, and during that time he made a number of his most important researches. These dealt first of all with the physiology of people living in tropical regions. He was able to demonstrate that a number of theories had no factual basis.

Eijkman realized that the real cause of beriberi was the deficiency of some vital substance in the staple food of the natives, which is located in the so-called “silver skin” (pericarpium) of the rice. This discovery has led to the concept of vitamins.

Eijkman noticed that when fowl were fed a diet solely consisting of polished white rice, they developed symptoms similar to beriberi. By adding rice polishings, the material removed from whole rice to produce white rice, to the feed, Eijkman was able to cure the fowl of beriberi.

In 1926, pure thiamine, the true anti-beriberi vitamin, was isolated by two Dutch scientists, Barend Jansen and W. F. Donath, working in Java.

www.nobelprize.org

Translational medicine

The term *translational medicine* was introduced in the 1990s but only gained wide usage in the early 2000s. Its definition varies according to the stakeholder. Patients, physicians, and other practitioners tend to use the term to refer to the need to accelerate the incorporation of benefits of research into clinical medicine and to close the gap between “what we know” and “what we practice.” Academics tend to interpret *translational medicine* as the testing of novel concepts from basic research in clinical situations, which in turn provide opportunity for the identification of new concepts. In industry it is used in reference to a process that is aimed at expediting the development and commercialization of known therapies. Although different, these interpretations are not mutually exclusive. Rather, they reflect different priorities for achieving a common goal.

www.britannica.com

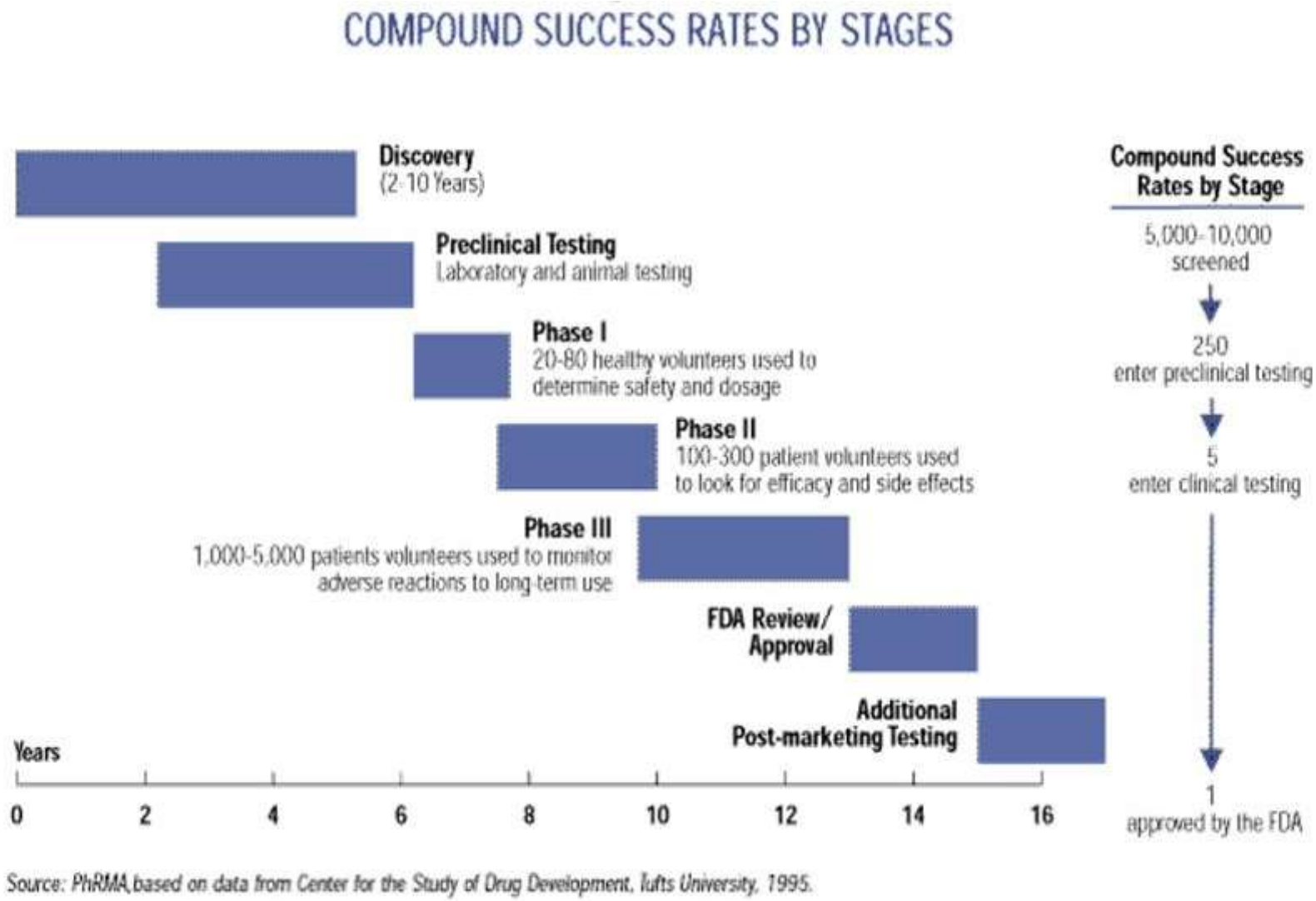
Phase 1 (T1): move basic discovery to clinical application

Phase 2 (T2): assess the value of a clinical application to develop therapeutic guidelines

Phase 3 (T3): move evidence-based guidelines into health practice

Phase 4 (T4): evaluate the real world health outcomes.

Drug development

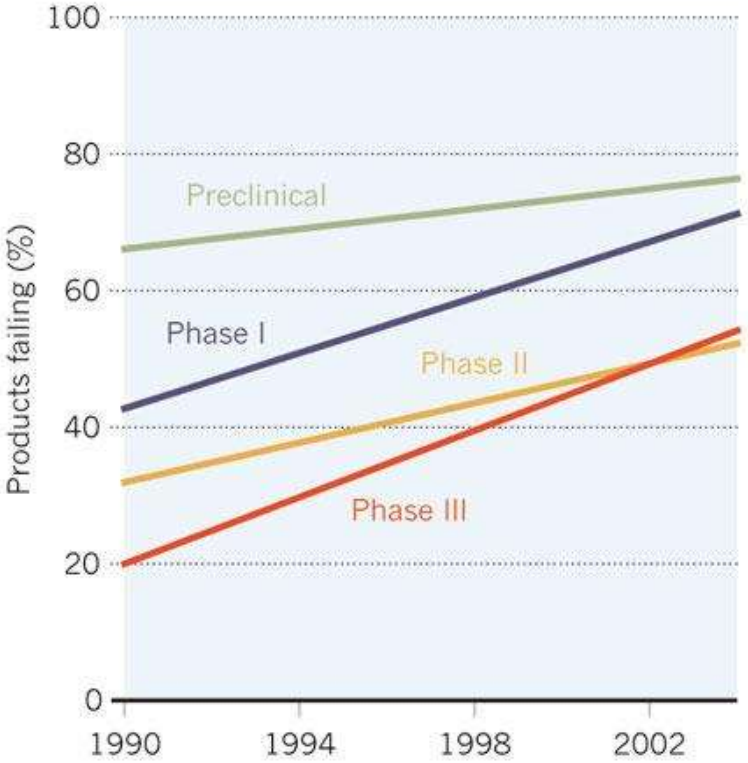


Source: *PhRMA, based on data from Center for the Study of Drug Development, Tufts University, 1995.*

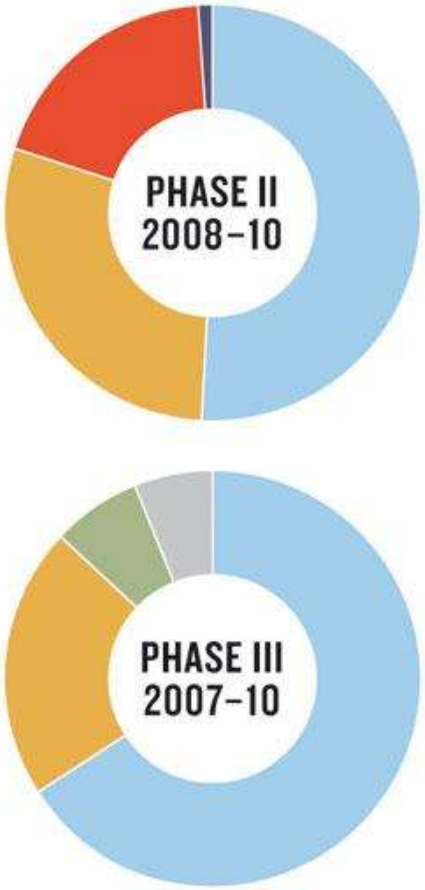
THE CLINICAL-TRIAL CLIFF

Drug companies are removing more compounds from the pipeline at all levels of testing than ever before.

For projects started between 1990 and 2004, the United States, Europe and Japan have seen sharp rises in the attrition of drugs tested in trials.



Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety.

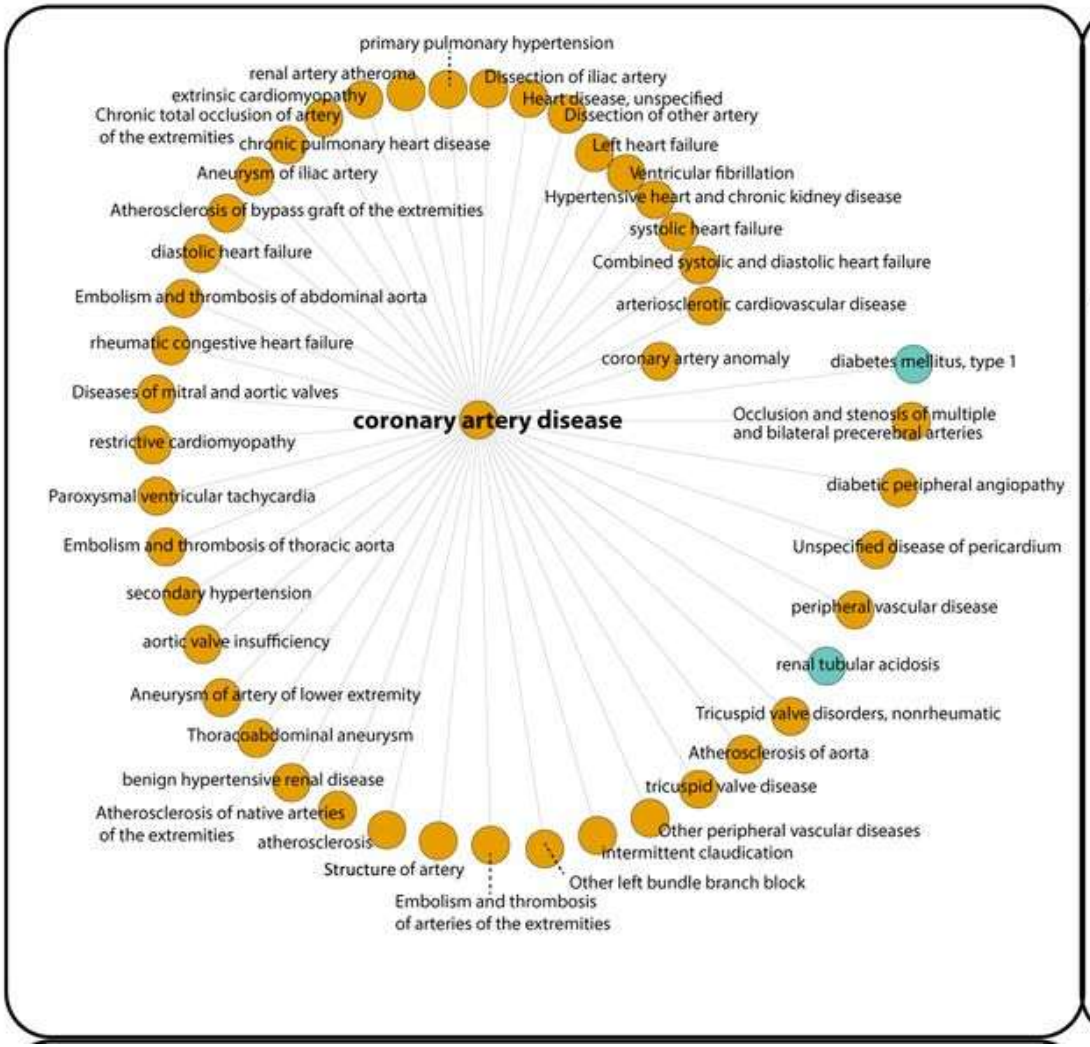


Nature 477, 526-528 (2011)

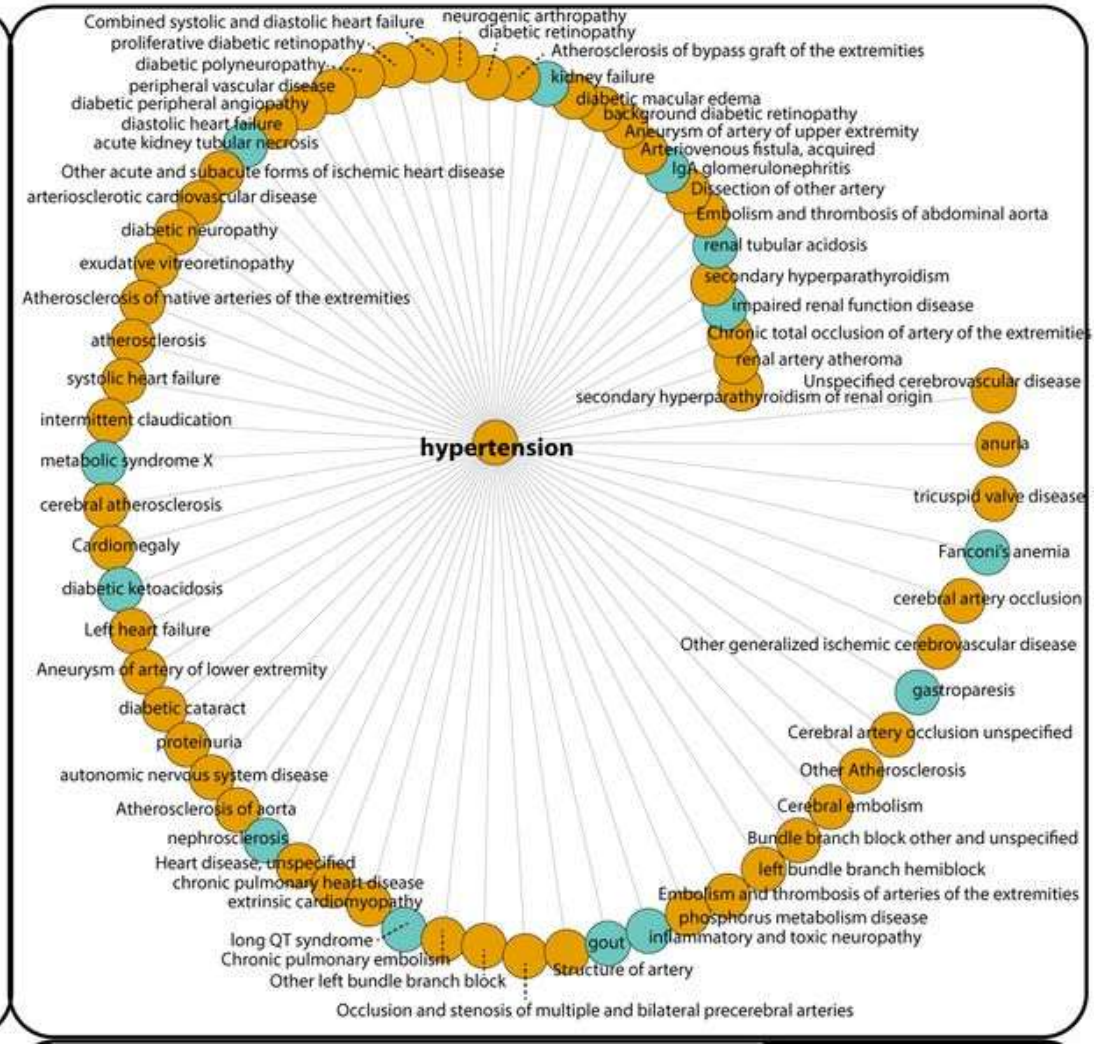
The complex picture of cardiovascular diseases

Comorbidities

Coronary Artery Disease

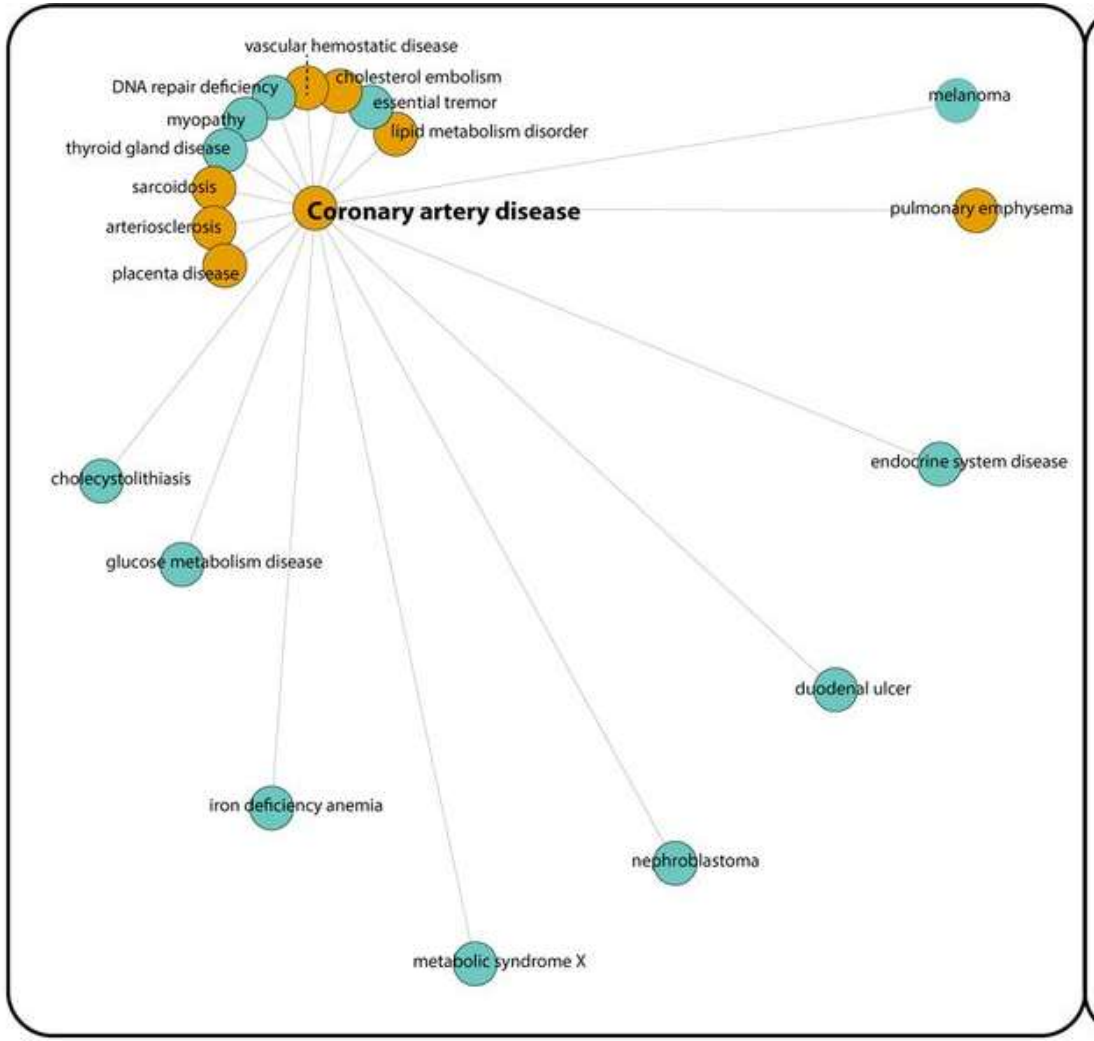


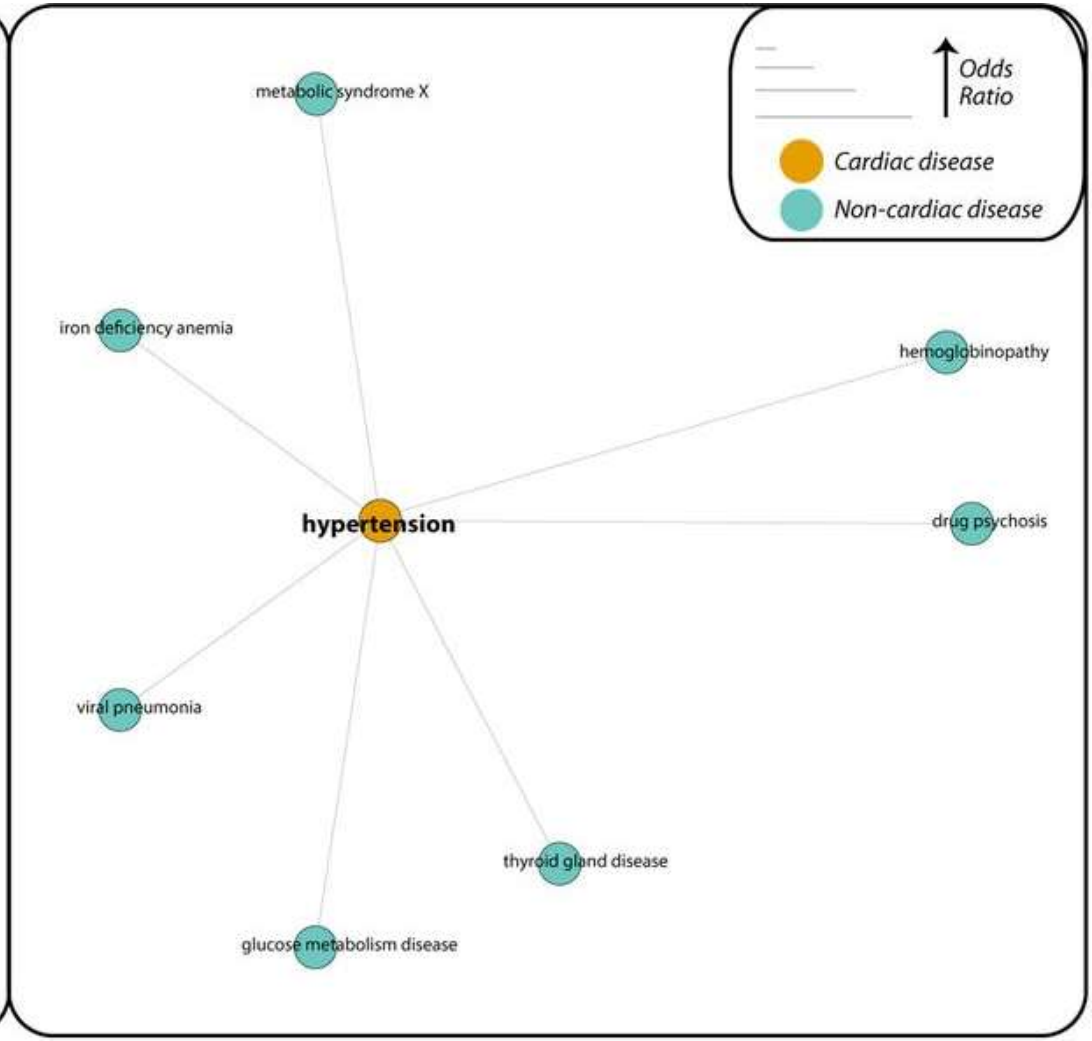
Hypertension



The complex picture of cardiovascular diseases

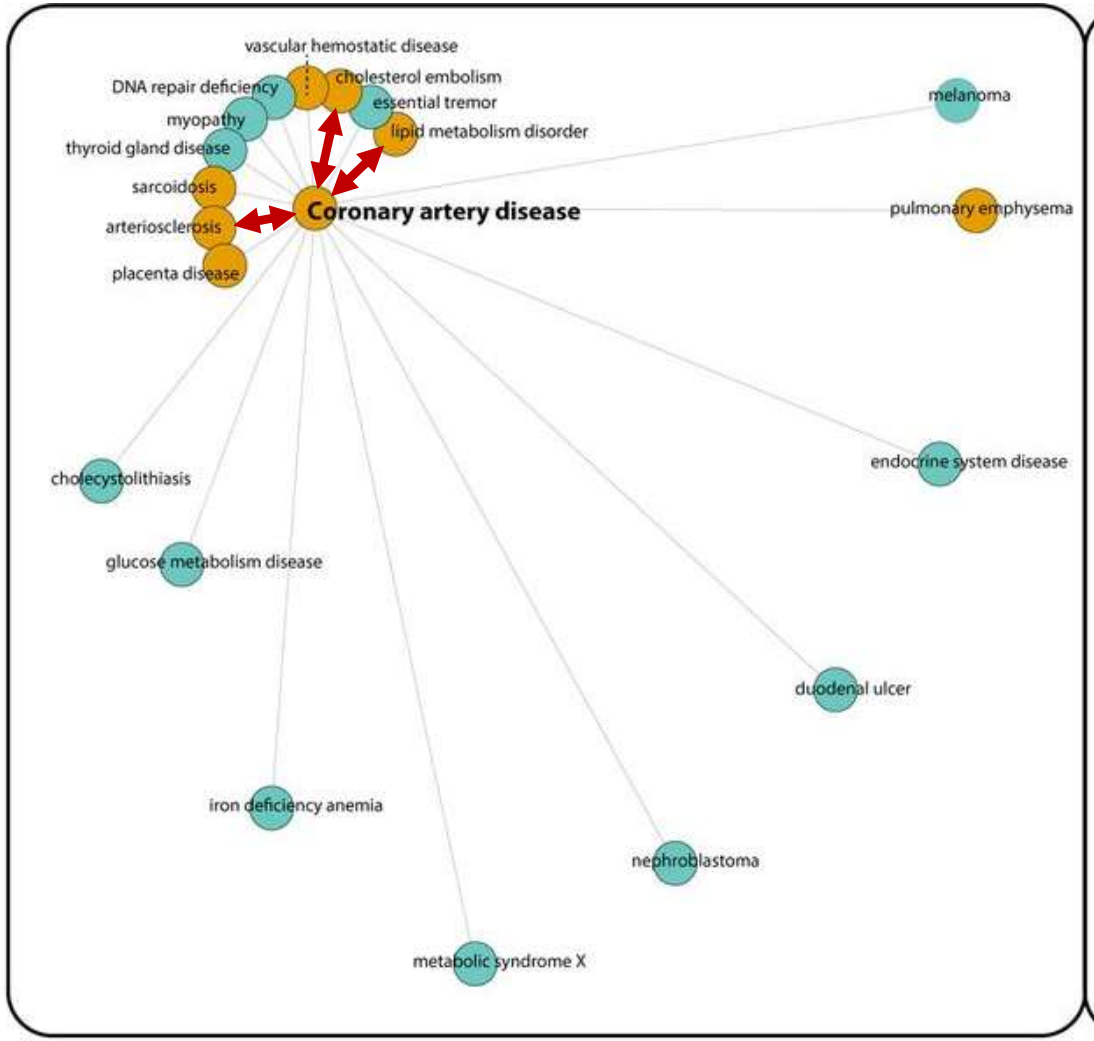
Shared Genetic Architecture

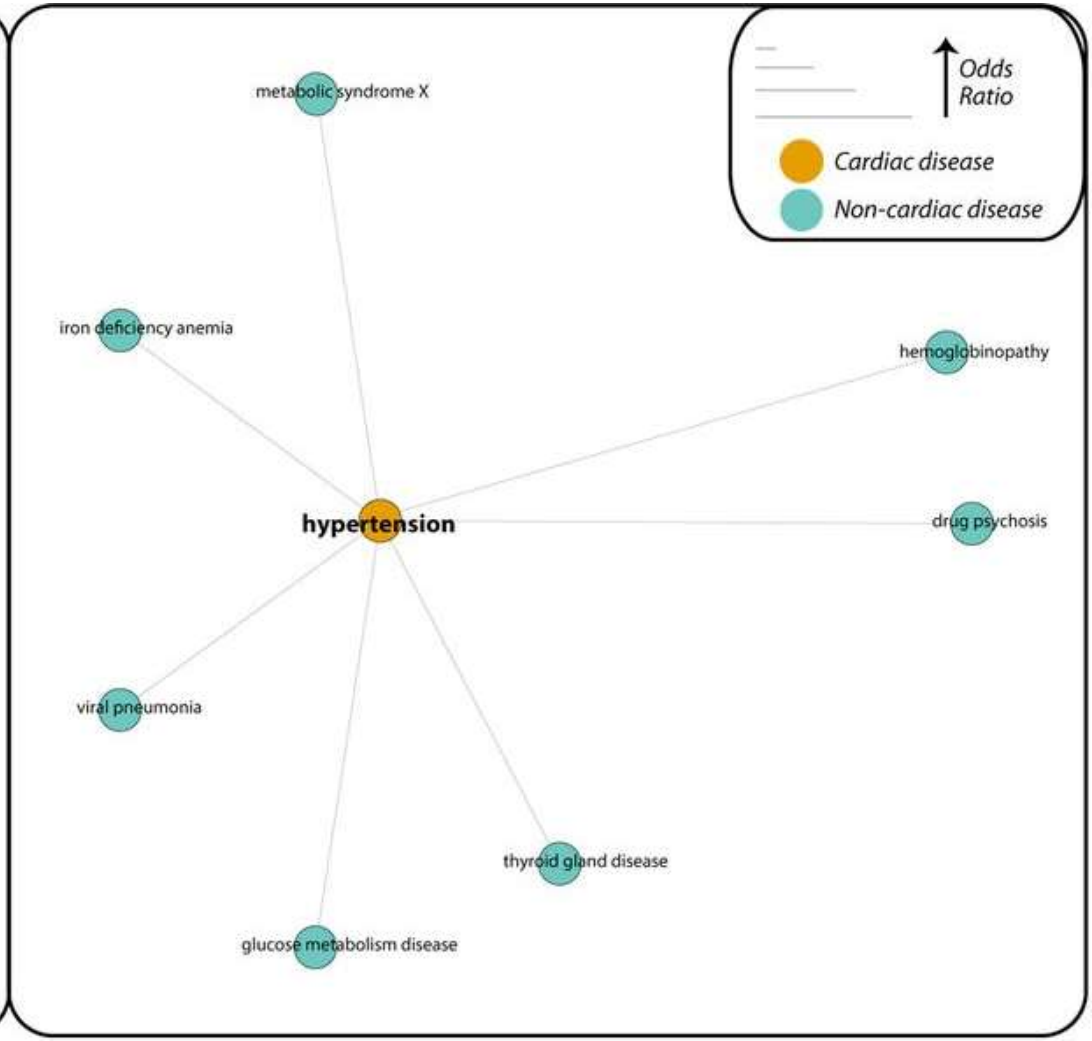




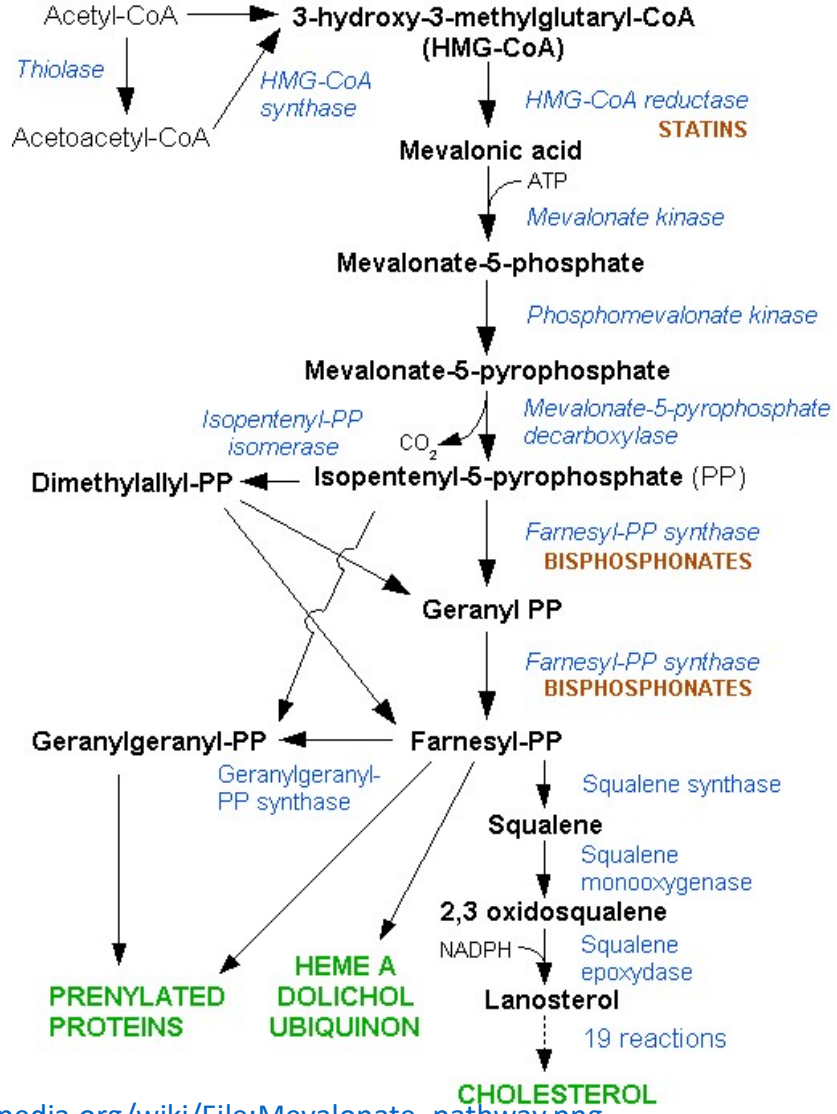
The complex picture of cardiovascular diseases

Shared Genetic Architecture

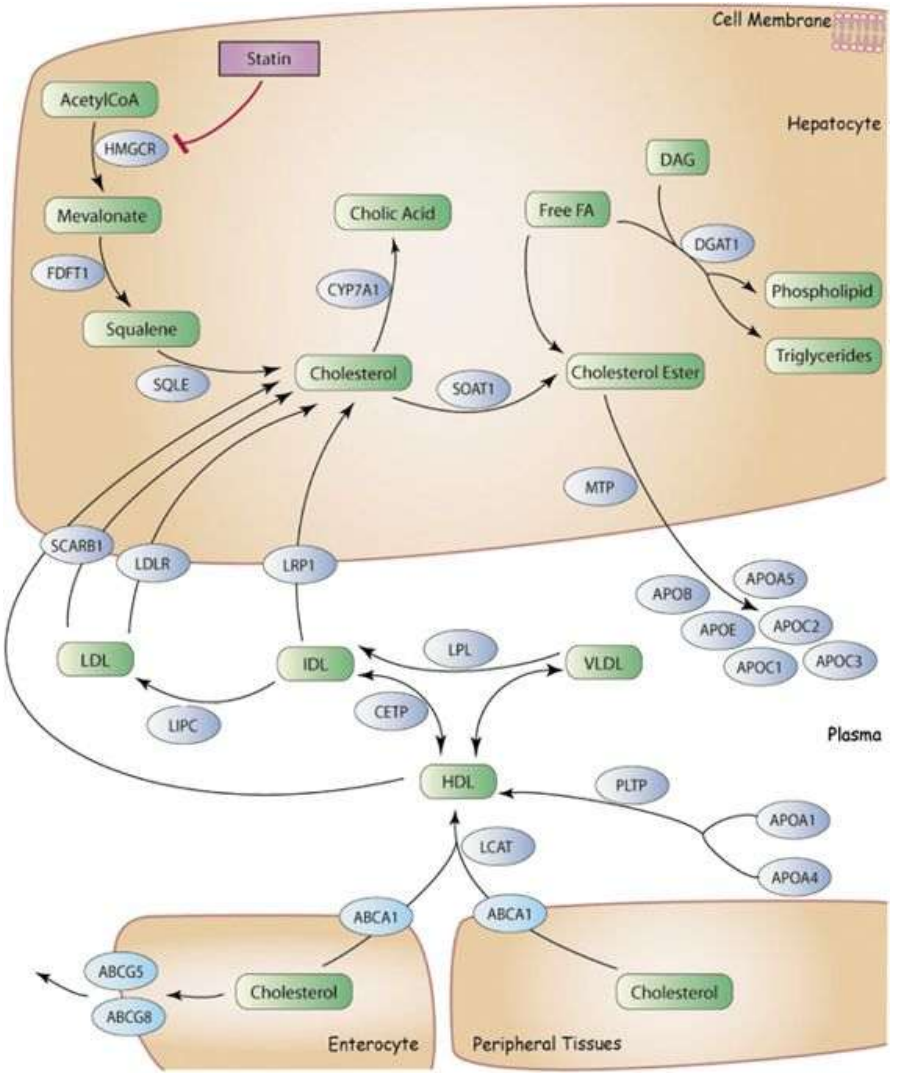




Example 1: lipid lowering therapy (statins)

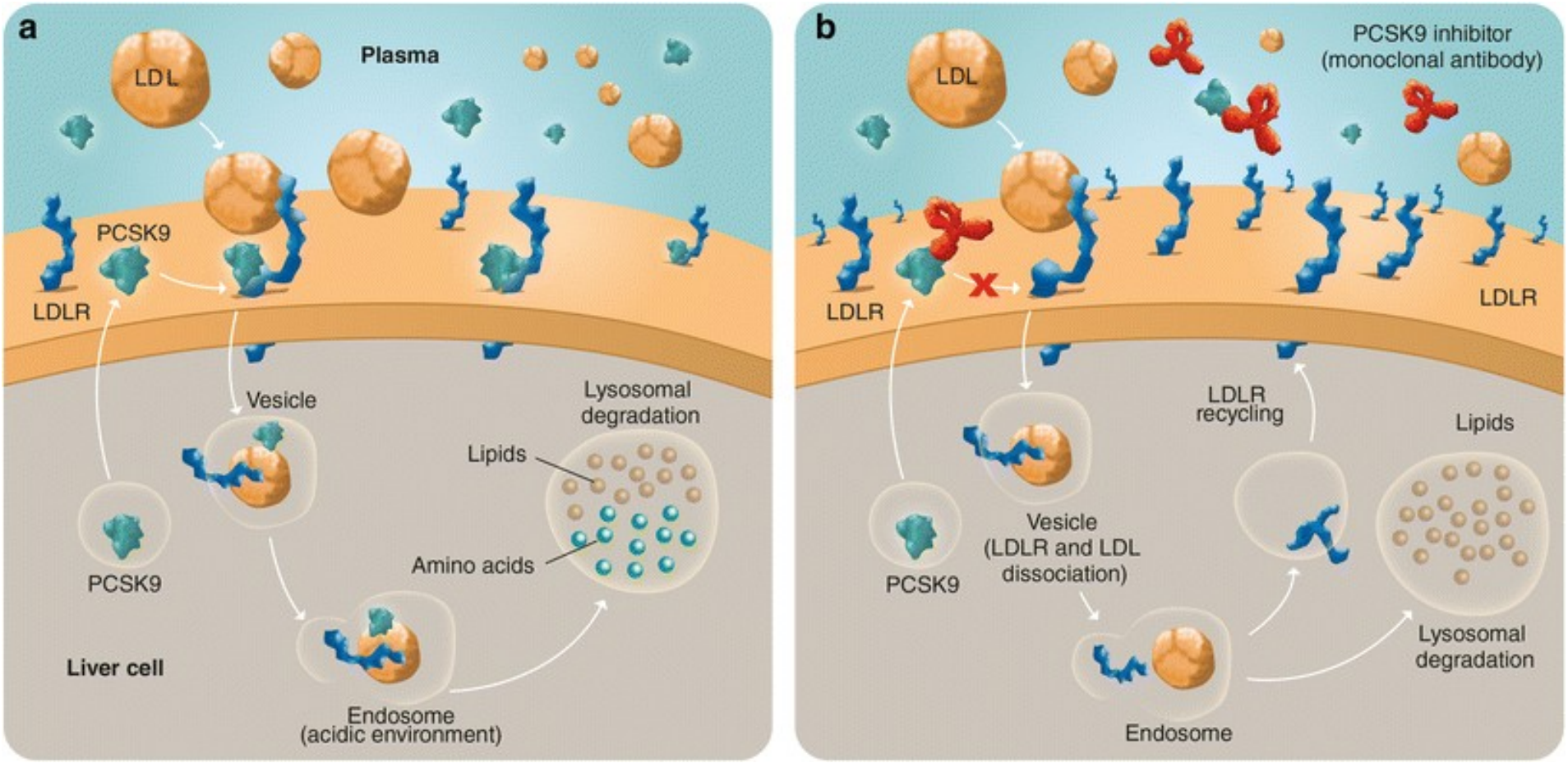


http://en.wikipedia.org/wiki/File:Mevalonate_pathway.png



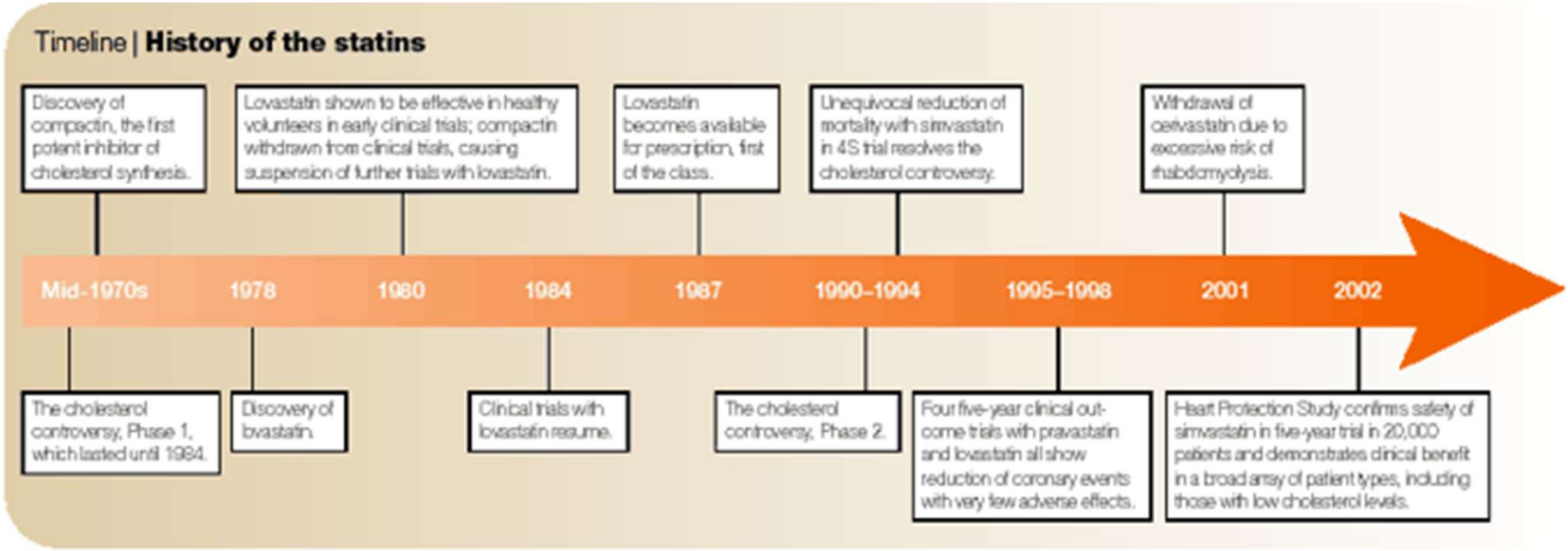
Mangravite et al, The Pharmacogenomics Journal **volume 6**, pages 360–374 (2006)

Recent alternative to statins: PCSK9 inhibotrs



Krähenbühl, S., Pavik-Mezzour, I. & von Eckardstein, A. Drugs (2016) 76: 1175. https://doi.org/10.1007/s40265-016-0613-0

Statin timeline



Jonathan A. Tolbert, Nature Reviews Drug Discovery **volume 2**, pages 517–526 (2003)

Clinically approved statins

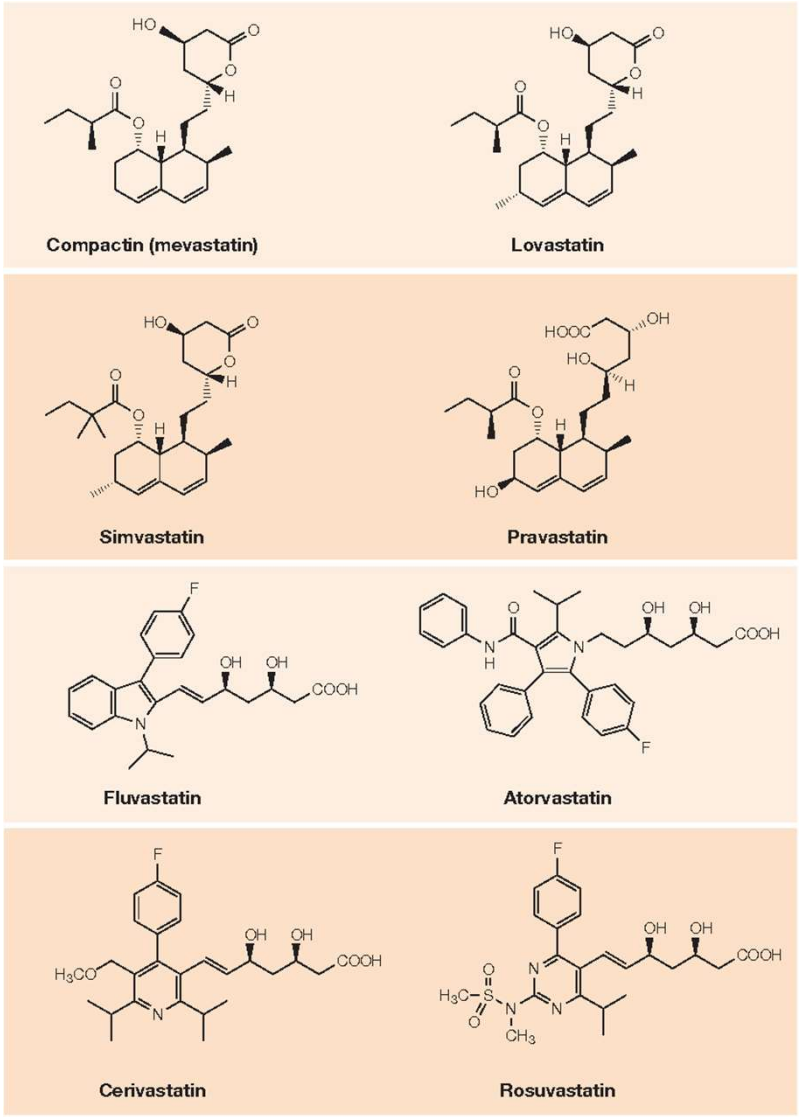
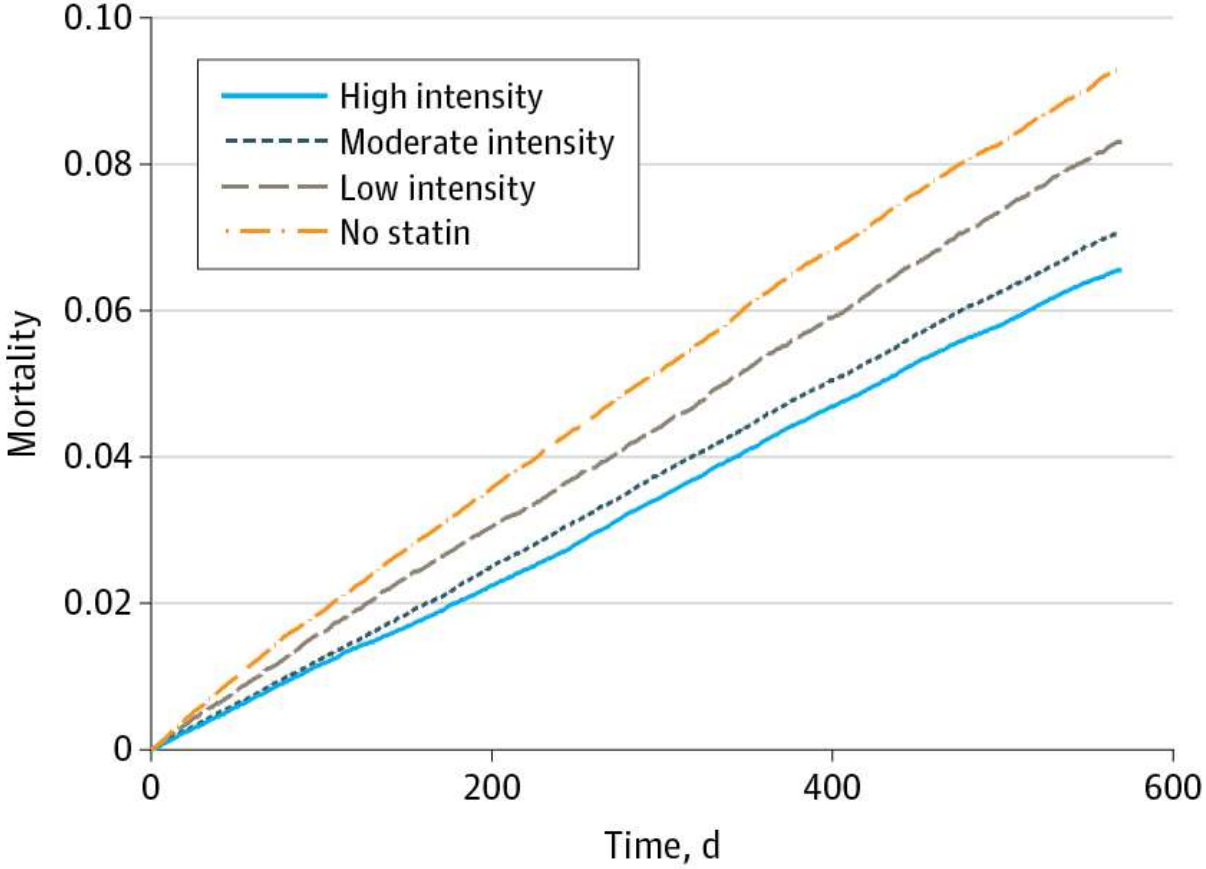


Figure 3 | **Structures of the statins.** Compactin and lovastatin are natural products. Pravastatin

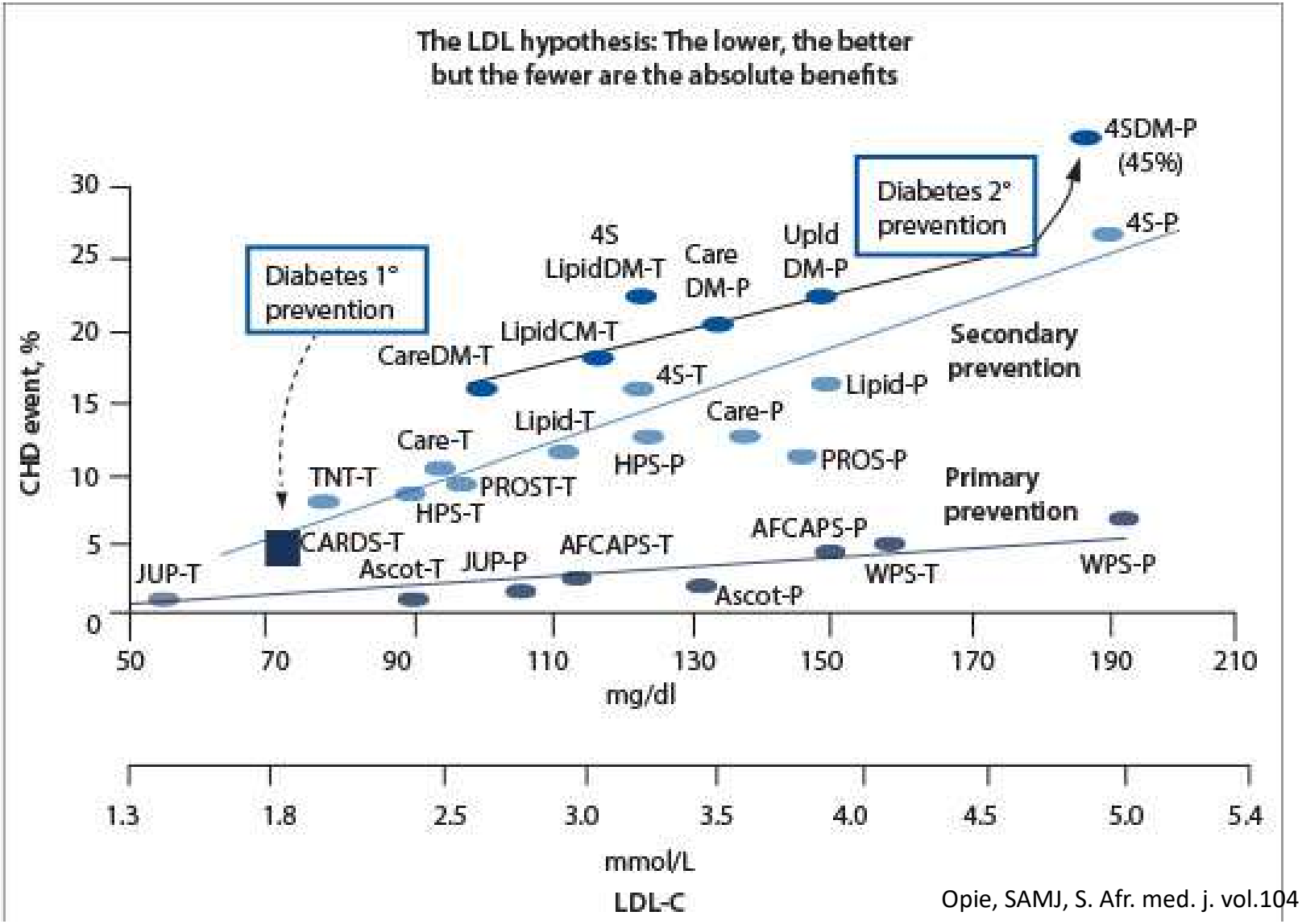
Clinical success: significantly improved mortality



No. at risk			
High	150 928	146 474	120 559
Moderate	232 293	223 664	190 147
Low	33 920	32 389	26 997
None	92 625	87 322	68 474

Rodriguez et al., JAMA Cardiol. 2017;2(1):47-54.

Clinical success: improvement in coronary heart disease



Opie, SAMJ, S. Afr. med. j. vol.104 n.3 Cape Town Mar. 2014

Comparative Efficacy of Statins on LDL-C

LDL-C reduction	34%	41%	48%	55%	62%
Rosuvastatin (Crestor)	—	5	10	20	40
Atorvastatin (Lipitor)	10	20	40	80	—
Simvastatin (Zocor)*	20	40	80*	—	—
Lovastatin **	40	80	—	—	—
Pravastatin**	40	80	—	—	—

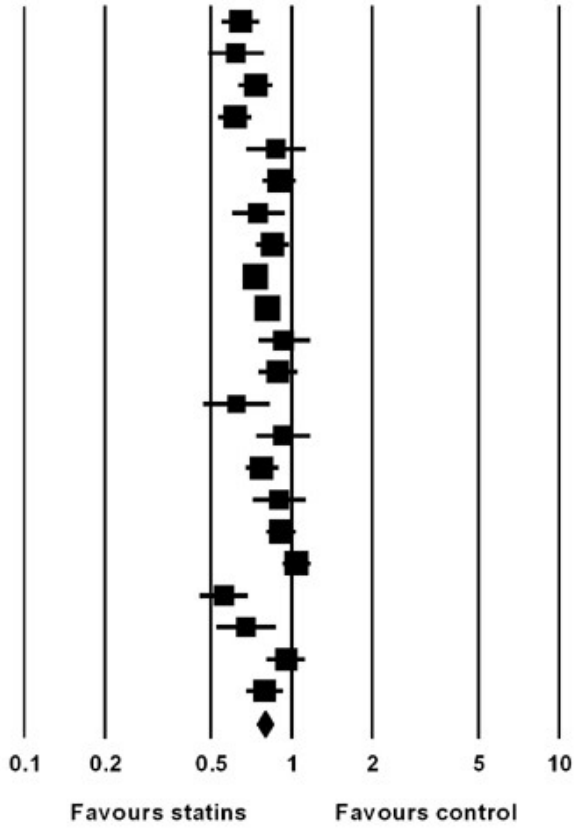
*Avoid due to high risk of toxicity

** Both availble for $10 for 3 months's supply at Wall mart

Roberts WC. Am J Cardiol 2004;93:808

Clinical success: overall 0.71 OR

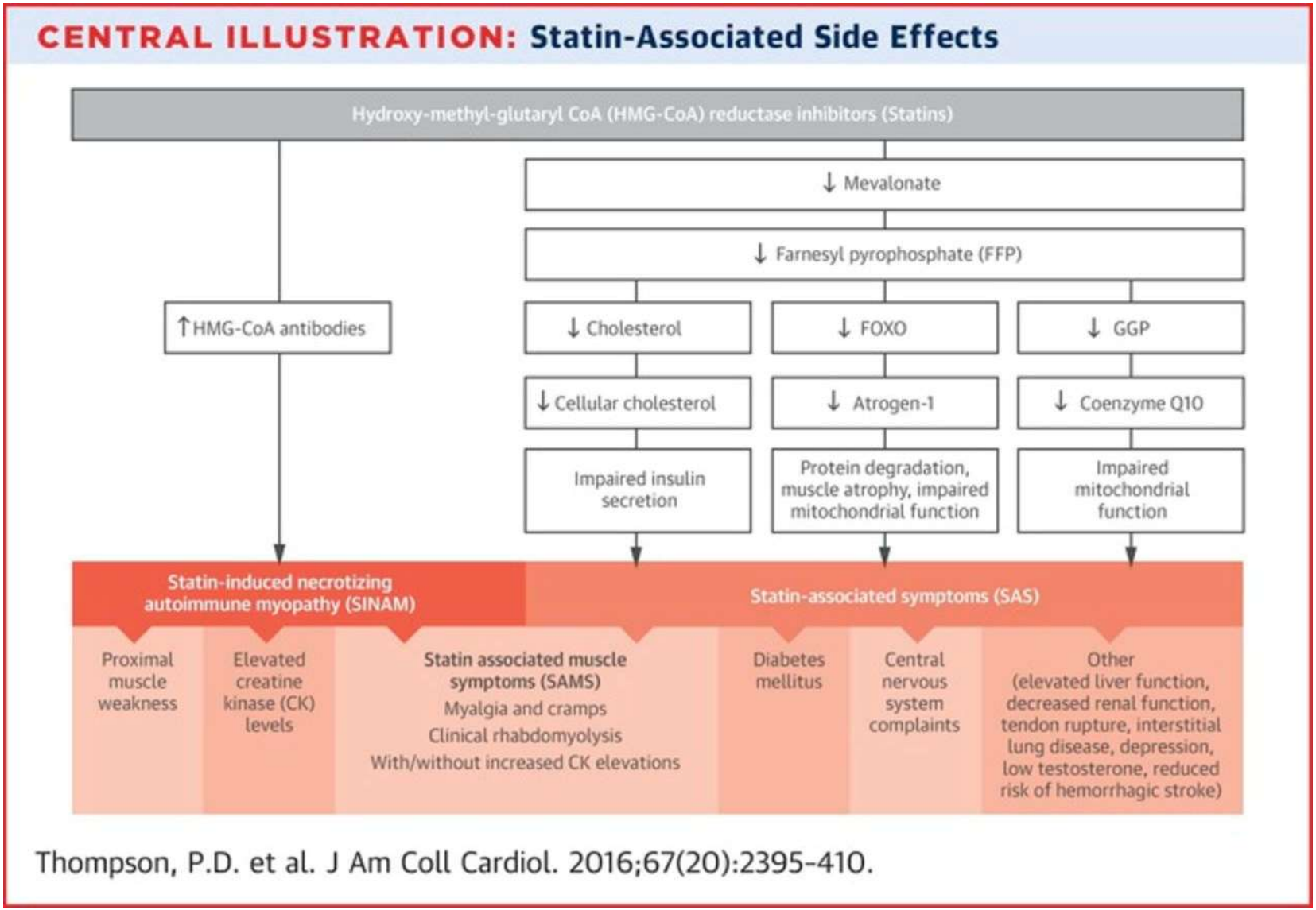
Model	Study name	Odds ratio	Lower limit	Upper limit	p-Value	CVD Events / Total: statin	CVD Events / Total: placebo
	WOSCOPS 1995	0.645	0.549	0.758	0.000	276 / 3302	408 / 3293
	AFCAPS/TexCAPS 1998	0.620	0.489	0.786	0.000	116 / 3304	183 / 3301
	CARE 1998	0.734	0.636	0.848	0.000	430 / 2061	549 / 2078
	4S 1999	0.614	0.533	0.706	0.000	425 / 2200	617 / 2198
	GISSI-P 2000	0.873	0.678	1.125	0.294	120 / 2138	136 / 2133
	ALLHAT-LLT 2002	0.898	0.777	1.037	0.143	380 / 5170	421 / 5185
	LIPS 2002	0.751	0.600	0.941	0.013	181 / 844	222 / 833
	PROSPER 2002	0.848	0.734	0.979	0.024	408 / 2891	473 / 2913
	HPS 2003	0.734	0.687	0.784	0.000	2033 / 10269	2585 / 10267
	LIPID 2003	0.813	0.747	0.885	0.000	1626 / 4512	1843 / 4502
	ALERT 2003	0.934	0.749	1.166	0.548	186 / 1050	197 / 1052
	ALLIANCE 2004	0.890	0.754	1.052	0.171	408 / 1217	443 / 1225
	CARDS 2004	0.623	0.468	0.831	0.001	83 / 1428	127 / 1410
	4D 2005	0.930	0.740	1.169	0.534	226 / 619	243 / 636
	ASCOT-LLA 2005	0.774	0.674	0.890	0.000	389 / 5168	486 / 5110
	ASPEN 2006	0.899	0.716	1.129	0.361	166 / 1211	180 / 1199
	CORONA 2007	0.916	0.810	1.035	0.160	692 / 2514	732 / 2497
	GISSI-HF 2008	1.043	0.928	1.173	0.480	1305 / 2285	1283 / 2288
	JUPITER 2008	0.559	0.454	0.688	0.000	142 / 8901	251 / 8901
	MEGA 2008	0.675	0.524	0.871	0.003	102 / 3866	153 / 3966
	AURORA 2009	0.954	0.810	1.124	0.574	396 / 1389	408 / 1384
	SPARCL 2011	0.794	0.679	0.930	0.004	335 / 2365	407 / 2366
Random		0.791	0.740	0.846	0.000	10425 / 68704	12347 / 68737



Chang et al, Rev Diabet Stud, 2013, 10(2-3):157-170

Statins for everyone?

Limitations: side effects

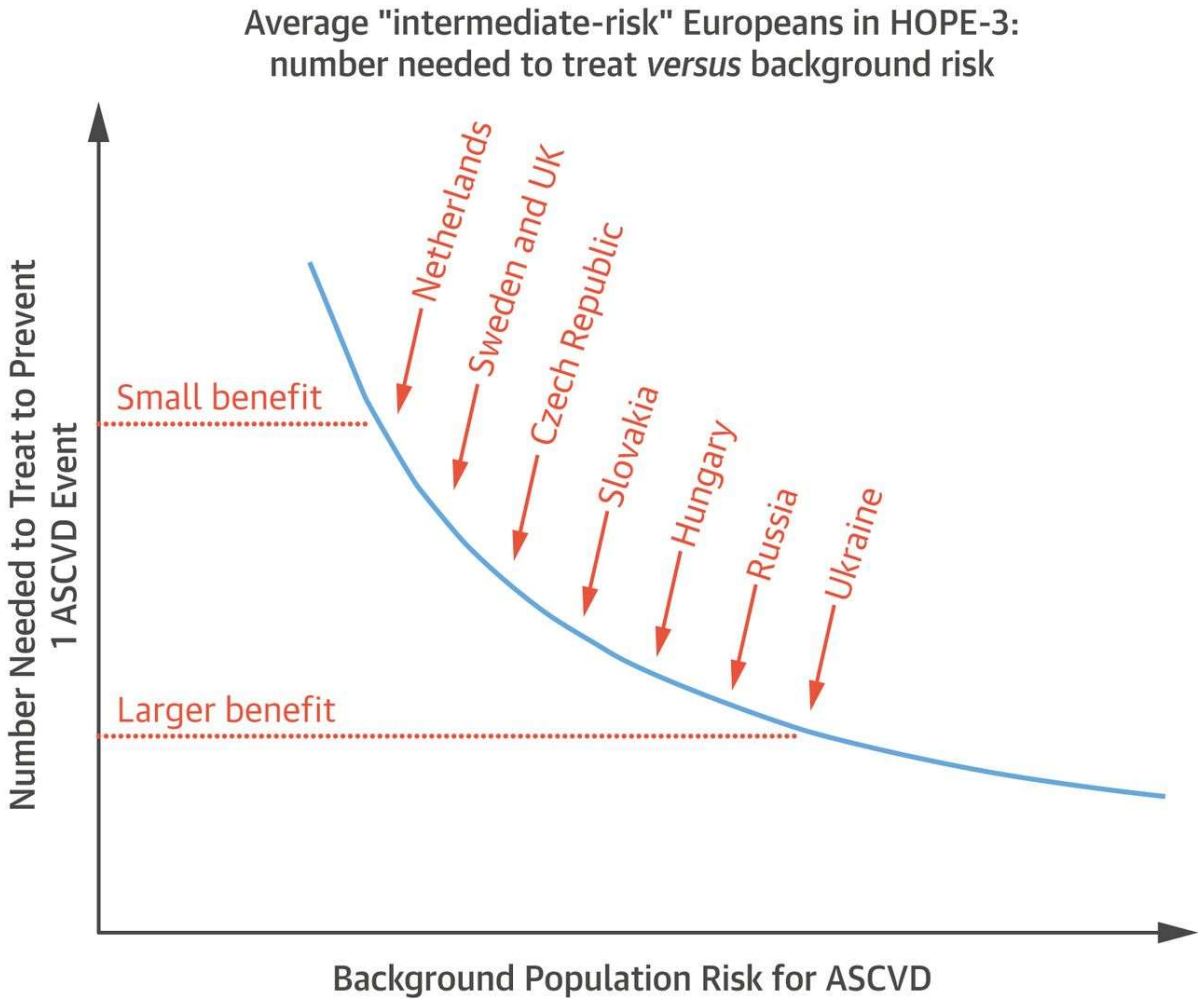


Thompson, P.D. et al. J Am Coll Cardiol. 2016;67(20):2395–410.

Limitations: cost effectiveness

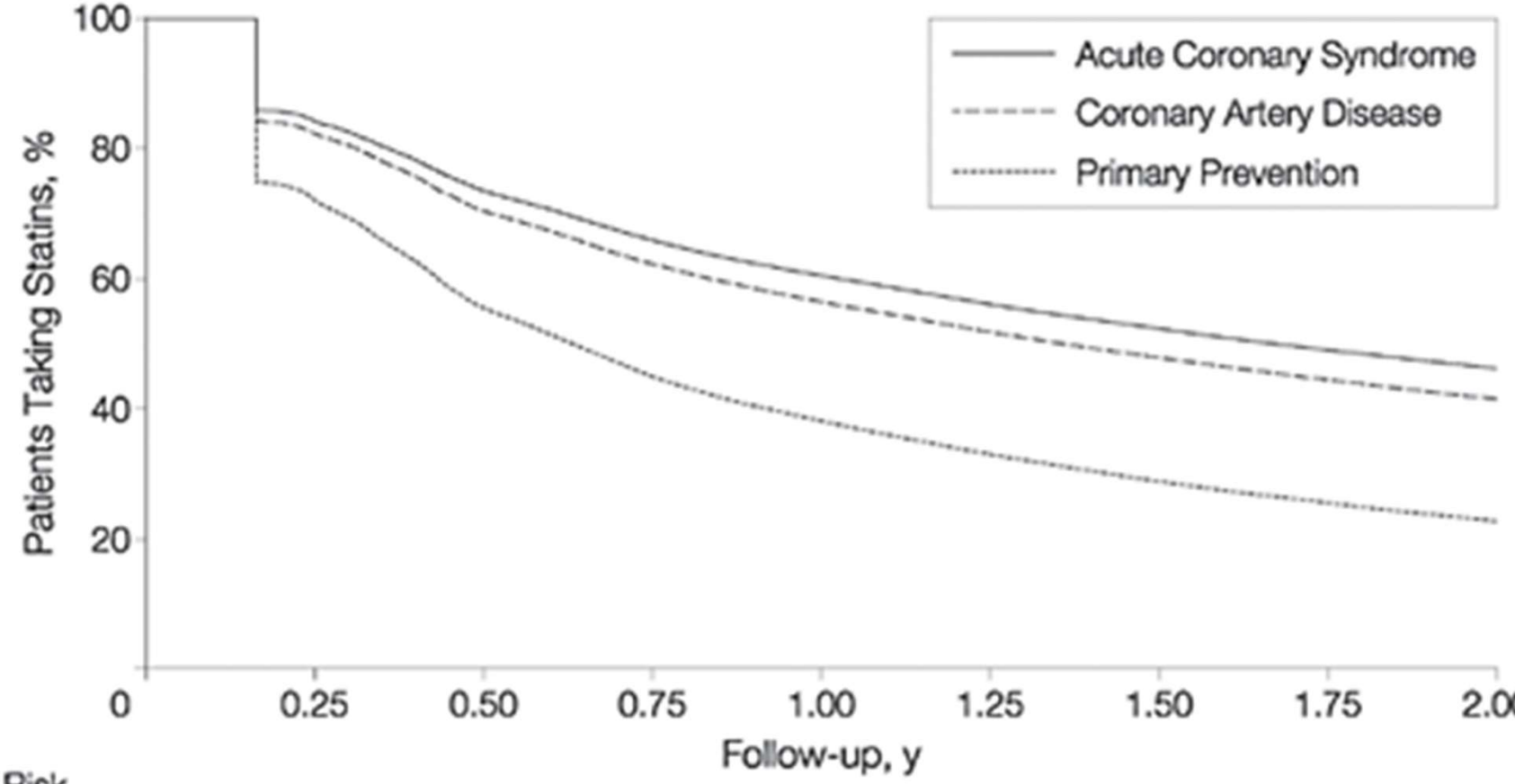
Age (years)	10-year vascular risk*	QALYs		)						
No statins	Statins	Absolute risk reduction	Statins	No statins	Incremental QALYs	Statins	No statins	Incremental costs (€)		ICER(€ per QALY
45										
	1.0%	0.9%	0.1%	9,162	9,166	-0,005	1192	236	956	NA
	2.5%	2.1%	0.4%	9,143	9,144	-0,001	1409	494	916	NA
	5.0%	4.3%	0.7%	9,111	9,107	0,004	1774	925	848	195 372
	7.5%	6.5%	1.0%	9,079	9,069	0,01	2141	1360	781	78 136
	10.0%	8.6%	1.4%	9,047	9,032	0,016	2511	1796	715	45 669
	15.0%	13.0%	2.0%	8,981	8,954	0,027	3262	2678	584	21 651
55										
	2.5%	2.1%	0.4%	8,937	8,938	0	1501	603	898	NA
	5.0%	4.3%	0.7%	8,9	8,893	0,007	1856	1024	832	125 544
	7.5%	6.5%	1.0%	8,862	8,849	0,013	2215	1448	767	57 442
	10.0%	8.6%	1.4%	8,824	8,804	0,02	2577	1875	702	34 995
	15.0%	13.0%	2.0%	8,746	8,712	0,033	3311	2737	574	17 158
	20.0%	17.4%	2.6%	8,666	8,619	0,047	4059	3611	448	9 572
	25.0%	21.8%	3.2%	8,584	8,523	0,06	4823	4499	324	5 395
65										
	5.0%	4.3%	0.7%	8,277	8,266	0,01	2052	1265	787	75 237
	7.5%	6.5%	1.0%	8,228	8,21	0,019	2374	1644	729	38 613
	10.0%	8.7%	1.3%	8,18	8,152	0,027	2698	2026	672	24 607
	15.0%	13.0%	2.0%	8,08	8,036	0,044	3357	2799	558	12 652
	20.0%	17.5%	2.5%	7,978	7,917	0,061	4030	3585	445	7 323
	25.0%	21.9%	3.1%	7,873	7,795	0,077	4719	4384	334	4 319
75										
	5.0%	4.3%	0.7%	6,928	6,912	0,016	2382	1696	686	42 439
	7.5%	6.5%	1.0%	6,865	6,838	0,027	2604	1961	643	23 846
	10.0%	8.7%	1.3%	6,802	6,764	0,038	2829	2230	600	15 901
	15.0%	13.1%	1.9%	6,673	6,614	0,059	3288	2774	514	8 695
	20.0%	17.5%	2.5%	6,54	6,46	0,08	3758	3328	429	5 343
	25.0%	21.9%	3.1%	6,403	6,301	0,101	4241	3895	346	3 410
	30.0%	26.4%	3.6%	6,26	6,138	0,122	4739	4475	264	2 156

Limitations: national specifics in benefit



Erling Falk, and Martin Bødtker Mortensen JACC 2016;68:2903-2906

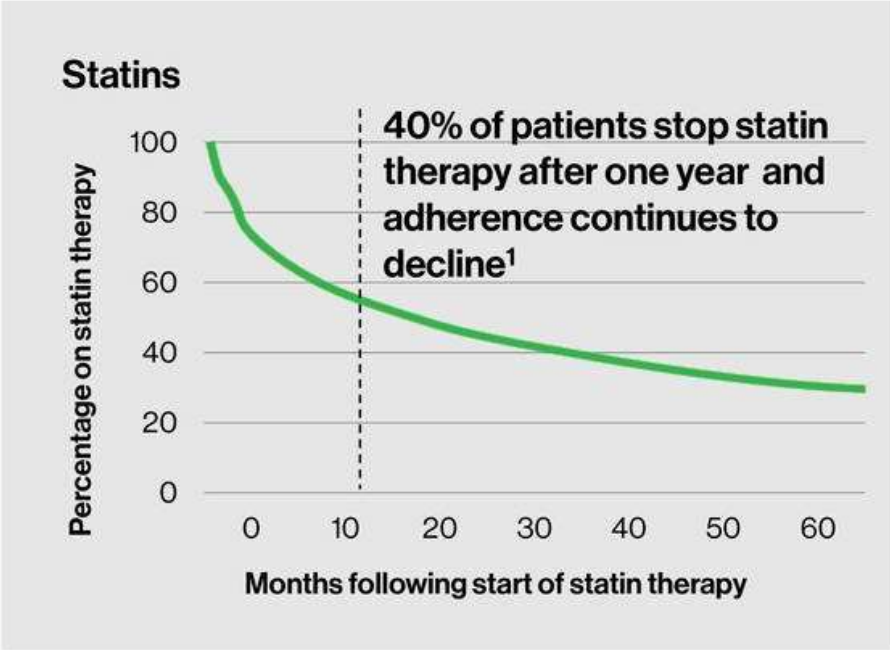
Real world situation: non-adherence

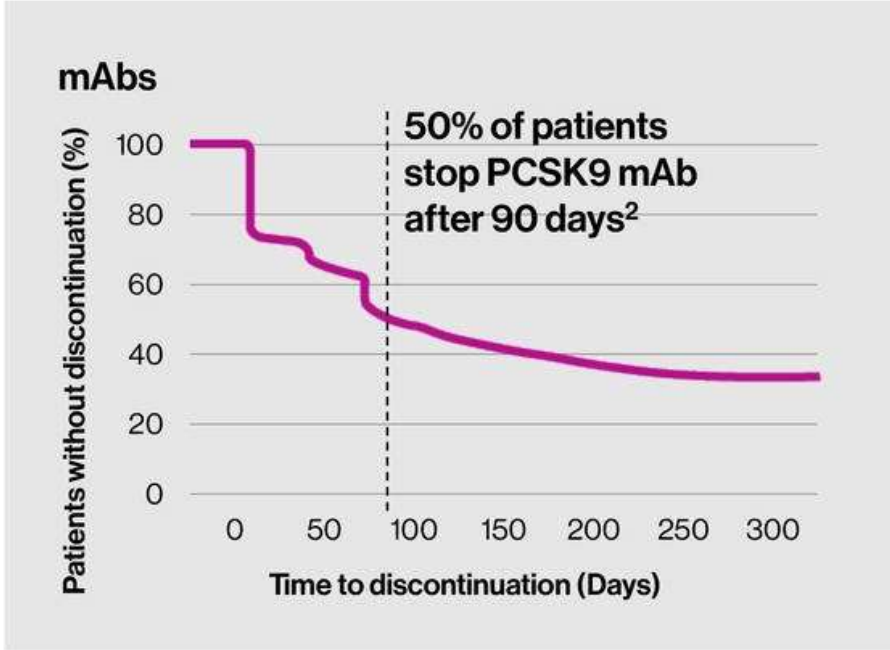


No. at Risk					
Acute Coronary Syndrome	22379	16312	12901	10662	8977
Coronary Artery Disease	36106	25416	19558	15823	13094
Primary Prevention	85020	47685	33564	26401	21602

Jackevicius et al., JAMA. 2002;288(4):462-467.

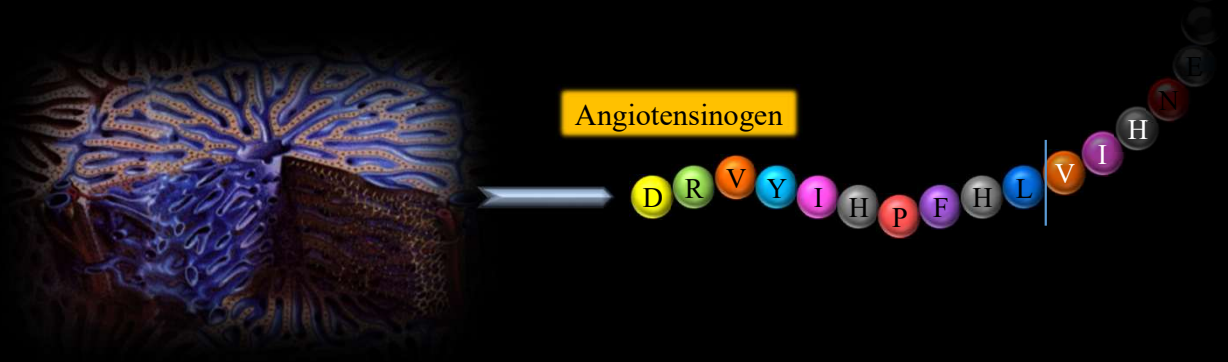
Real world situation: non-adherence



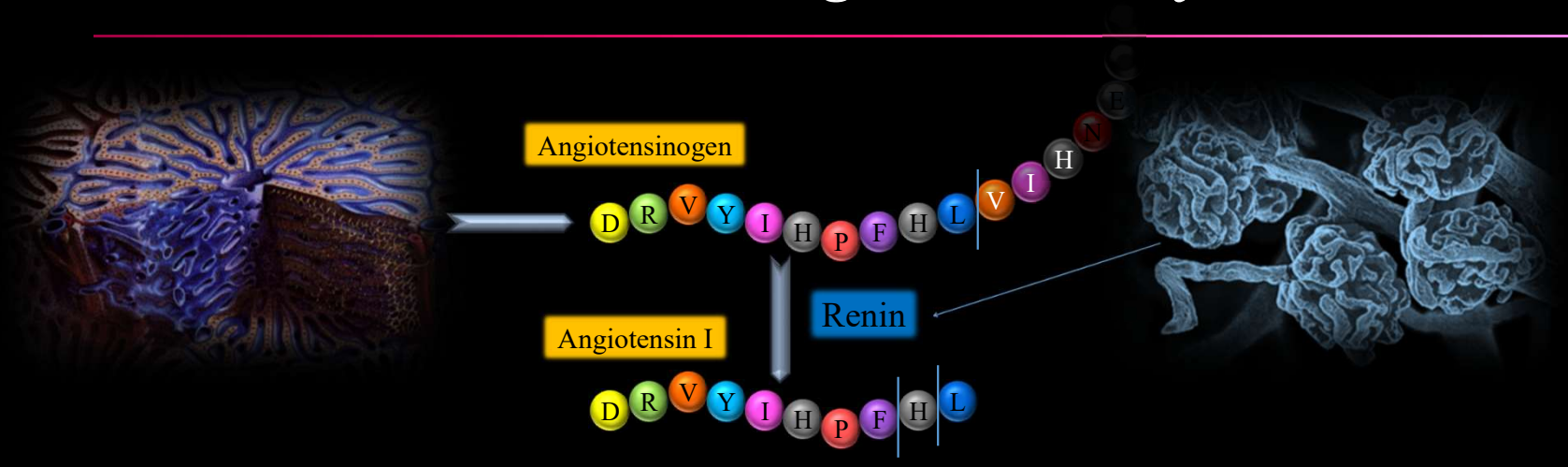


1. Lin, et al. *J Manag Care Pharm* 2016. 2. Hines DM et al. Poster presented at ACC 2017.

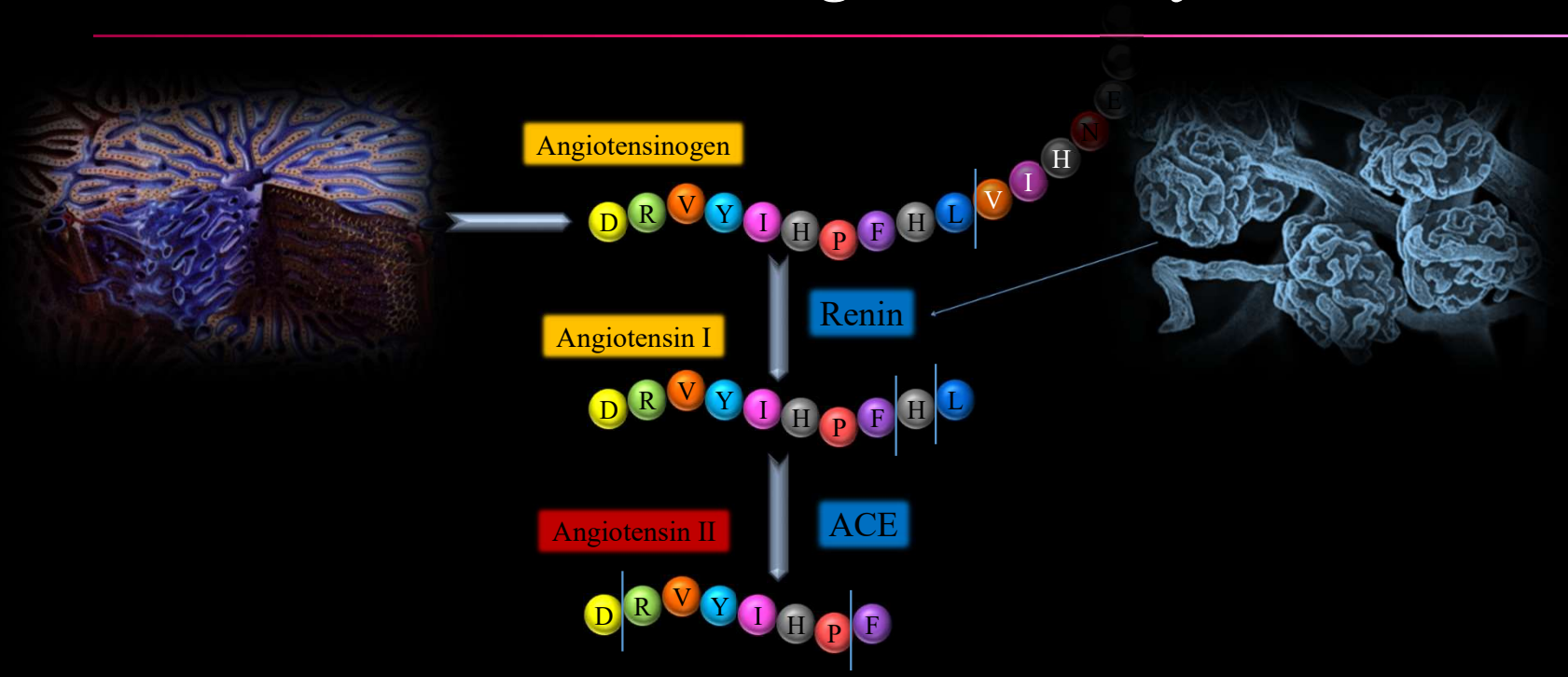
Example 2: angiotensin converting enzyme inhibitors



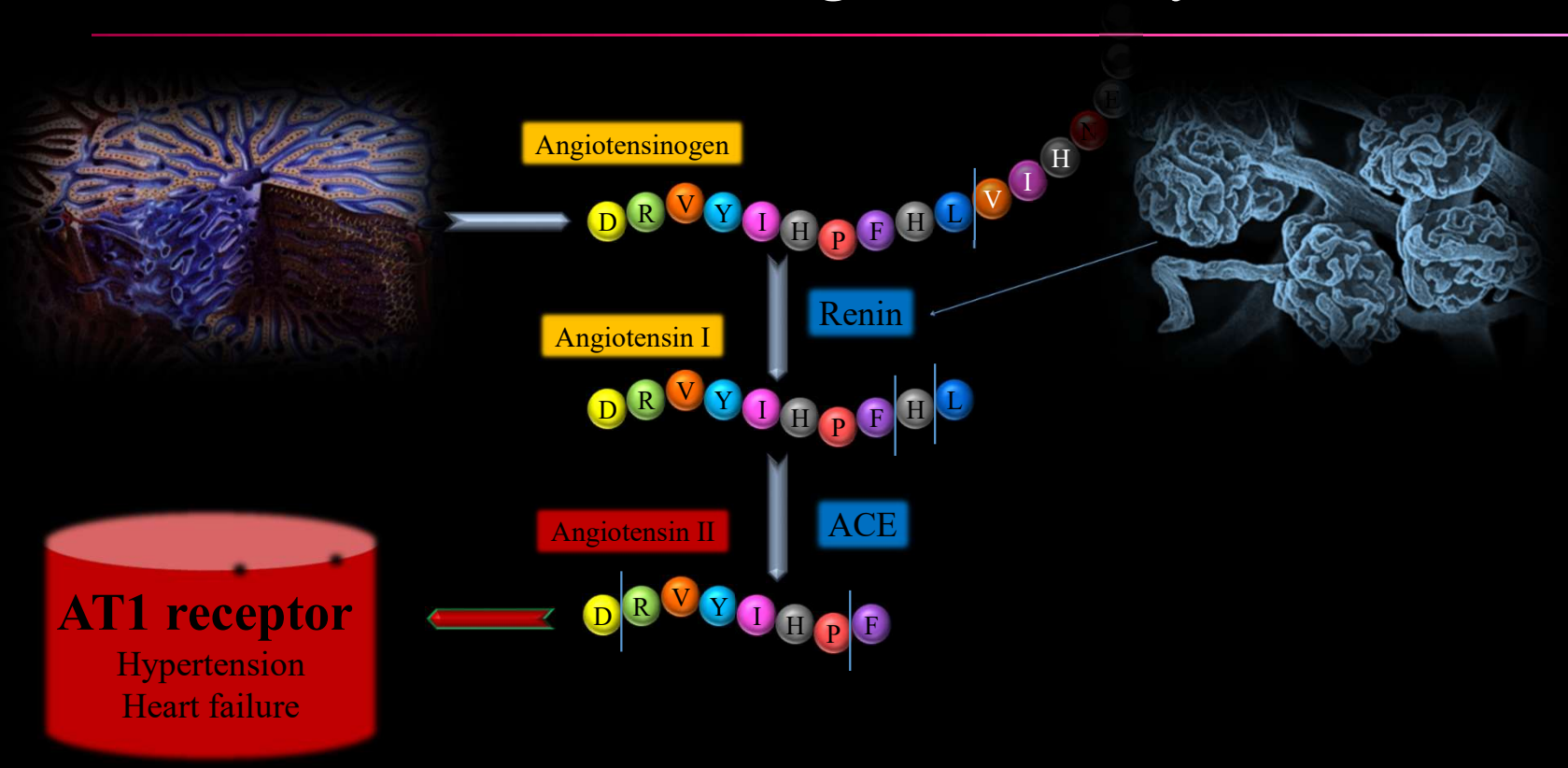
The renin-angiotensin-system



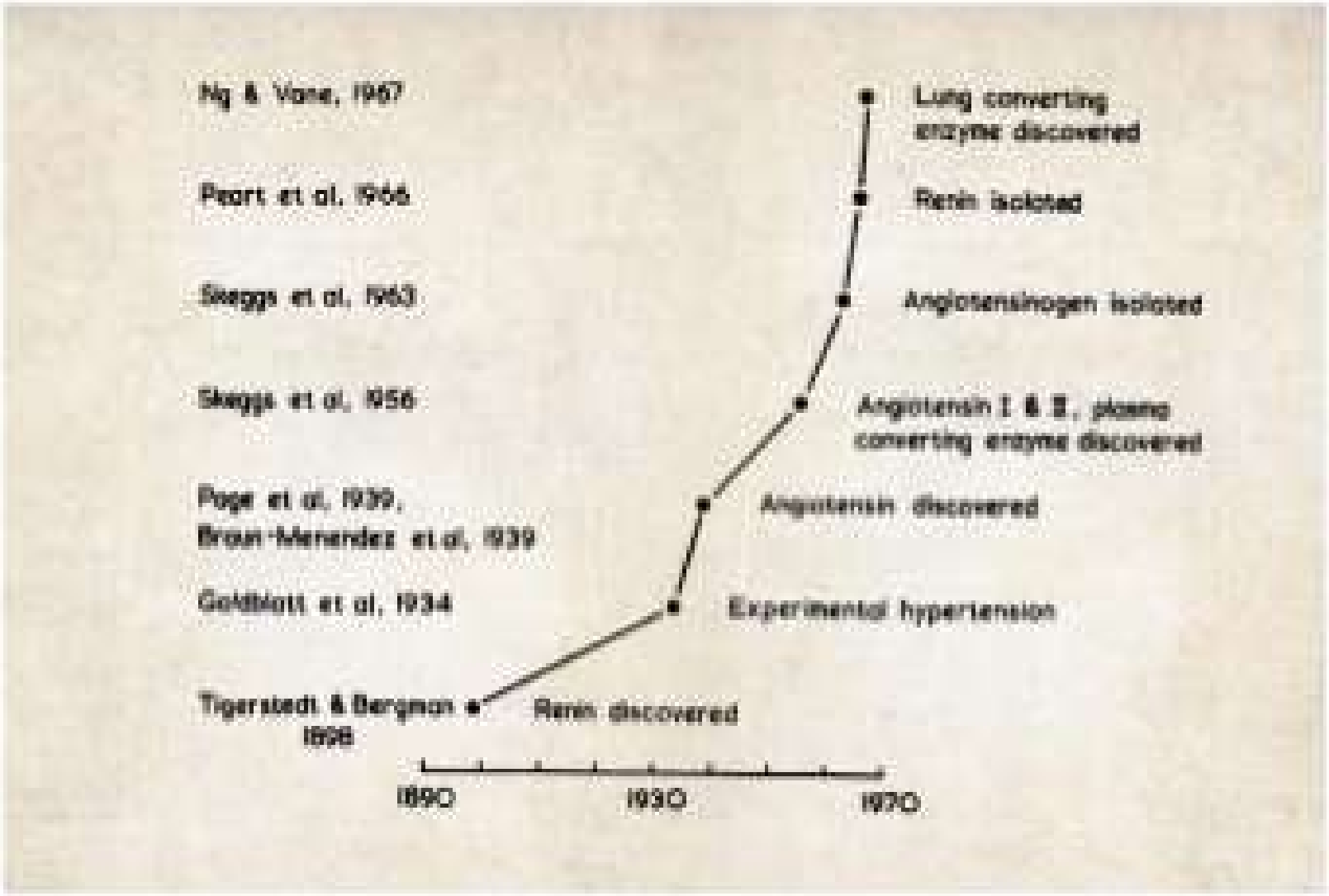
The renin-angiotensin-system



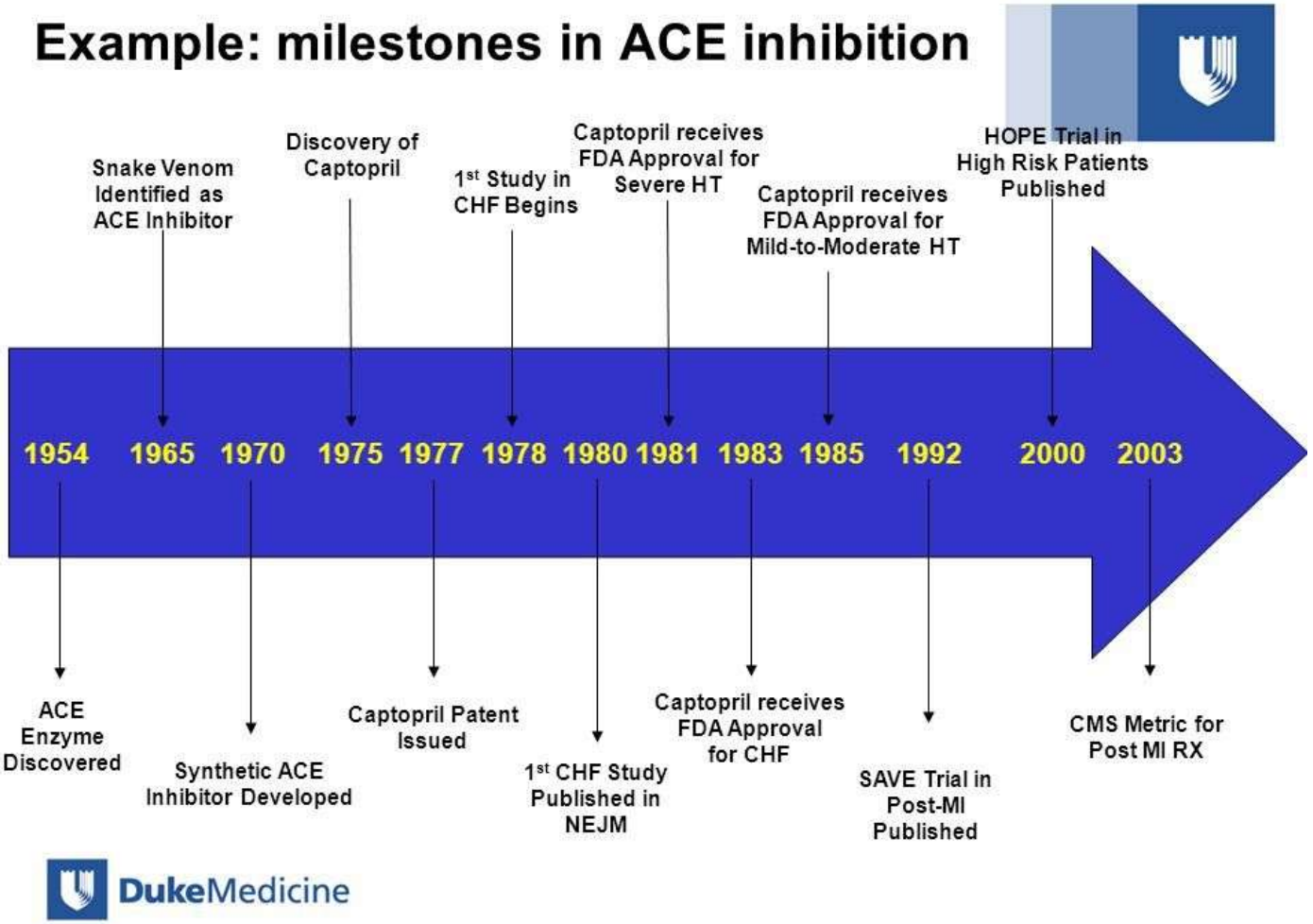
The renin-angiotensin-system



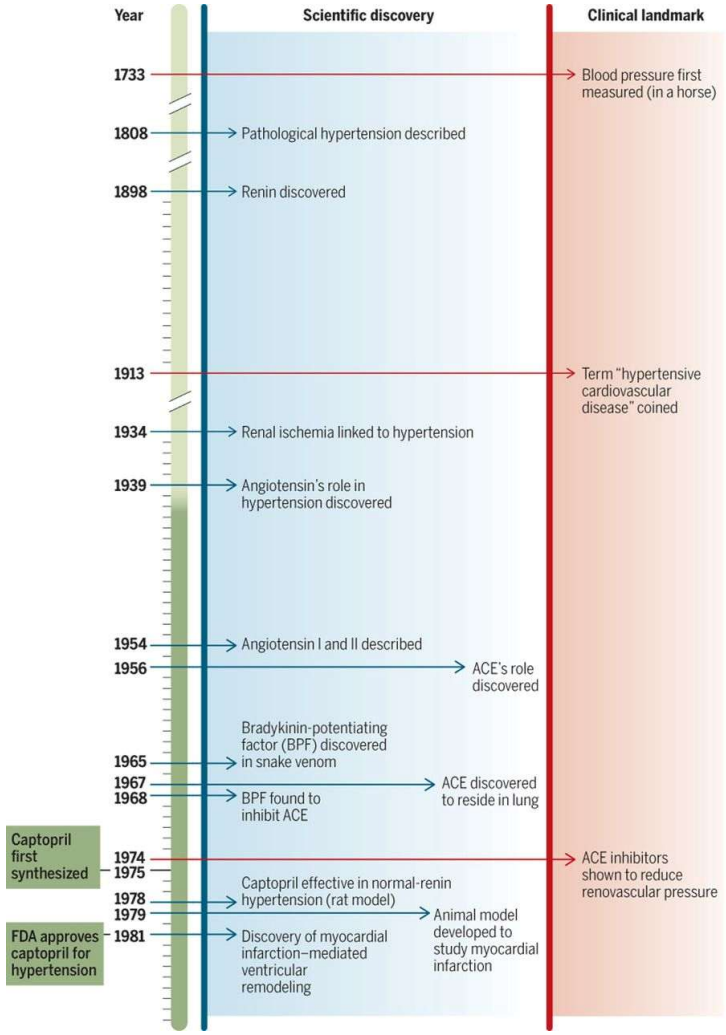
RAS timeline



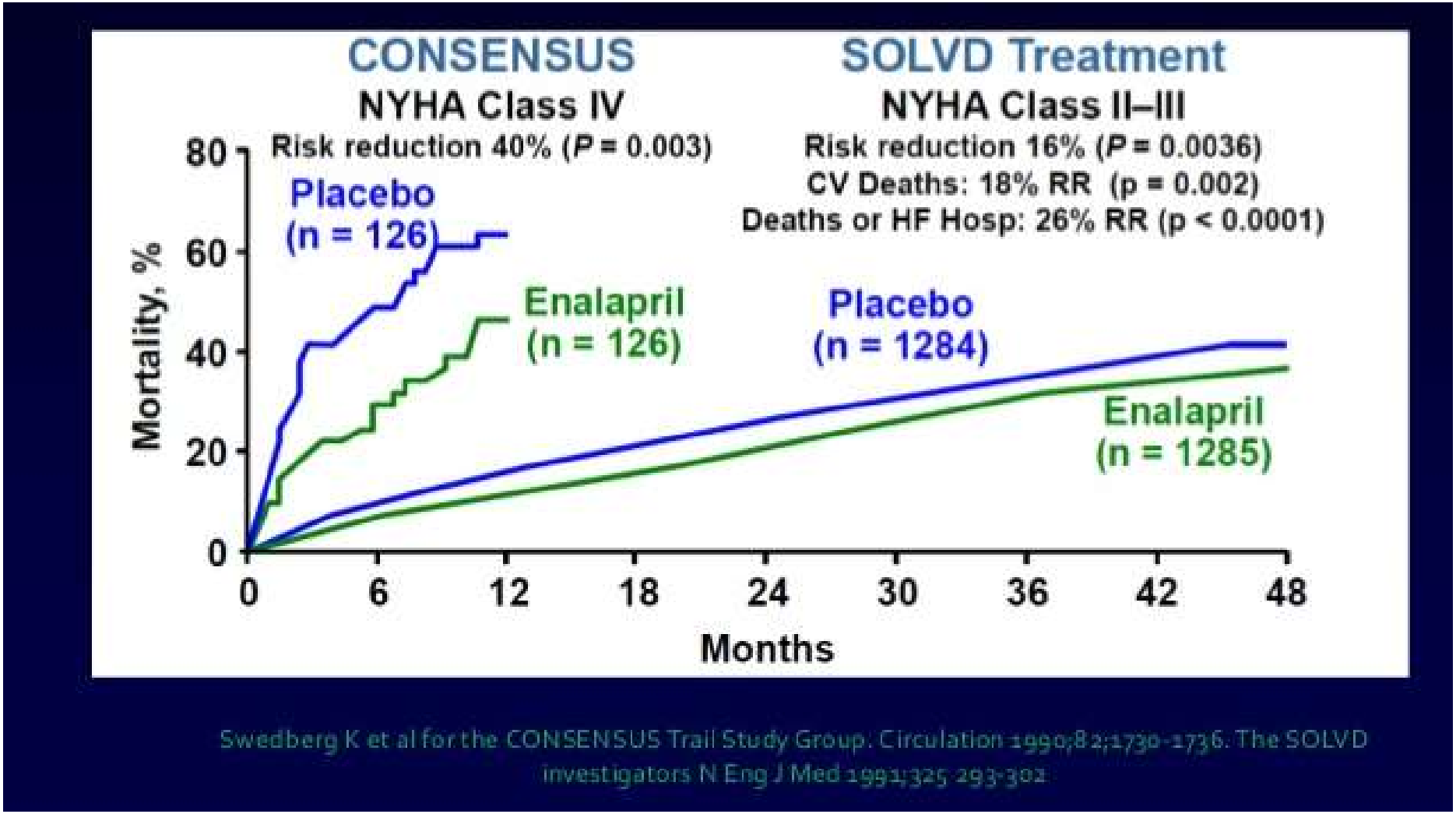
ACEi timeline



RAS timeline



Clinical success: significantly improved mortality



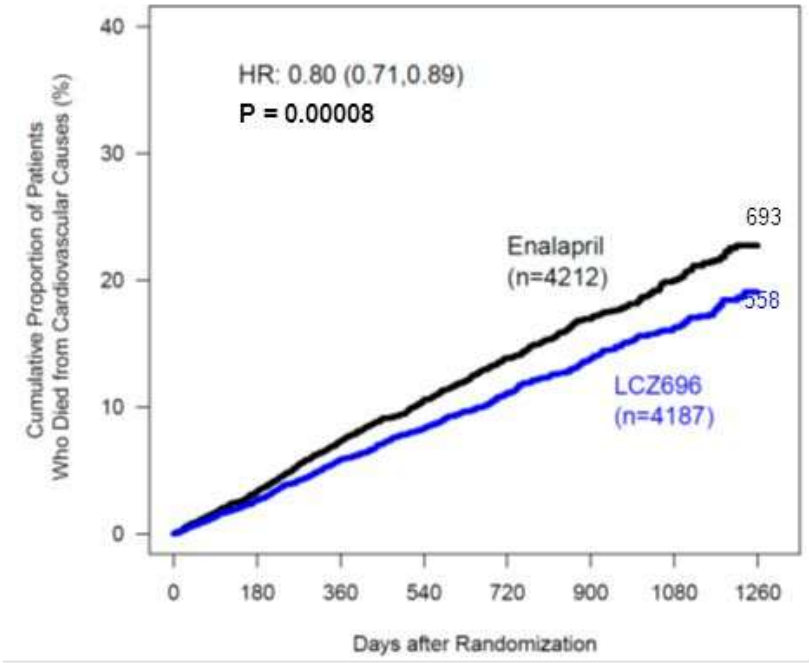
Swedberg K et al for the CONSENSUS Trail Study Group: Circulation 1990;82;1730-1736. The SOLVD investigators N Eng J Med 1991;325 293-302

PARADIGM-HF

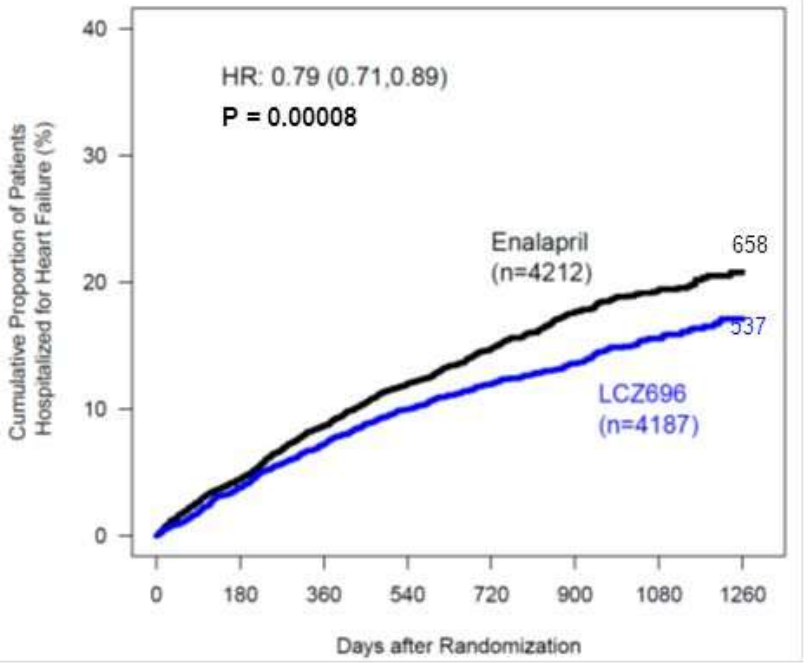
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Primary composite outcome
HR: 0.80 (0.73, 0.87) p = 0.0000004

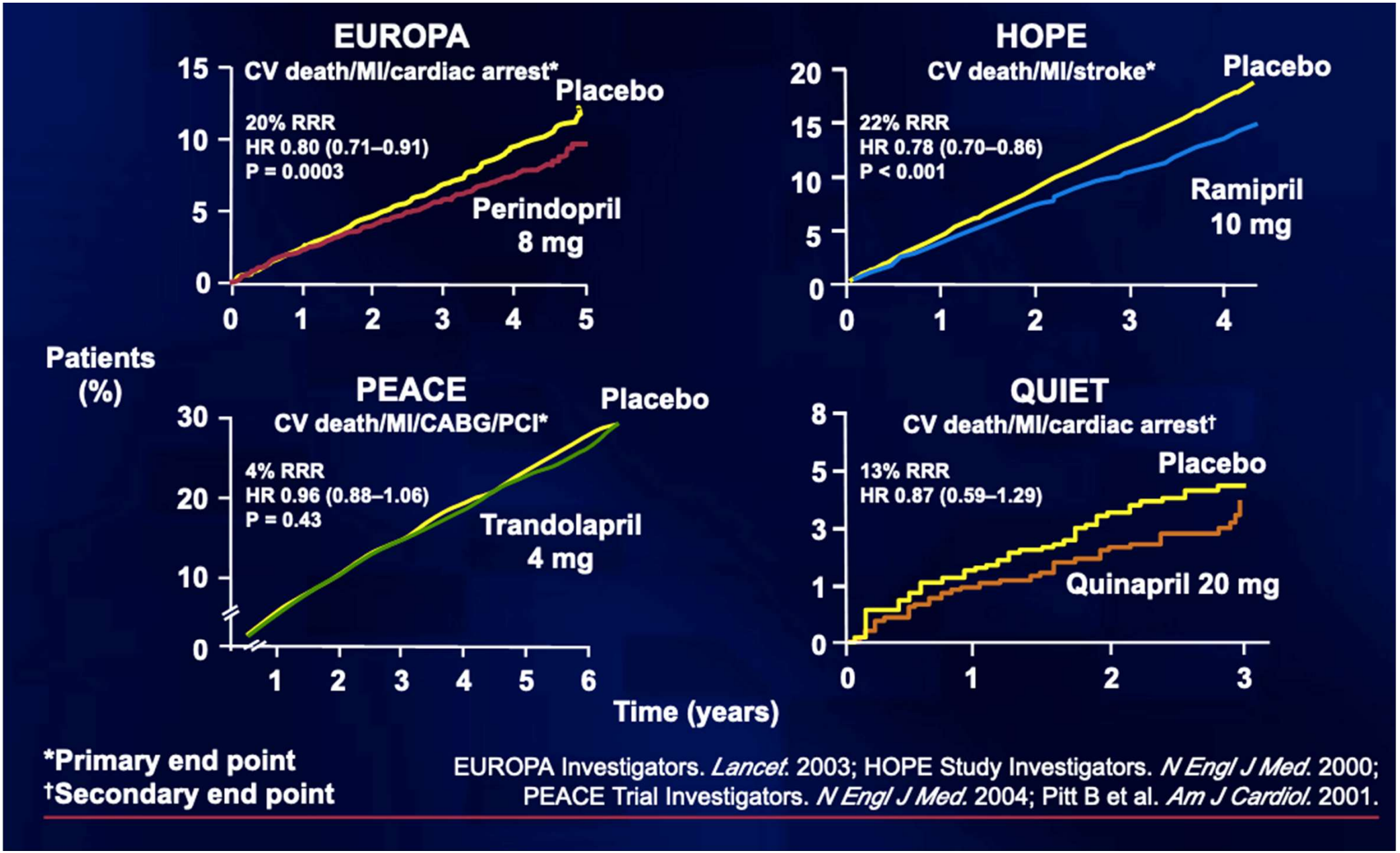
Death from CV causes
20% risk reduction



HF hospitalization
21% risk reduction



McMurray, Packer et al NEJM 2014


EUROPA
CV death/MI/cardiac arrest*
Placebo
20% RRR
HR 0.80 (0.71–0.91)
P = 0.0003
Perindopril
8 mg
HOPE
CV death/MI/stroke*
Placebo
22% RRR
HR 0.78 (0.70–0.86)
P < 0.001
Ramipril
10 mg
Patients
(%)
PEACE
CV death/MI/CABG/PCI*
Placebo
4% RRR
HR 0.96 (0.88–1.06)
P = 0.43
Trandolapril
4 mg
QUIET
CV death/MI/cardiac arrest†
13% RRR
HR 0.87 (0.59–1.29)
Placebo
Quinapril 20 mg
Time (years)
*Primary end point
†Secondary end point
EUROPA Investigators. Lancet. 2003; HOPE Study Investigators. N Engl J Med. 2000;
PEACE Trial Investigators. N Engl J Med. 2004; Pitt B et al. Am J Cardiol. 2001.

Limitations: side effects

SIDE EFFECTS OF CAPTOPRIL / ACE INHIBITORS

C	COUGH
A	ACUTE RENAL FAILURE
P	PREGNANCY (C/I)
T	TASTE ALTERATION
O	ANGIOEDEMA
P	PROTEINURIA
R	RASH, URTICARIA
I	INCREASE K^+
L	LOW BLOOD PRESSURE

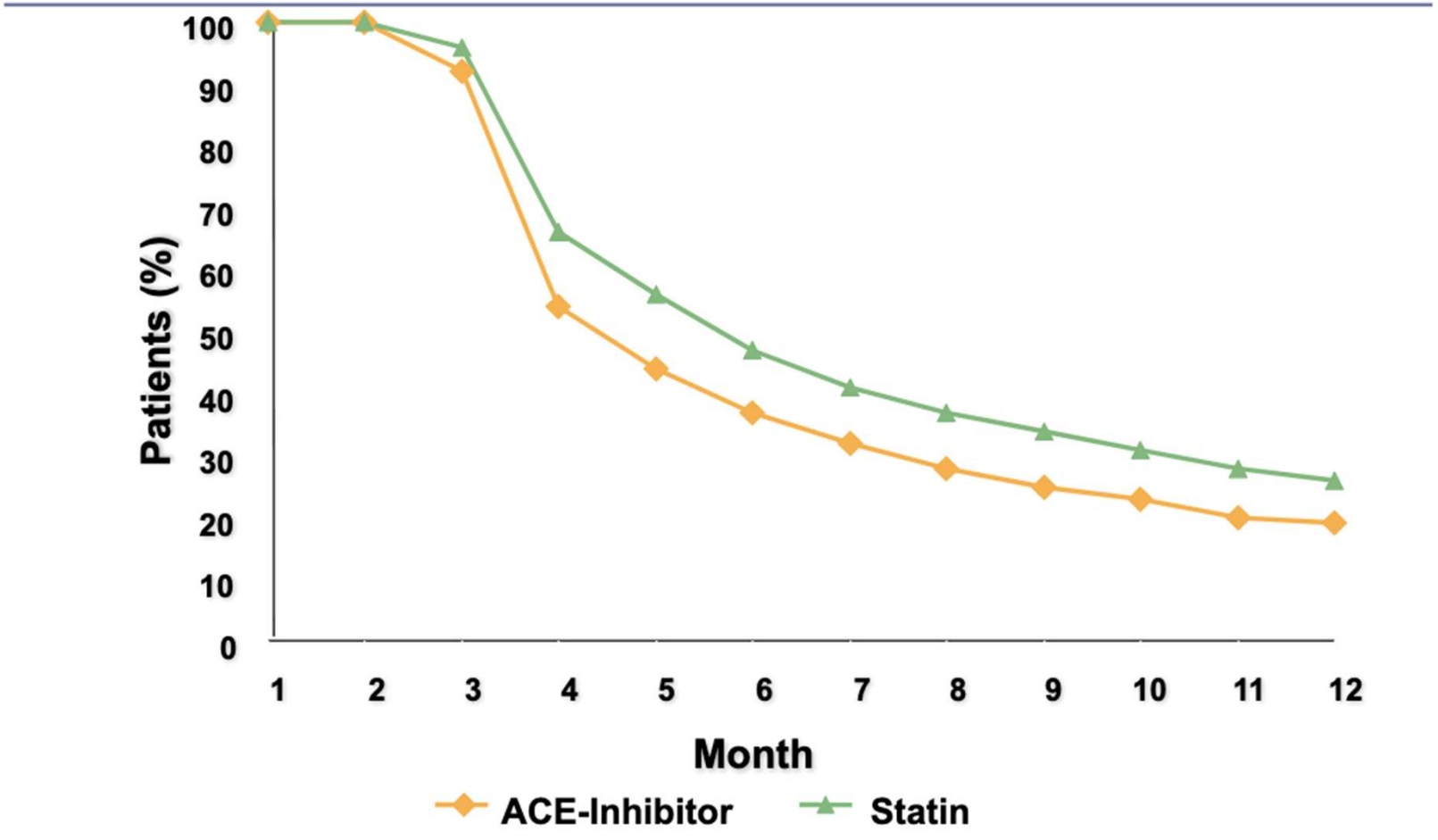
OTHER MEMBERS

Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril

ONLY L & C ARE NOT PRODRUGS

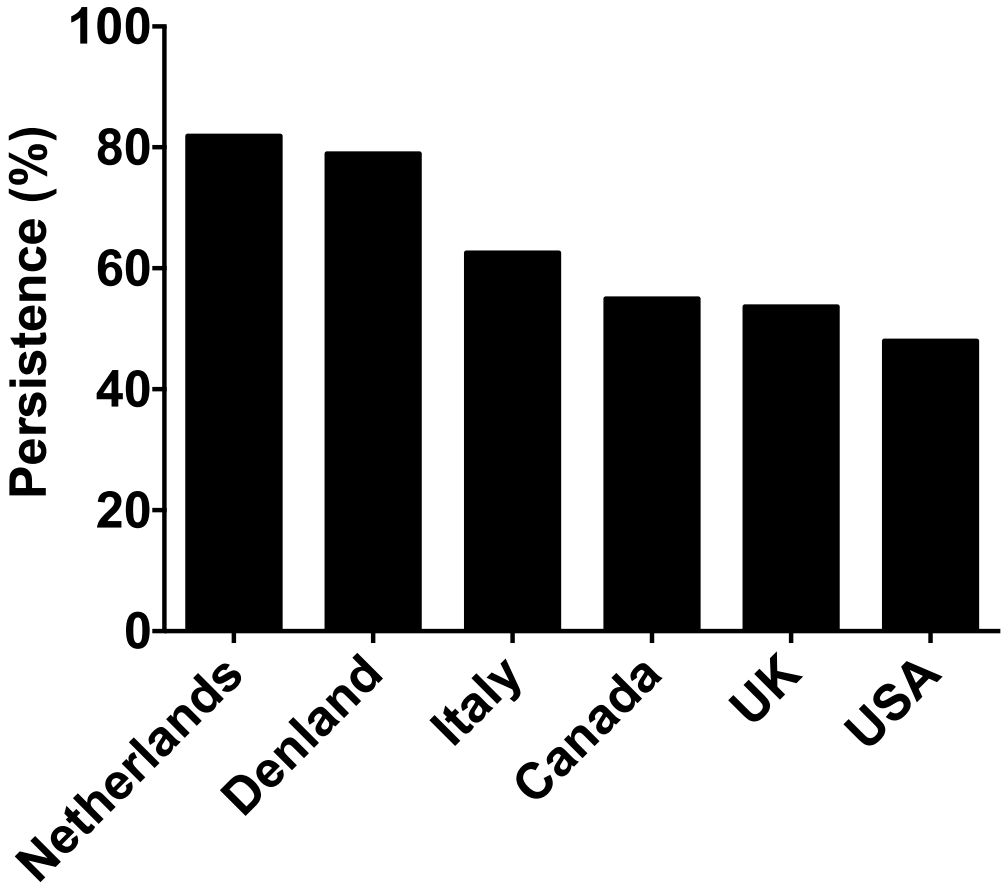
Real world situation: non-adherence

Real world situation: non-adherence

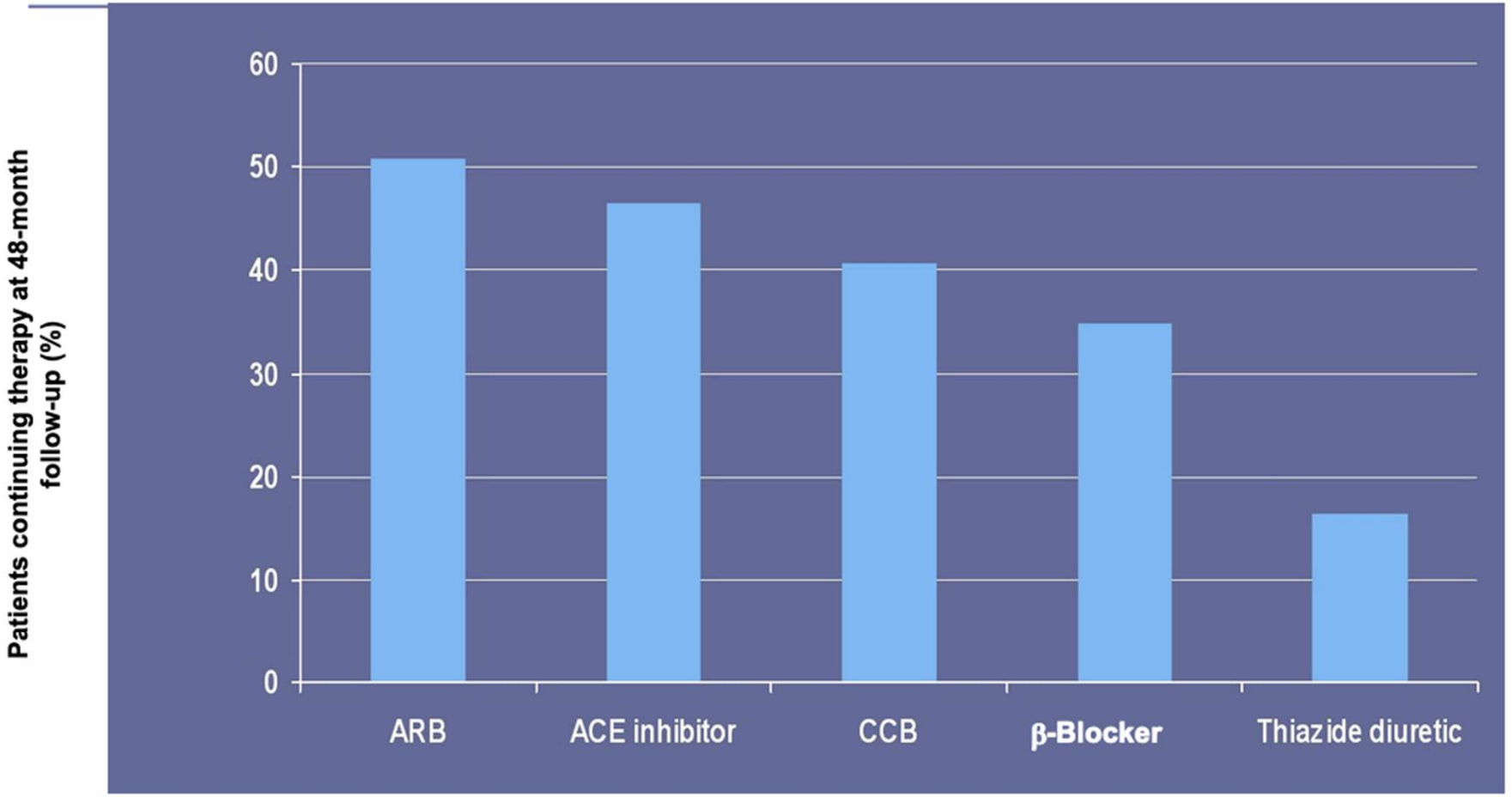


Courtesy: Ockene IS; Source: IMS Health data, 1996.

Persistence for ACE inhibitors – Global



Persistence for cardiovascular drugs



Retrospective, records-based, cohort study of patients on antihypertensive medication using the Merck-Medco Managed Care LLC Research Convenience Sample database (N=15,175).

Conlin PR et al. *Clin Ther.* 2001;23:1999-2010.

Personalized medicine

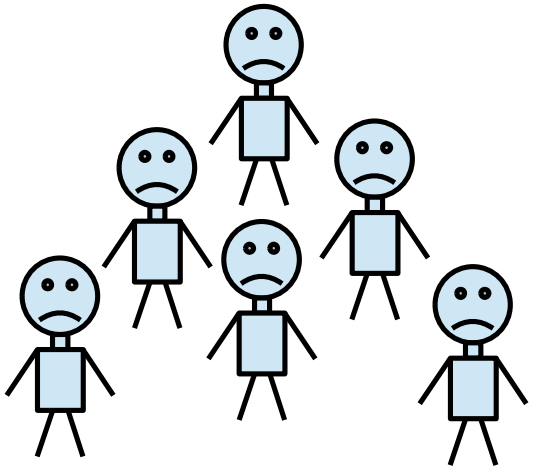
Personalized medicine, precision medicine, or **theranostics** is a medical model that separates people into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. The terms personalized medicine, precision medicine, **stratified medicine** and P4 medicine are used interchangeably to describe this concept though some authors and organisations use these expressions separately to indicate particular nuances.
While the tailoring of treatment to patients dates back at least to the time of Hippocrates, the term has risen in usage in recent years given the growth of new diagnostic and informatics approaches that provide understanding of the molecular basis of disease, particularly genomics. This provides a clear evidence base on which to stratify (group) related patients.

www.wikipedia.org

Precision medicine is an approach to patient care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their disease. This may also be called personalized medicine.

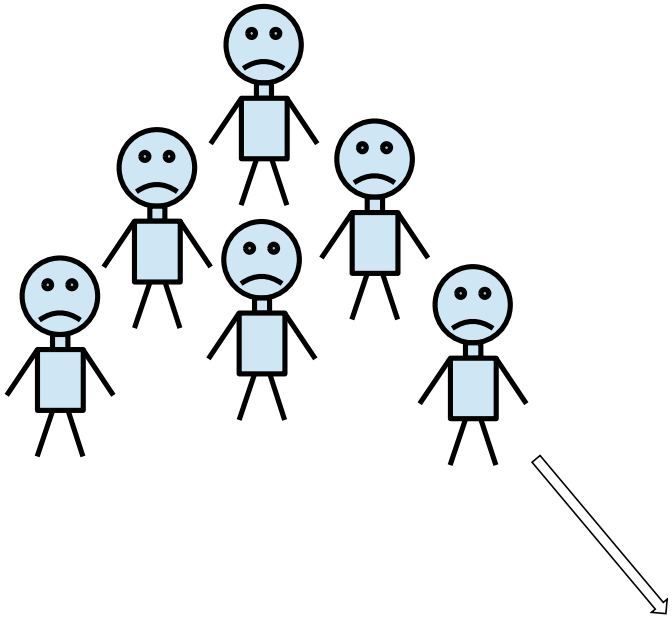
www.cancer.gov

Evidence based medicine



Stratification
According to the guidelines
(hypertensive, diabetic, etc.)

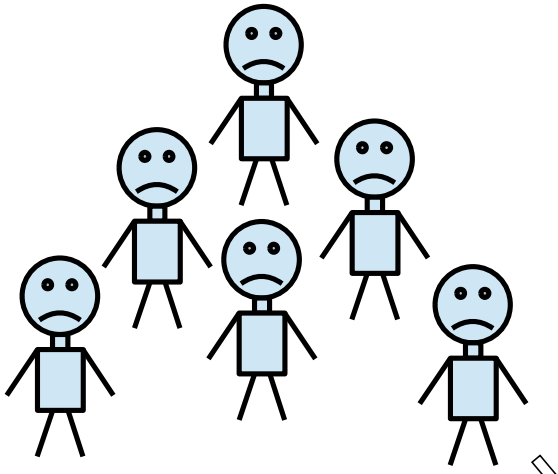
Evidence based medicine



Stratification
According to the guidelines
(hypertensive, diabetic, etc.)

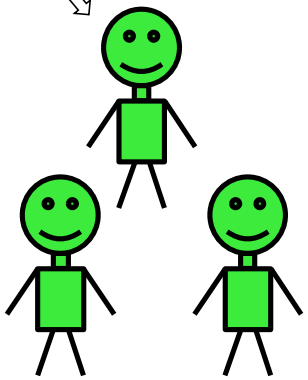
Prescription of medication
According to the guidelines

Evidence based medicine



Stratification
According to the guidelines
(hypertensive, diabetic, etc.)

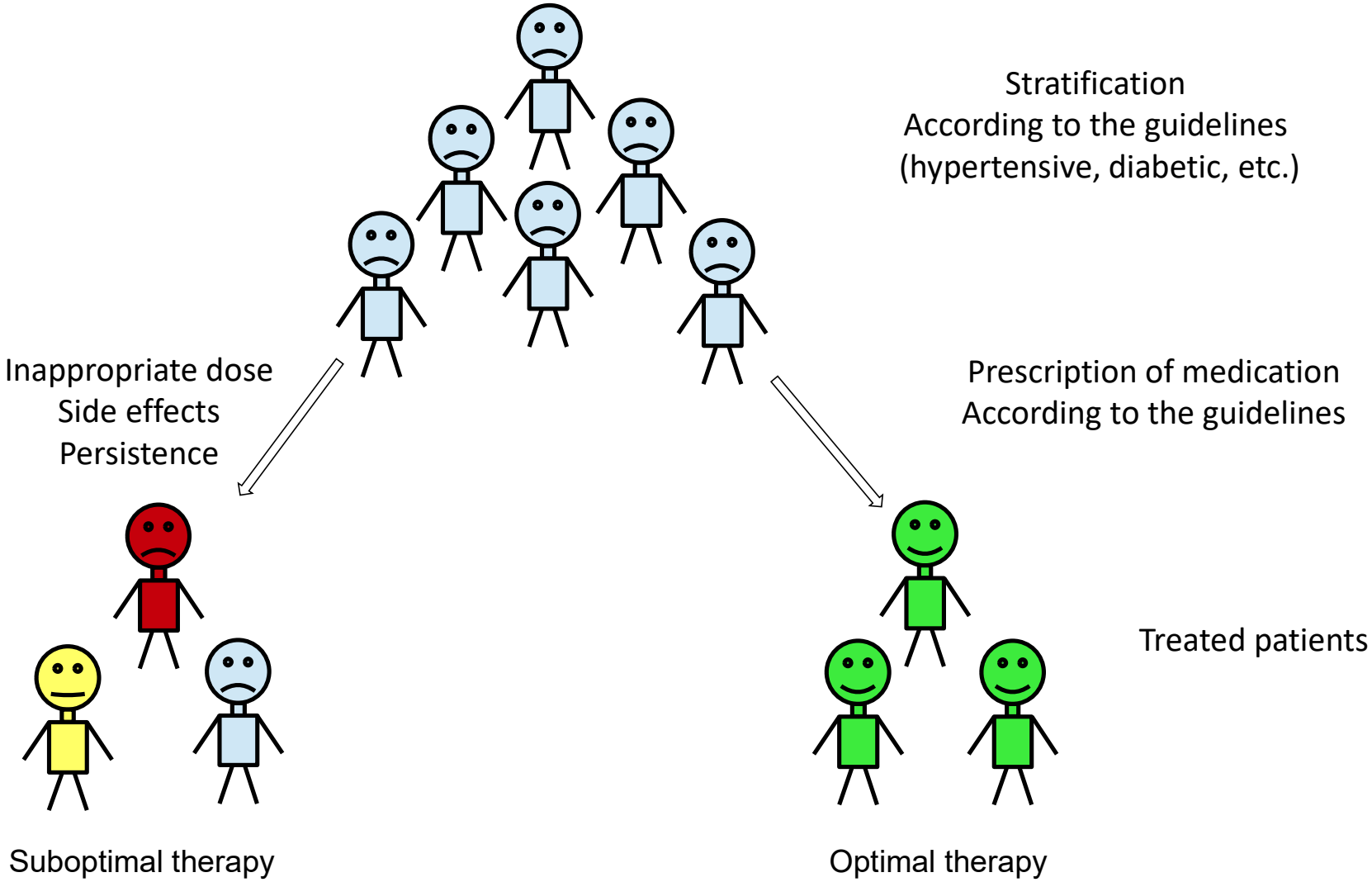
Prescription of medication
According to the guidelines



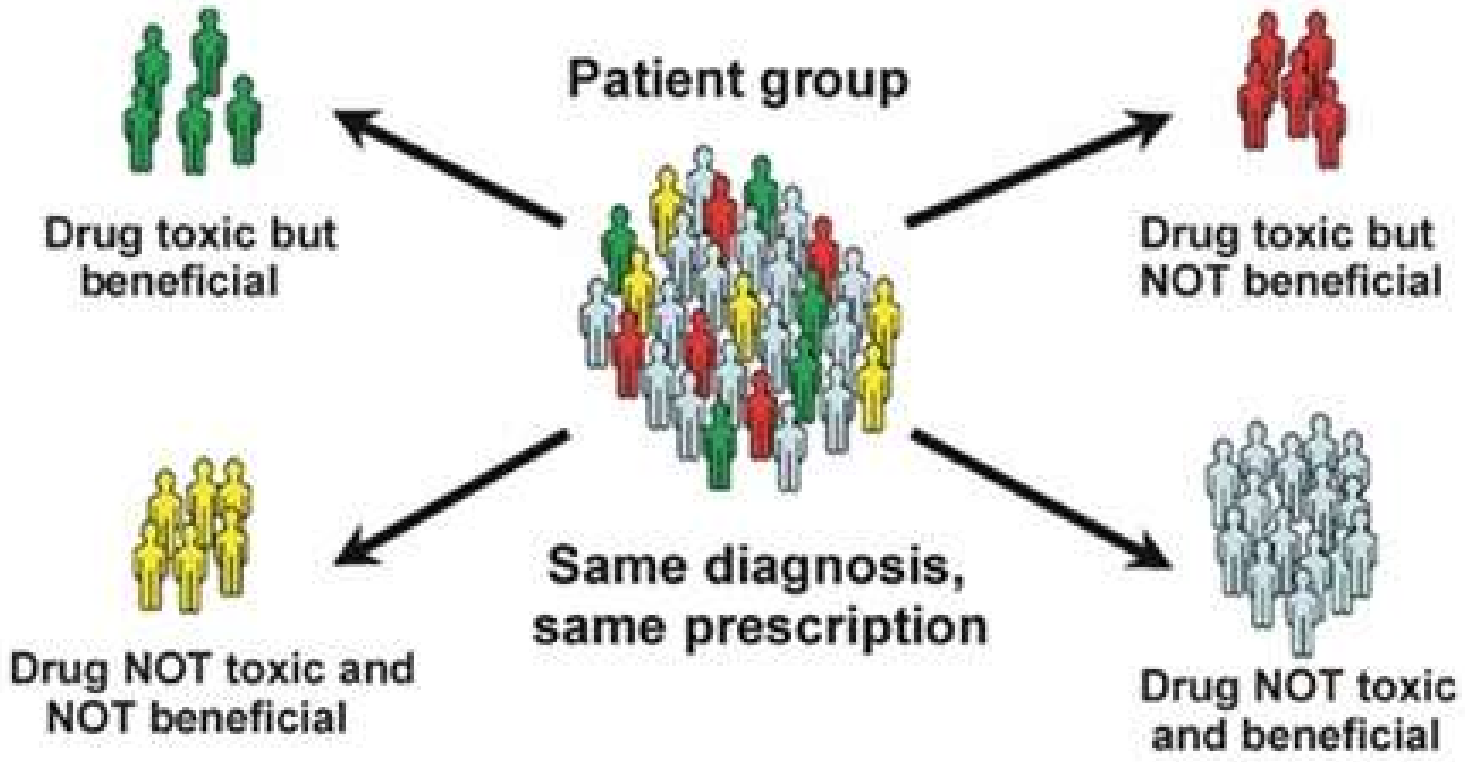
Treated patients

Optimal therapy

Evidence based medicine

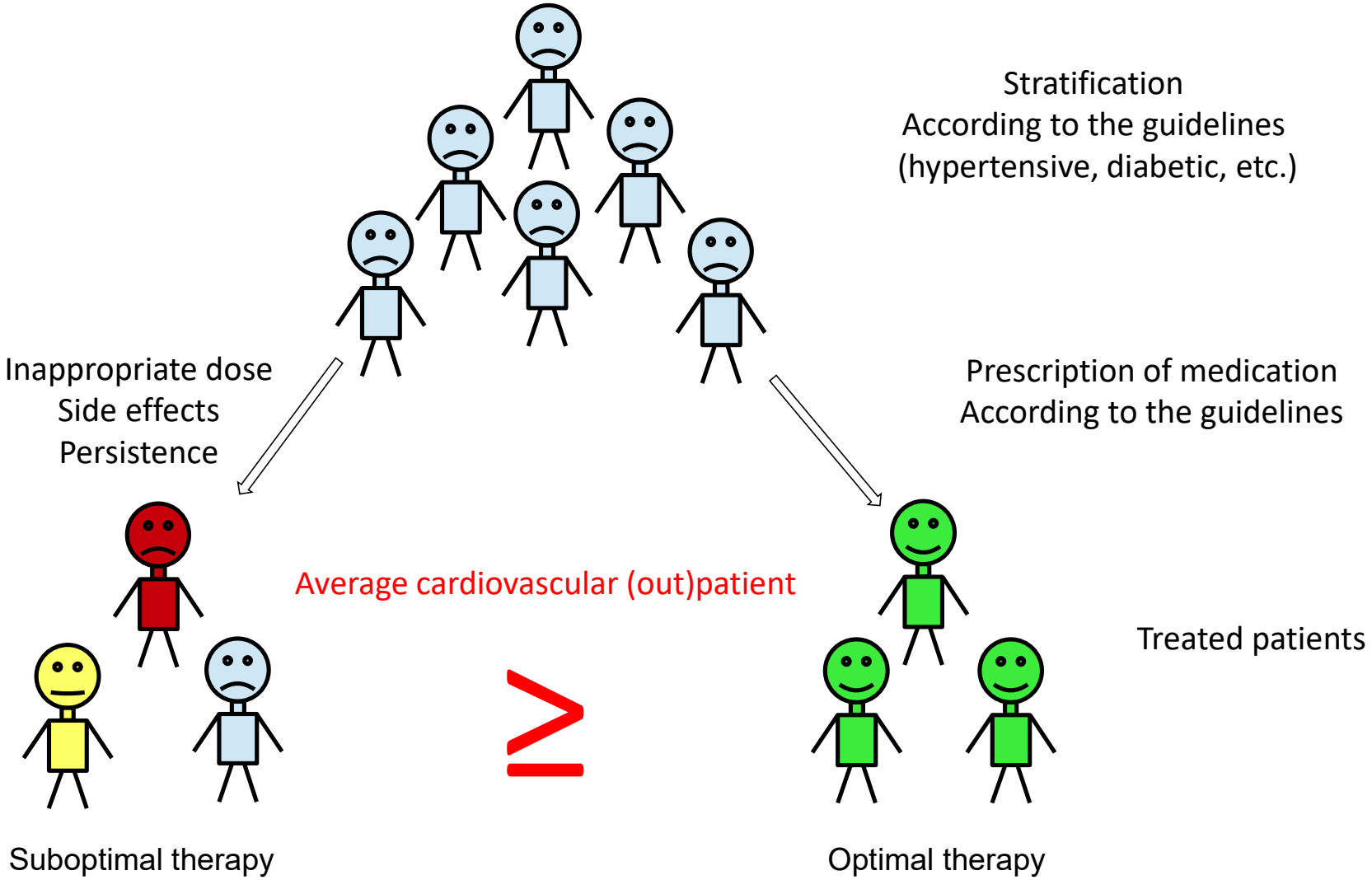


Appropriate dose

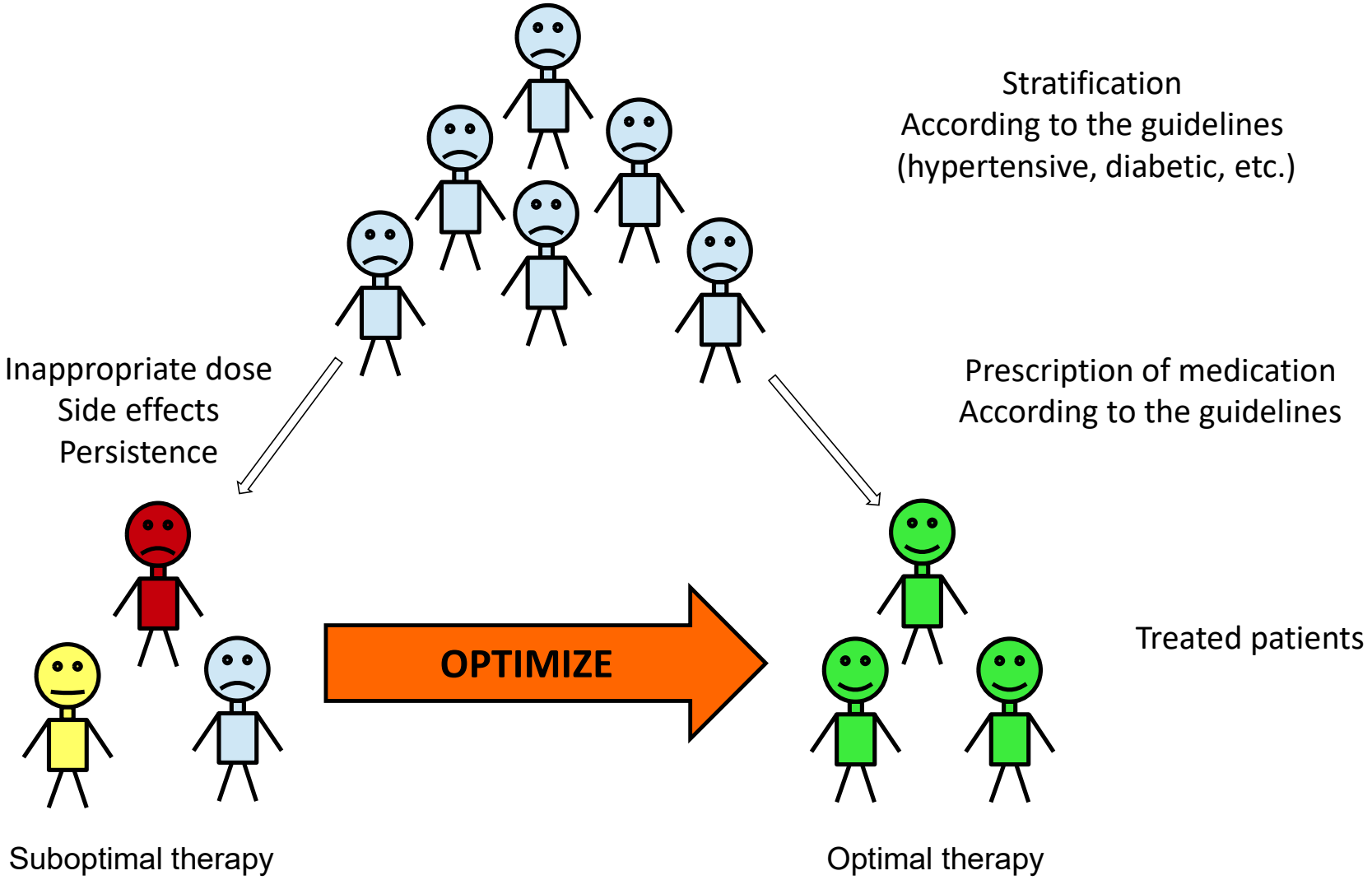


http://stevebetz.wordpress.com/

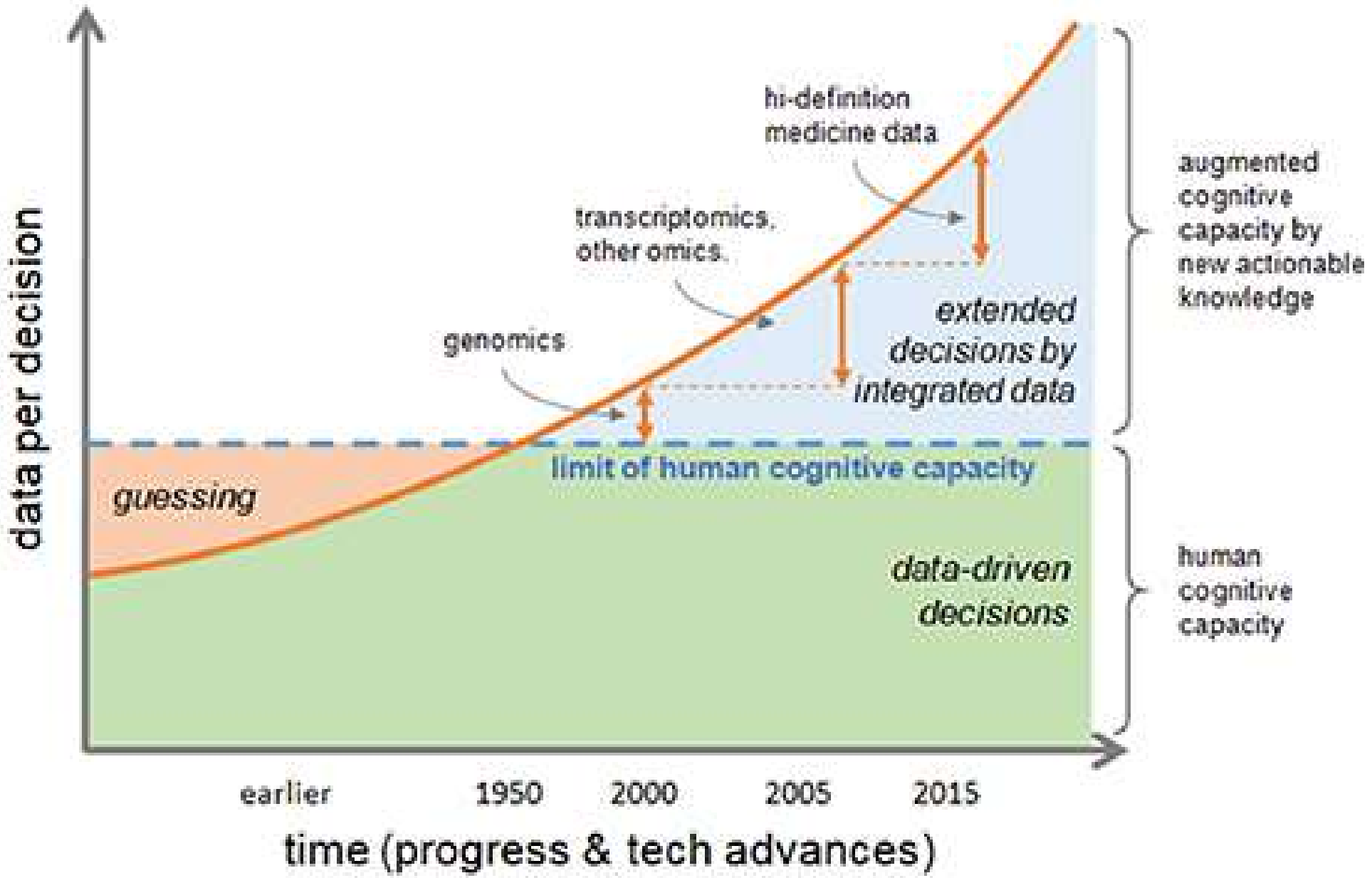
Evidence based medicine



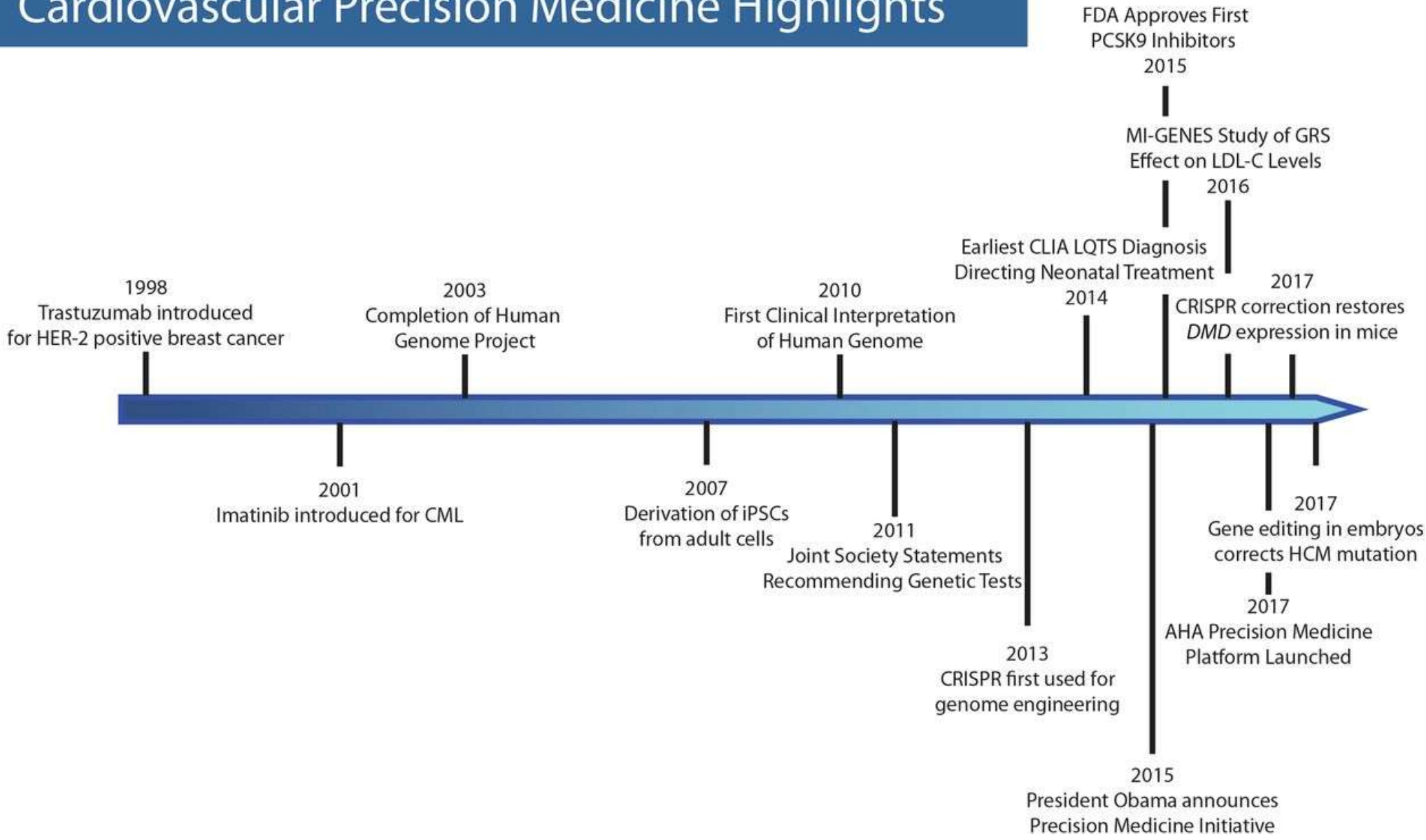
Evidence based medicine

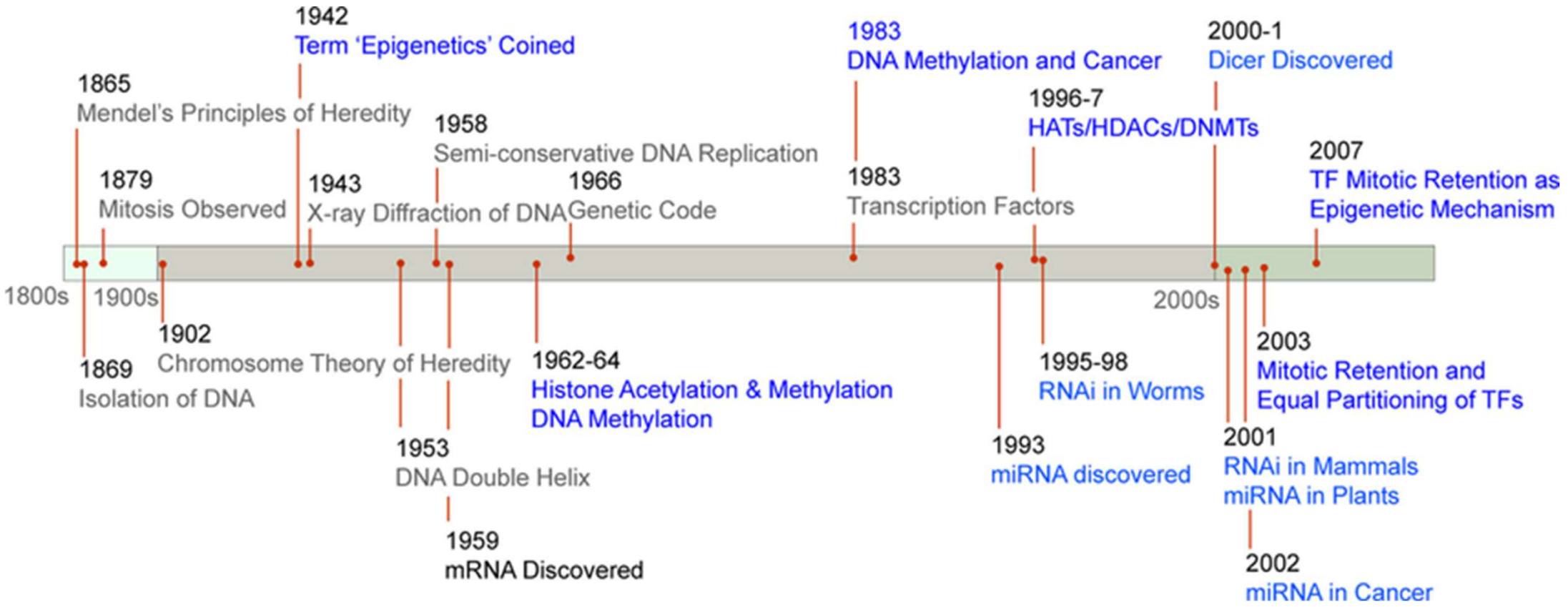


The genomic approach

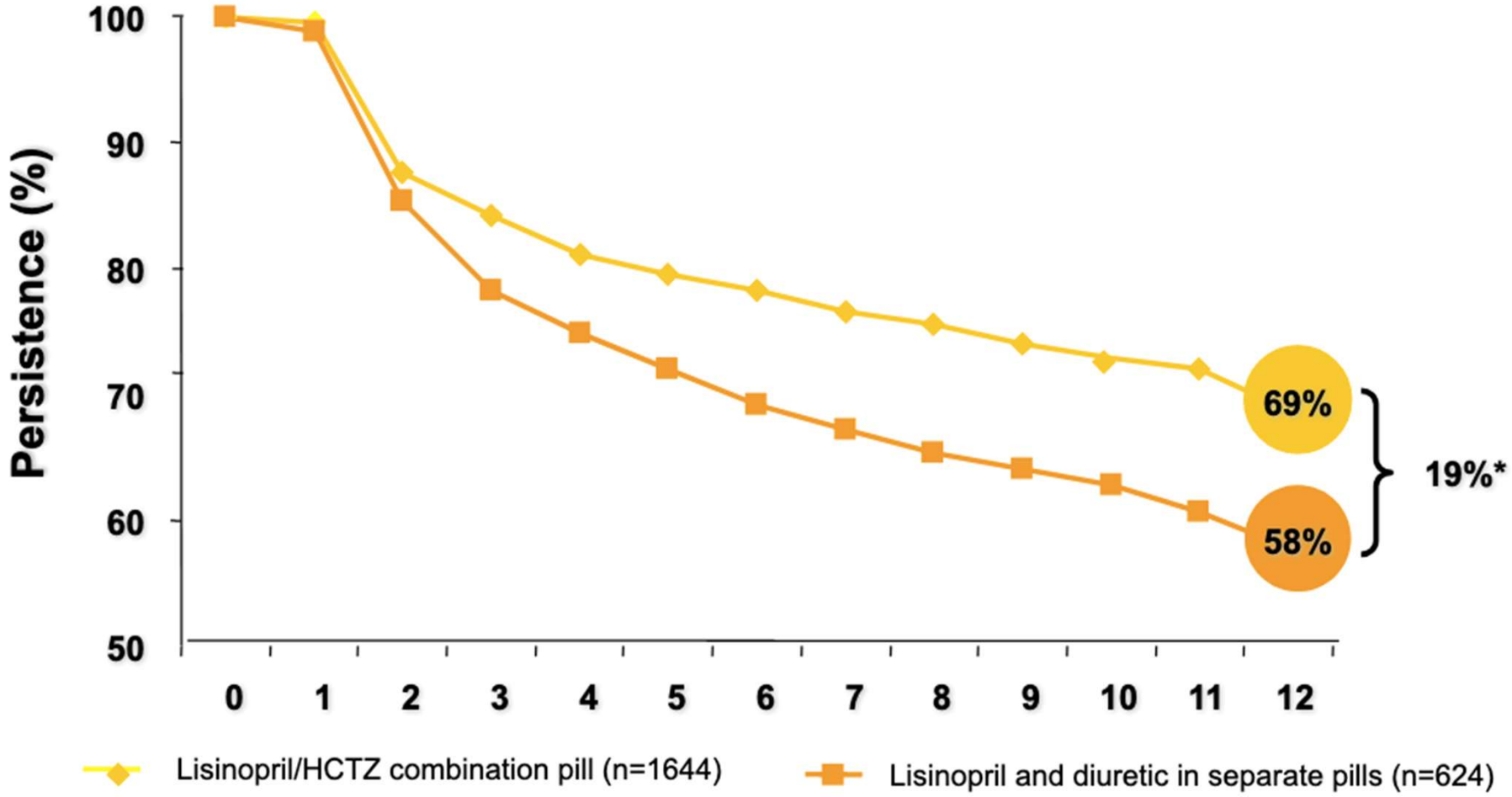

data per decision
hi-definition
medicine data
transcriptomics,
other omics,
genomics
extended
decisions by
integrated data
augmented
cognitive
capacity by
new actionable
knowledge
limit of human cognitive capacity
guessing
data-driven
decisions
human
cognitive
capacity
earlier
1950
2000
2005
2015
time (progress & tech advances)

Cardiovascular Precision Medicine Highlights




1942
Term 'Epigenetics' Coined
1865
Mendel's Principles of Heredity
1958
Semi-conservative DNA Replication
1879
Mitosis Observed
1943
X-ray Diffraction of DNA
1966
Genetic Code
1983
DNA Methylation and Cancer
1983
Transcription Factors
1996-7
HATs/HDACs/DNMTs
2000-1
Dicer Discovered
2007
TF Mitotic Retention as
Epigenetic Mechanism
1800s
1900s
2000s
1902
Chromosome Theory of Heredity
1869
Isolation of DNA
1962-64
Histone Acetylation & Methylation
DNA Methylation
1995-98
RNAi in Worms
2003
Mitotic Retention and
Equal Partitioning of TFs
1953
DNA Double Helix
1993
miRNA discovered
2001
RNAi in Mammals
miRNA in Plants
1959
mRNA Discovered
2002
miRNA in Cancer

The combination approach: one pill for all

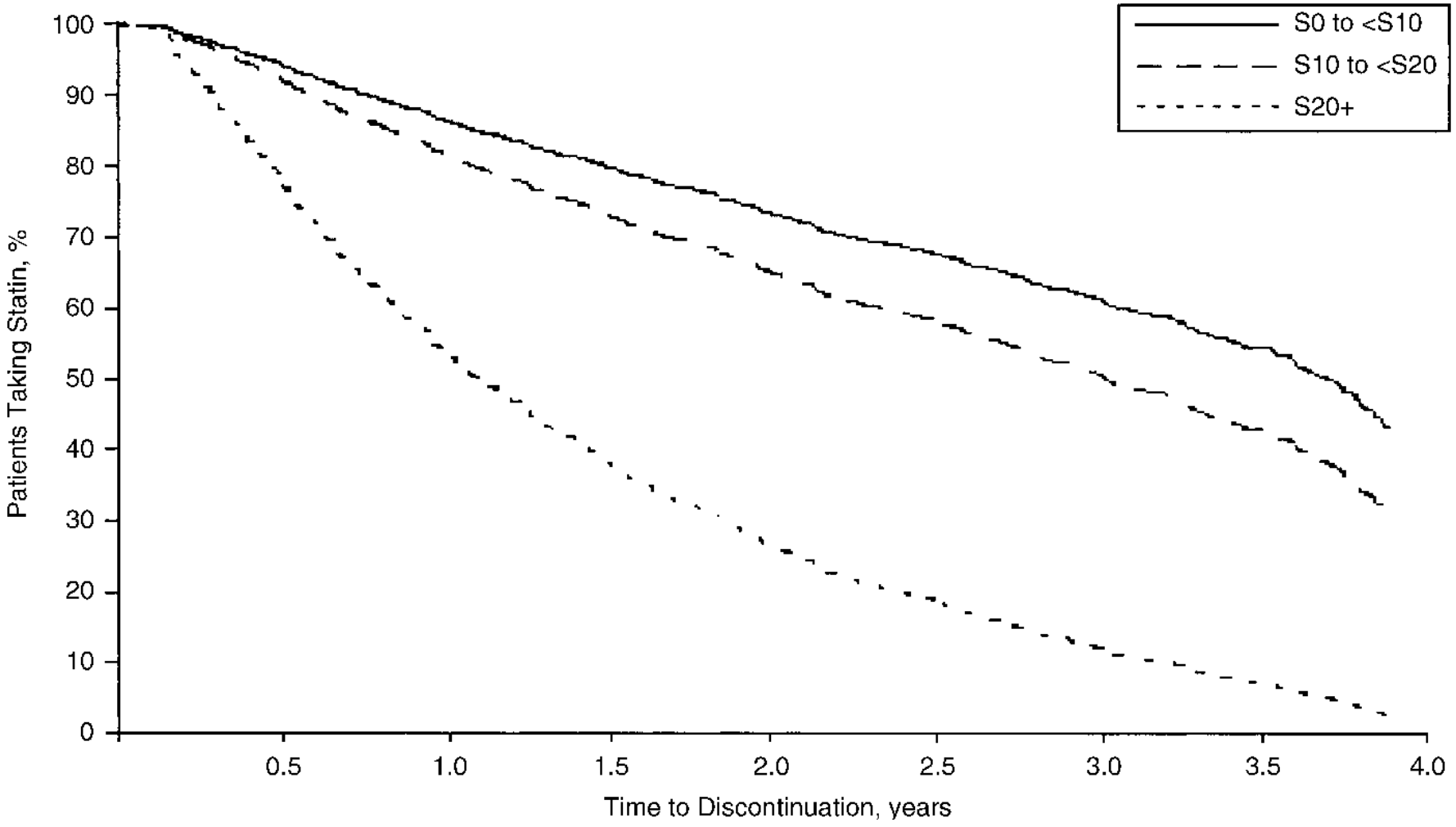


*$P<0.05$ vs. fixed-dose combination

Dezii C. *Managed Care*. 2000;(Suppl 2):6-10.

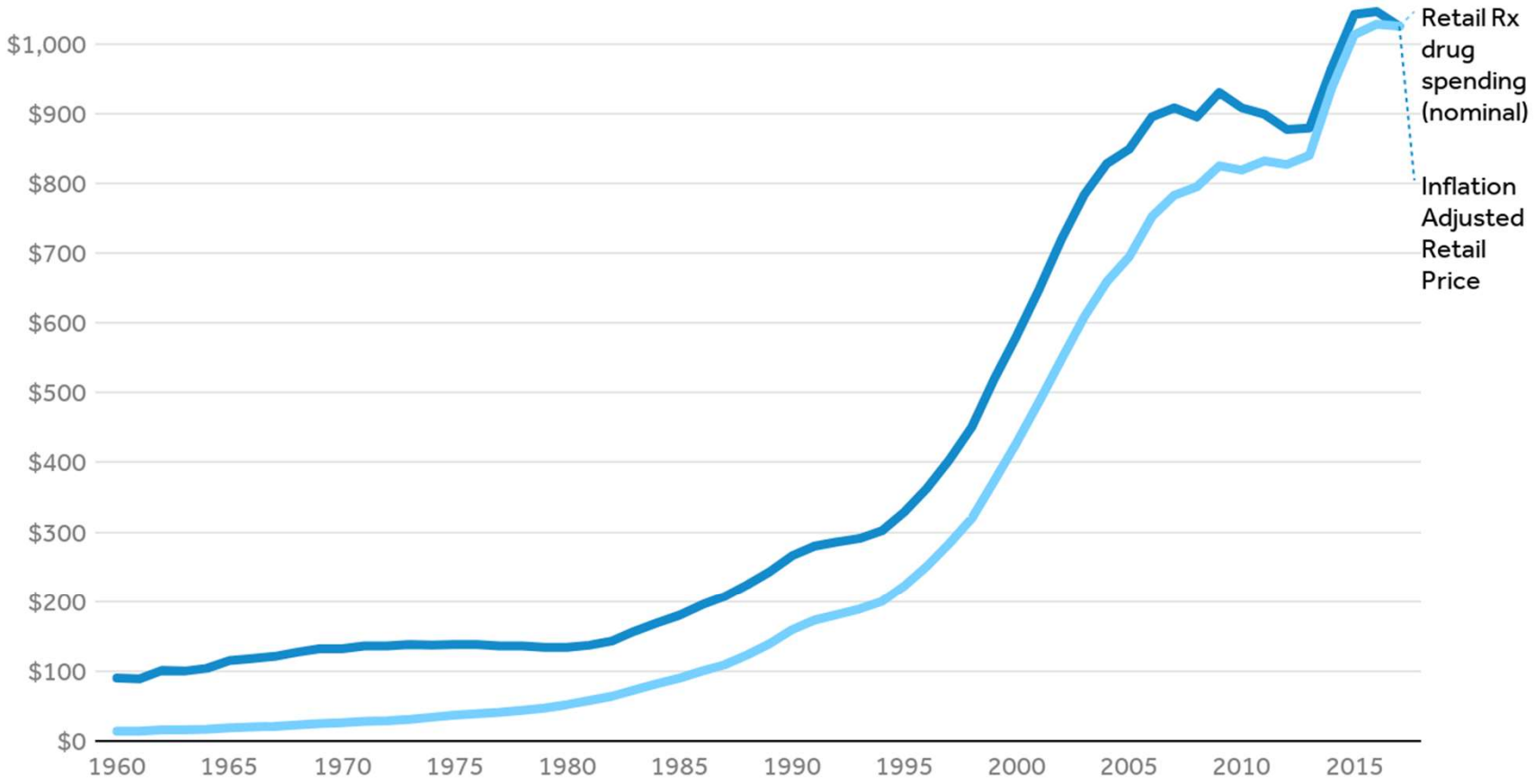
The economic approach

Real world situation: cost of treatment



Bernstein et al., Journal of General Internal Medicine, 19, 638-645.

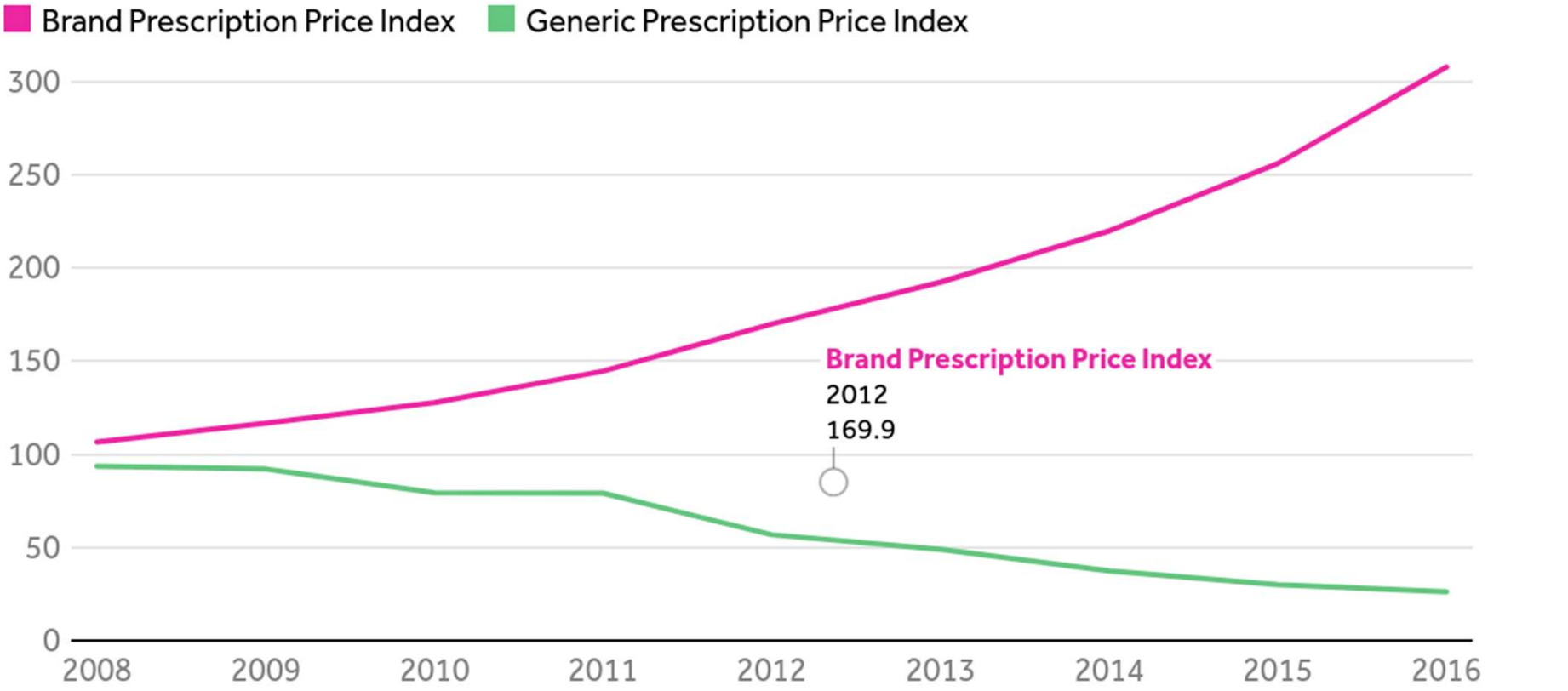
Nominal and inflation-adjusted per capita spending on retail prescription drugs, 1960-2017



Source: Kaiser Family Foundation Analysis of National Health Expenditures Account • Get the data • PNG

Peterson-Kaiser
Health System Tracker

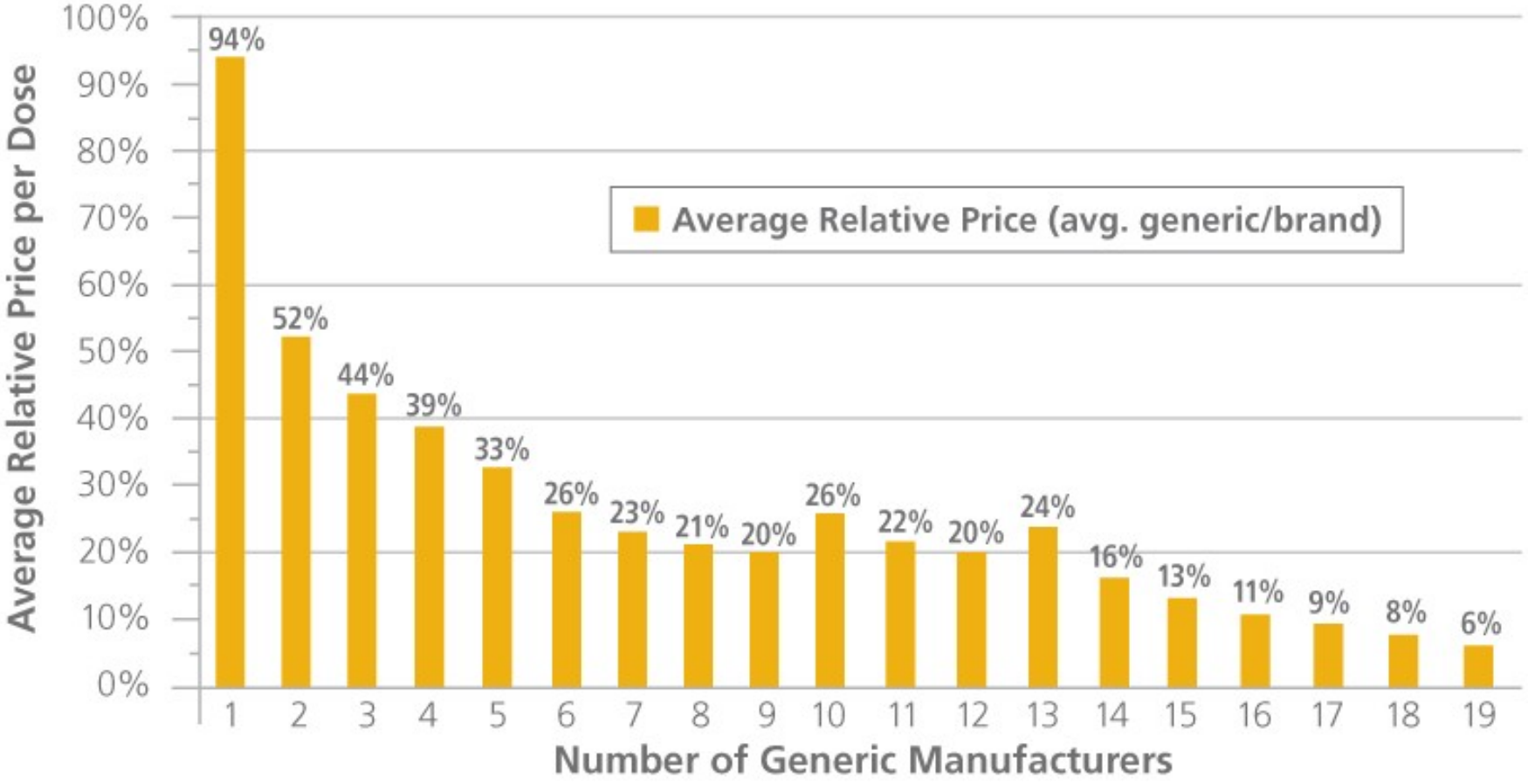
Express Scripts Prescription Price Index, 2008 - 2016



Source: Express Scripts Prescription Price Index • Get the data • PNG

Peterson-Kaiser
Health System Tracker

Generic Competition and Drug Prices



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective (TM), 1999-2004, extracted February 2005

FDA. Generic Competition and Drug Prices 03/01/2010. Accessed at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm on 12.02.2014.

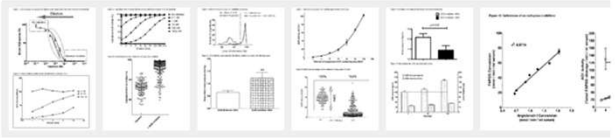
The biomarker approach

Dilution based inhibition assay

Abstract

The present invention provides for a process to assess the level of reversible inhibition of an enzyme by an inhibitor, in particular in the field of assessment the effectiveness of a medical treatment. In a particularly preferred embodiment the effectiveness of angiotensin converting enzyme (ACE) inhibitor (ACEi) therapy is disclosed. The invention also relates to uses of enzyme substrates and kits for the assessment of inhibition level as well as an apparatus designed for use in a process of the present invention.

Images (8)



Classifications

C12Q1/37 Measuring or testing processes involving enzymes, nucleic acids or microorganisms; Compositions therefor; Processes of preparing such compositions involving hydrolase involving peptidase or proteinase

View 1 more classifications

EP2664920A1
European Patent Office

Download PDF · Find Prior Art · Similar

Other languages: German, French

Inventor: Attila Dr. Tóth, Miklós Dr. Fagyas, Zoltán Prof. Dr. Papp, István Prof. Dr. Édes

Current Assignee : Debreceni Egyetem (Debrecen University)

Worldwide applications

2012 · *HU* 2013 · EP

Application EP13168263.5A events

2012-05-18 • Priority to HU1200299A

2013-05-17 • Application filed by Debreceni Egyetem (Debrecen University)

2013-11-20 • Publication of EP2664920A1

2019-04-01 • Application status is Pending

Info: Patent citations (8), Non-patent citations (63), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, EPO GPI, EP Register, Global Dossier, Discuss

Description

FIELD OF THE INVENTION

[0001] The present invention provides for a process to assess the level of reversible inhibition of an enzyme by an inhibitor, in particular in the field of assessment the effectiveness of a medical treatment. In a particularly preferred embodiment the effectiveness of an anti-hypertensive reversible enzyme inhibitor drug was tested. In particular the method was tested in angiotensin converting enzyme (ACE) inhibitor (ACEi) therapy. The invention also relates to uses of enzyme substrates and kits for the assessment of inhibition level as well as an apparatus designed for use in a process of the present invention.

BACKGROUND ART

[0002] The problem to assess efficiency or efficacy of enzyme inhibitor therapies obviously has been raised in the art. In these methods first of all a specific condition of the experiment is set, wherein typically enzyme activity of the patient treated is compared to the "normal" activity level of a healthy control group or a control group wherein the therapy is effective. However, this traditional method raises several issues. For example, a control group of subjects may be required, whereas said subjects necessarily have different pathophysiological properties (i.e. do not suffer in the same

Claims (15)

1. A process to assess the effectiveness of a medical treatment by an enzyme inhibitor by assessment of the level of reversible inhibition of the enzyme by the inhibitor, which process comprises:

   (a) obtaining at least one initial sample;

   (b) taking at least two aliquots from said at least one initial sample;

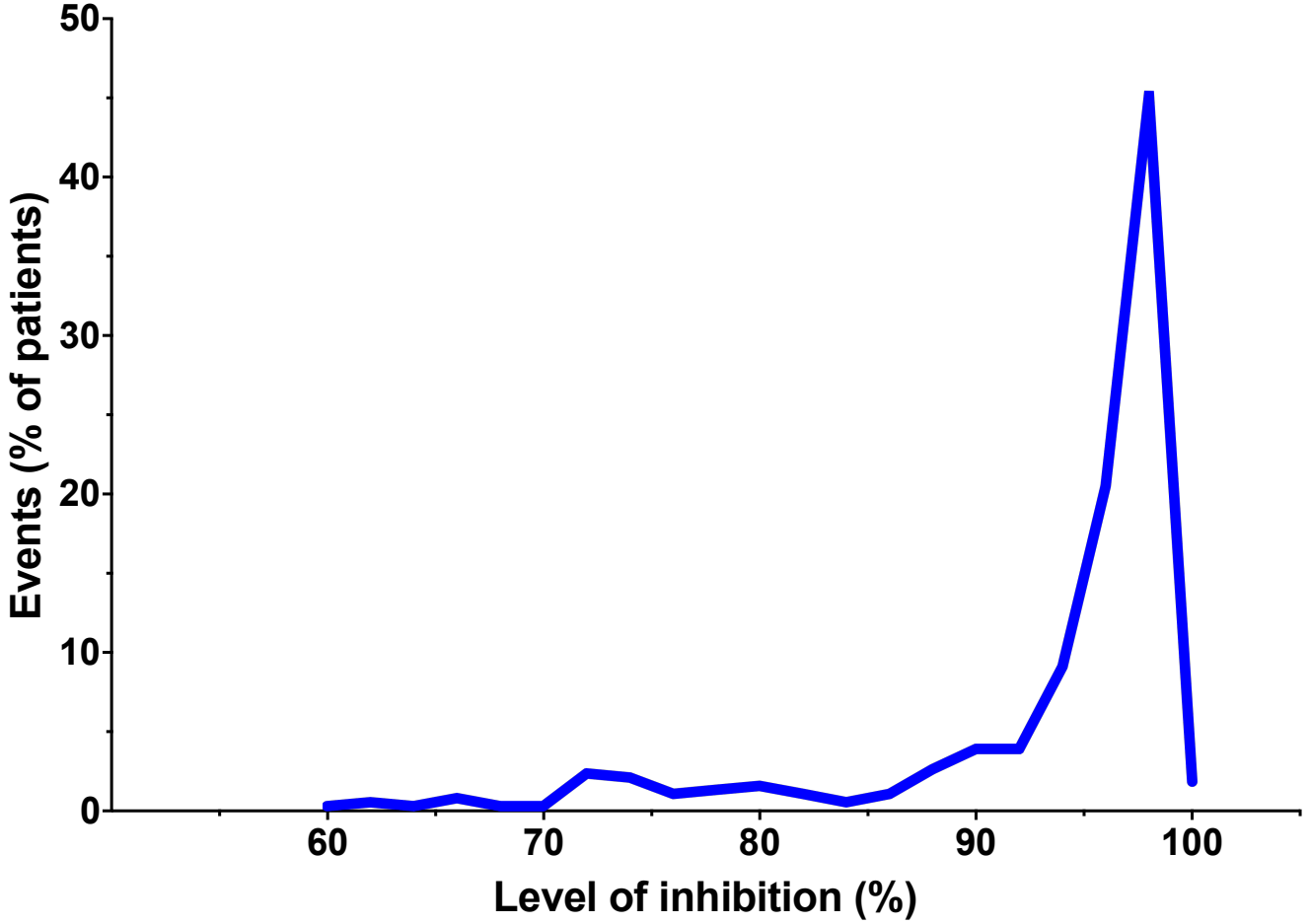
   (c) preparing reaction samples containing the aliquots and if desired further constituents to dilute said aliquots by different dilution factors thereby obtaining different ratios of the active and inhibited forms of said enzyme in said reaction samples, provided that said inhibitor is present;

   (d) measuring the activity of said enzyme in said reaction samples to obtain measured activity values;

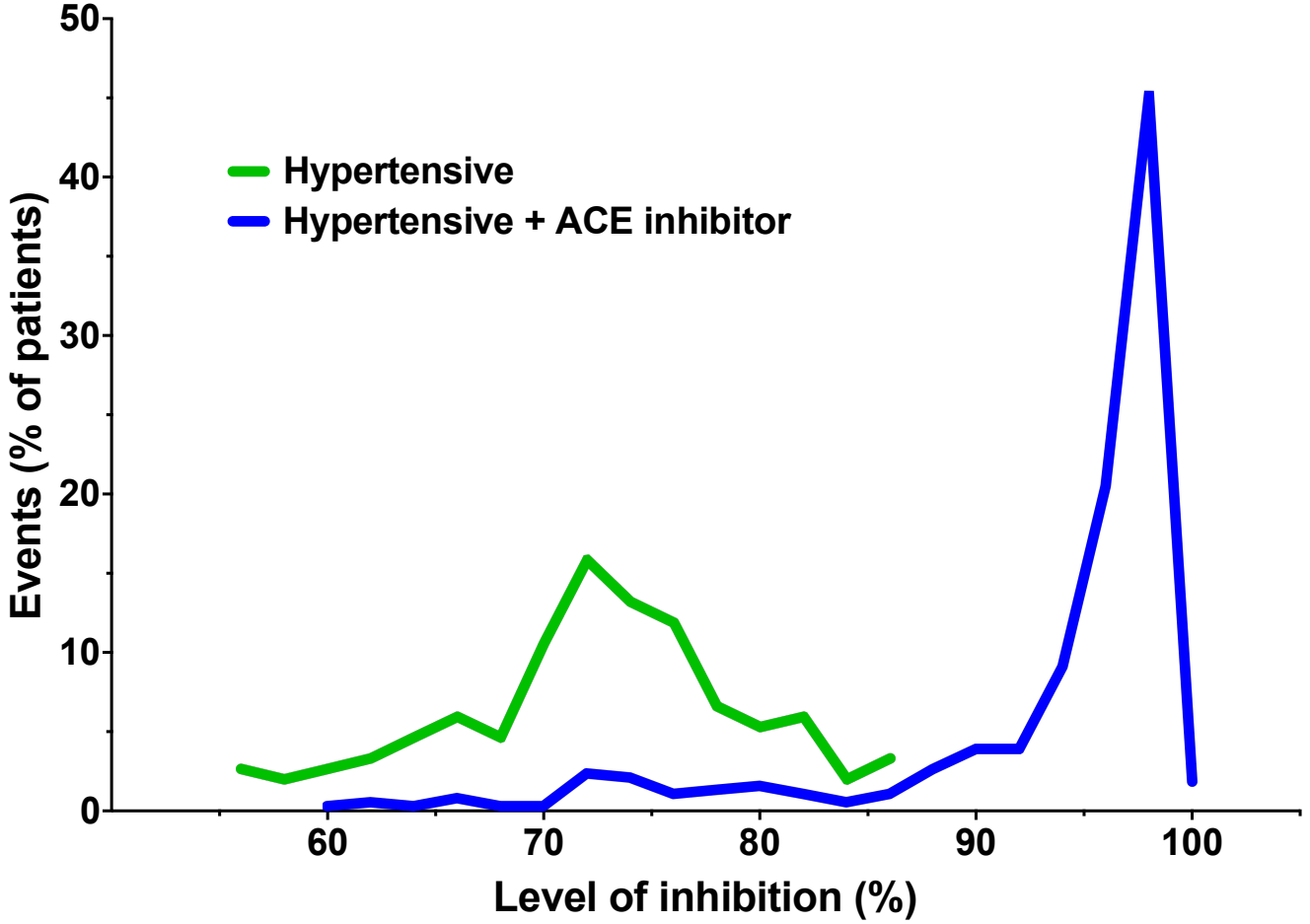
   (e) multiplying the measured activity values by the respective dilution factors to obtain calculated enzyme activity values.

   (f) assessing the level of reversible inhibition of said at least one

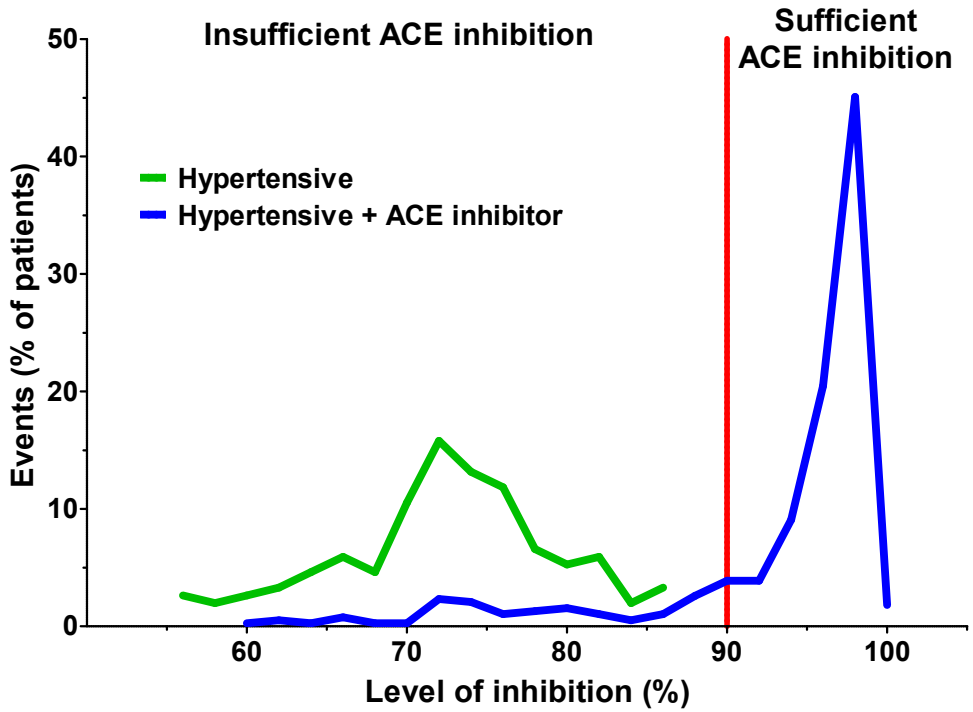
Biochemical effectiveness of ACE inhibition



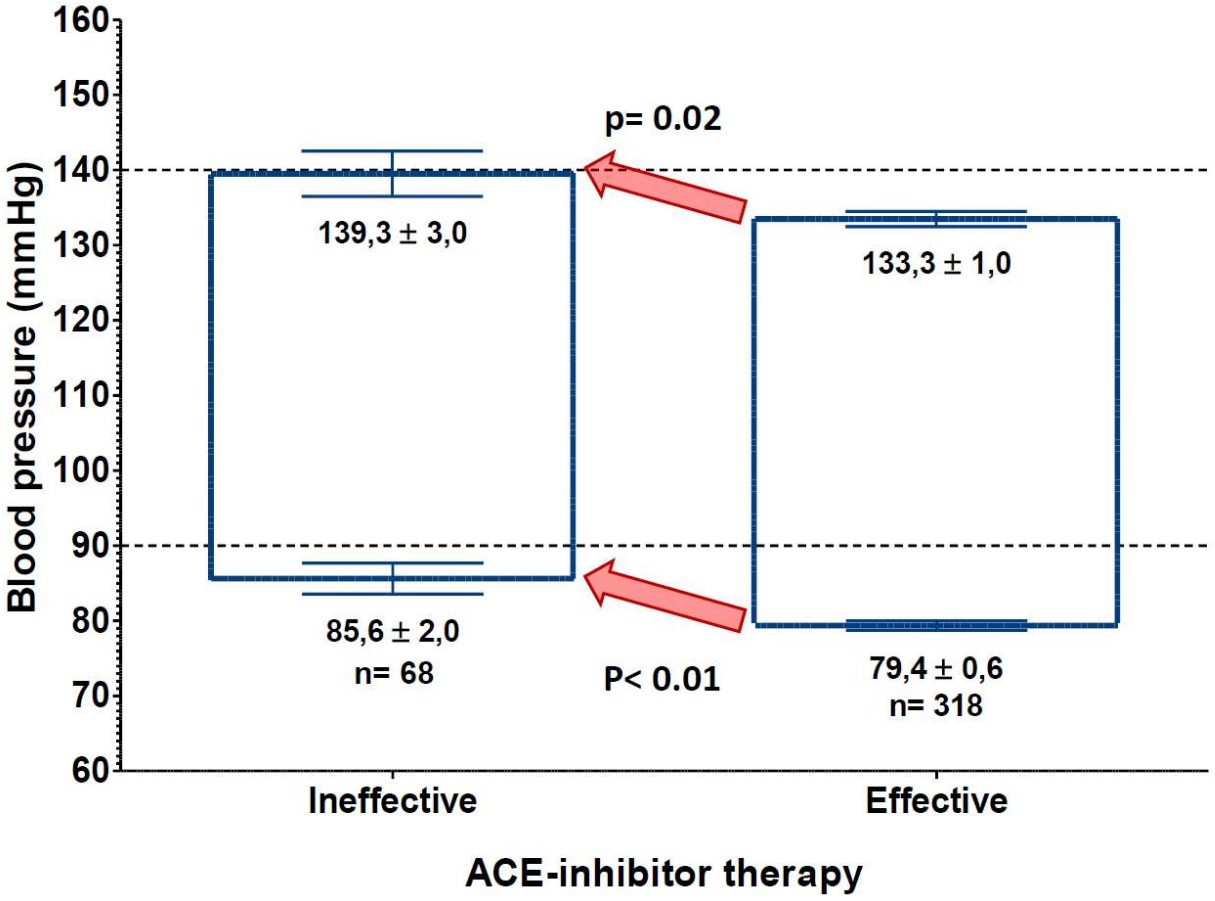
Endogenous ACE inhibition



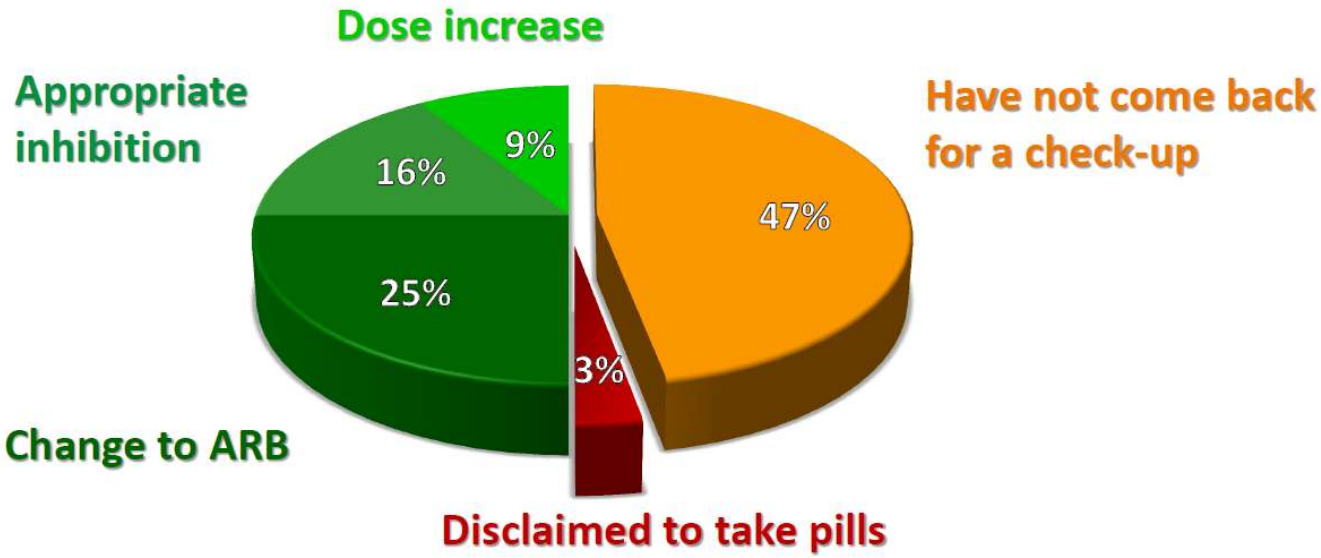
Optimize the effectiveness of ACE inhibition



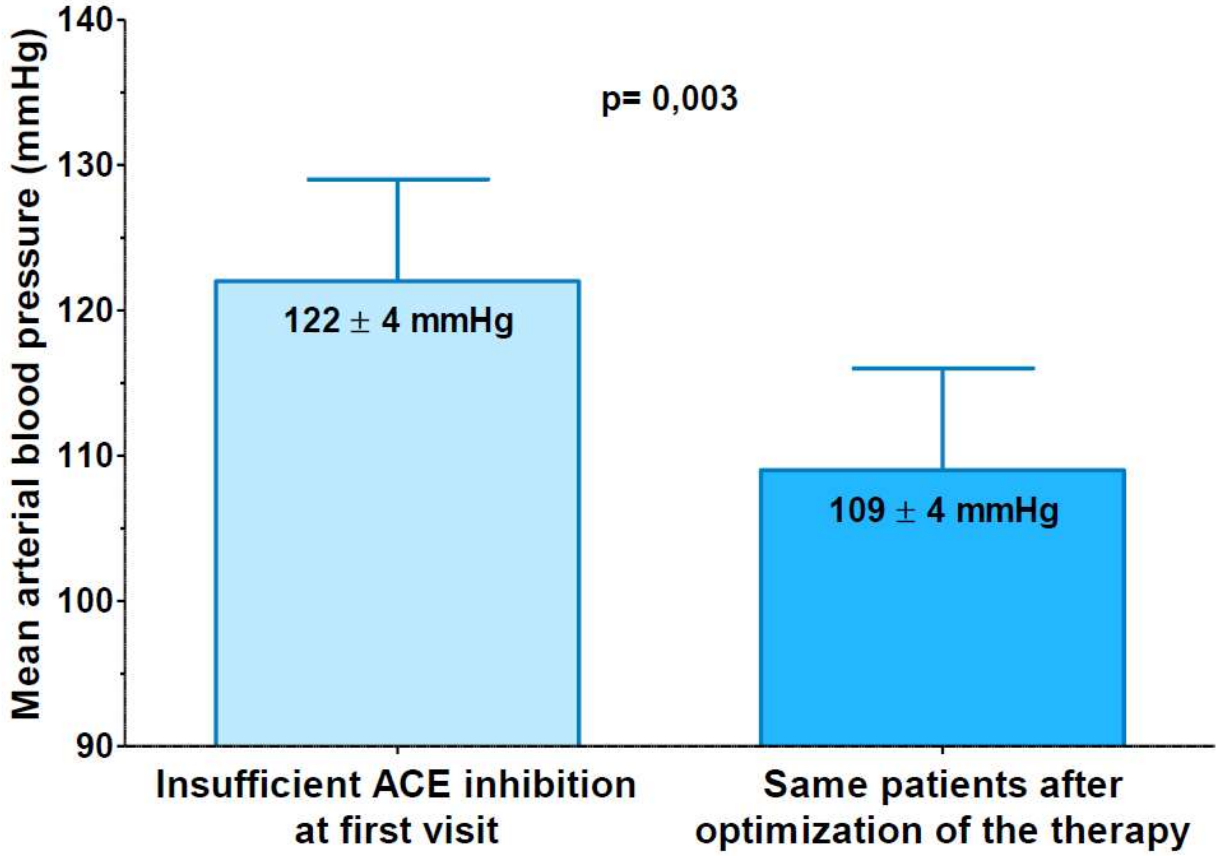
Optimize the effectiveness of ACE inhibition



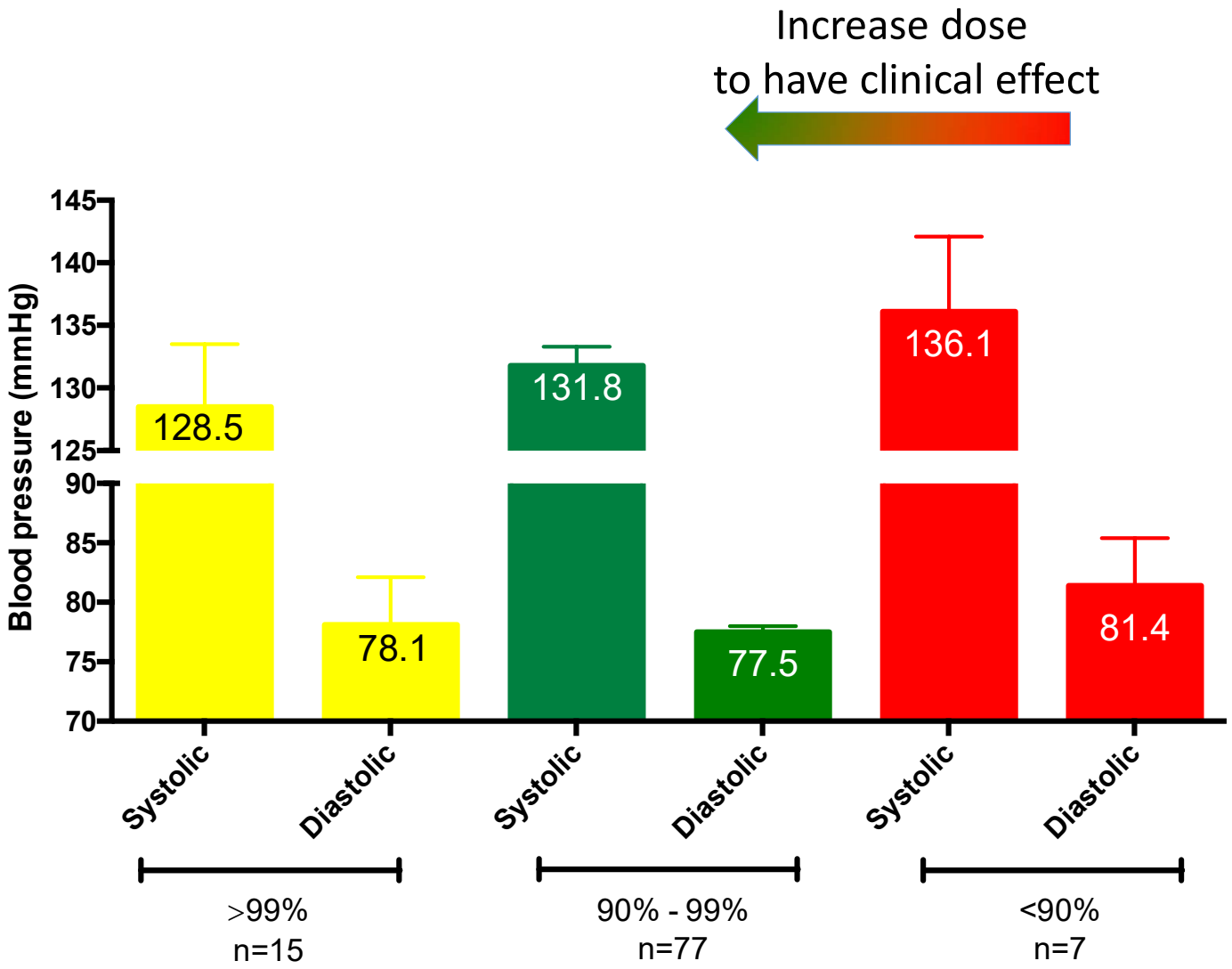
Optimize the effectiveness of ACE inhibition



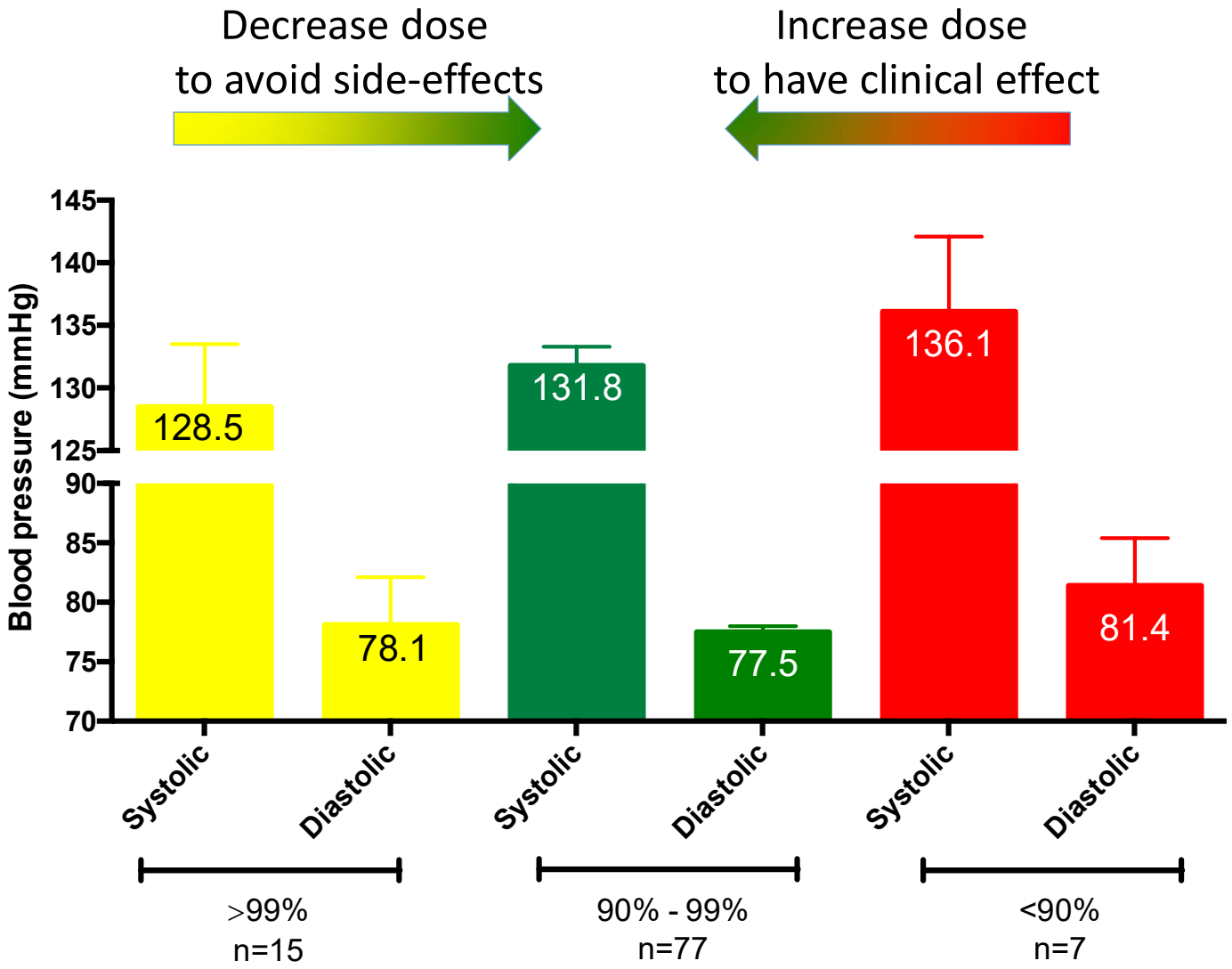
Optimize the effectiveness of ACE inhibition



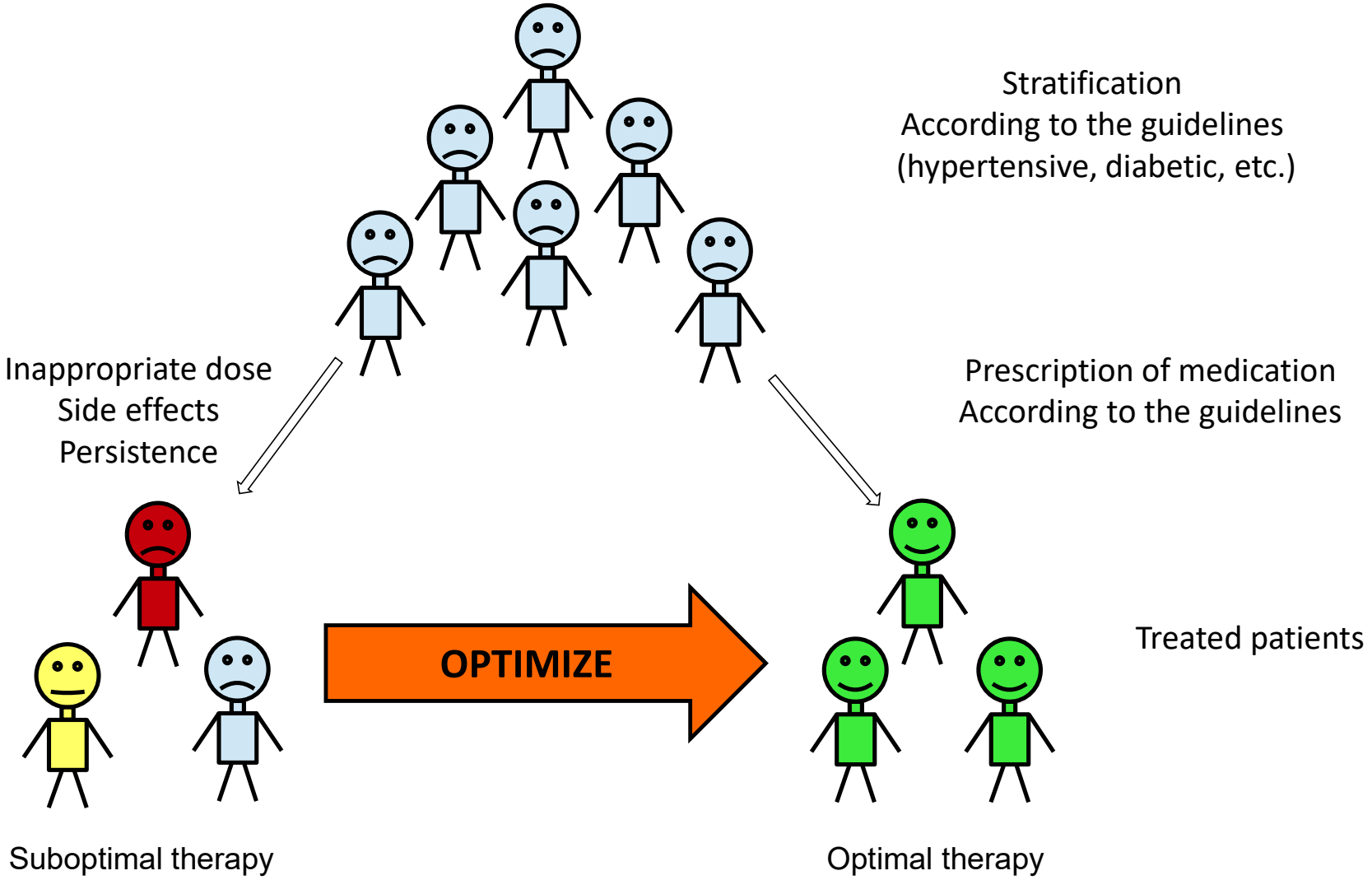
Optimize the effectiveness of ACE inhibition



Optimize the effectiveness of ACE inhibition



Evidence based medicine



Take home messages

Today's medicine learnt in the medical school will most probably be outdated when you will be practicing.

Translational medicine is important to be able to incorporate new knowledge and to open up new directions.

Translational medicine is important to reveal hidden limitations in the white noise of clinical information/marketing:

- The pill-based medication is well established and formulated as clinical guidelines.
- The pill-based medicine is usually a treatment option, very rarely results in curing of a disease.
- The pill-based medicine is economic venture generating ever growing profit.
- The pill-based medication seems to fail to provide societal benefit for various reasons.
- The pill-based medication results in a variety of unwanted side effects, hampering proper clinical decisions.

Personalized medicine defines the future of medical treatments. It is developing:

- Genomic information is lost in big data right now, so far it provided limited success.
- Gene therapy is available, restricted by regulation, ethical issues, while big-pharma is antagonistic.
- No breakthrough in economic approaches, prices are exponentially increasing, while generics become cheaper.
- Biomarker based approaches has promising results.
- Patient tailored therapies may provide a breakthrough: future medication can be cheaper and more effective.
- Patient tailored therapies need to be introduced, nurtured and observed.

Being a medical doctor needs a mindset able to think outside the box. **DANGER!** Your training is not supporting that.