Können Medikamente Erkrankungen in der Realität vorbeugen?

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NEPI´s Aufgabe:
Verbesserung der medizinischen und ökonomischen Anwendung von Arzneimitteln durch Forschung und Information

Ziel aller Therapien: Patient-Nutzen

Kann man den Nutzen von Pharmakotherapie in dem *individuellen* Patient bewerten?

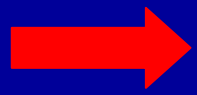
Heilung: *Ja, z.B. Penicillin gegen Angina tonsillaris*
Substitution: *Ja, z.B. Insulin in Typ 1-Diabetes*
Linderung: *Ja, z.B. Morphin gegen schwere Schmerzen*

Vorbeugung: *Nein, z.B. Antihypertensivum gegen Herzinfarkt*

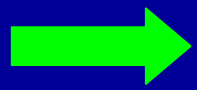
Vorbeugender Nutzen in dem individuellen Patient zu beweisen (oder abweisen) ist per Definition unmöglich

Man kann nicht heute wissen was morgen geschehen wird…

Vorbeugen in dem individuellen Patient?

Behandlung  **kein Infarkt:**

kein Beweis für Effektivität der Behandlung; der Infarkt könnte auch ohne Behandlung ausbleiben

Behandlung  **Infarkt:**

kein Beweis für Ineffektivität der Behandlung; der Infarkt könnte ohne Behandlung früher geschehen und könnte eben tötlich sein

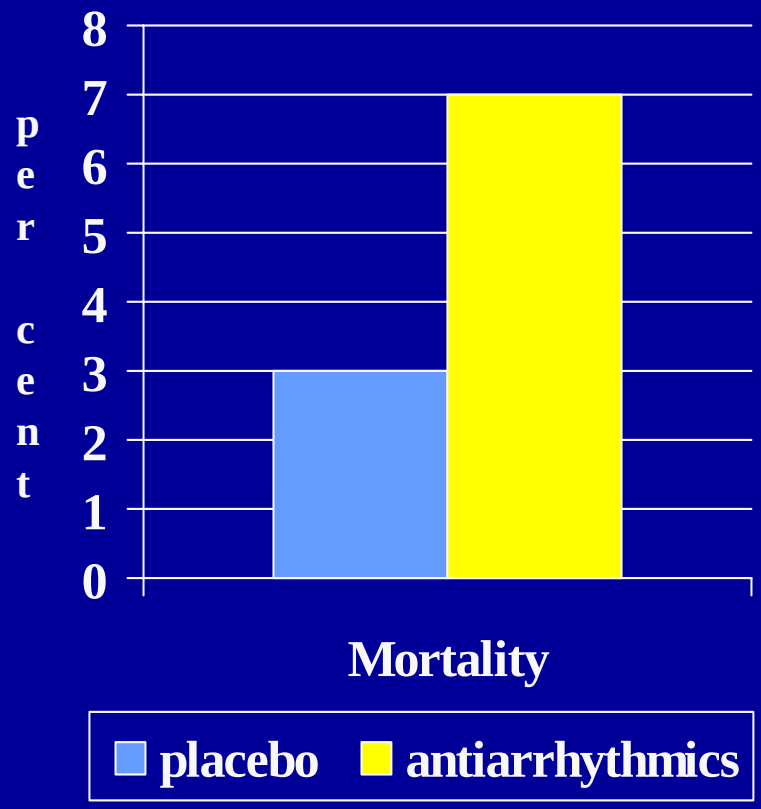
Surrogat-Parameter, z.B. EKG und Blutdrucksenkung, sind nicht genug:

Example 1:
Antiarrhythmic drugs in secondary prevention of acute MI

CAST*: flecainide och encainide vs placebo

Antiarrhythmics seem to improve EKG patterns. However, their use was accompanied by **increased mortality:**

RR 2.5 (1.6-4.5)



*Cardiac Arrhythmia Suppression Trial

NEJM 1989; 321: 406-412

Example 2:
Alpha adrenergic blockers in hypertension
ALLHAT* (doxazosine vs Tz, CCB and ACEI)

Alpha adrenergic blockers

reduce blood pressure as well as other antihypertensives
may reduce plasma triglyceride levels
may increase plasma HDL cholesterol levels
may decrease plasma glucose levels

but they promoted
twice as many cases of heart failure

*Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial

JAMA 2002; 288: 2981-97

Accordingly, evidence-based prevention must rely on results from Randomised Clinical Trials (RCTs) with hard end-points

However, RCTs may be interpreted in very different ways:

RCT of a new drug, assumed to protect against myocardial infarction (MI)

1000 subjects on drug	1000 subjects on pcbo
20 MI	30 MI

How large was the risk reduction?

30 – 20 = 10 **10/30 = 33 % fewer MI**

Relative risk reduction (RRR) = 33 %

RCT of a new drug, assumed to protect against myocardial infarction (MI)

1000 subjects on drug	1000 subjects on pcbo
20 MI	30 MI

How many treated subjects had benefit of the treatment?

10 of 1000 = 1 %

Absolute risk reduction (ARR) = 1 %

RCT of a new drug, assumed to protect against myocardial infarction (MI)

1000 subjects on drug	1000 subjects on pcbo
20 MI	30 MI

How many had to be treated to prevent* one *MI?

Number Needed to Treat (NNT) = 1000/10 = 100

NNT = 1/ARR

RCT of a new drug, assumed to protect against myocardial infarction (MI)

1000 subjects on drug	1000 subjects on pcbo
20 MI	30 MI

How great was the chance to avoid MI without and with treatment, respectively?

without:	**1000 – 30 = 970**	**970/1000 = 97 %**	**1 %**
with:	**1000 – 20 = 980**	**980/1000 = 98 %**	

Efficacy by RCT

Number Needed to Treat (NNT) =

no. of subjects needed to be treated to prevent *one* event, under the exact conditions of the RCT

i.e. same risk/disease spectrum, same age span, same distribution of gender and ethnicity, same dosage, same treatment duration and same additional treatment

In practice, therefore, many treated subjects do not have the proper RCT-based indication

In practice, moreover,
all subjects with the appropriate (RCT-based) indication do not receive treatment (subjects not discovered or being untreated for other reasons)

Furthermore,
all subjects with appropriate indication who do receive treatment are not adherent with their medication

Actual impact on disease by preventive treatment

In real life, all subjects with indication are not treated

Disease Impact Number (DIN) =

no. of subjects with indication (treated + untreated) needed to prevent *one* event by the actual treatment = ratio between NNT and proportion of subjects actually treated among all subjects having the indication

Actual impact on public health by preventive treatment

Population Impact Number (PIN) =

population size needed in an area
(e.g. a GP´s catchment area)
in order to prevent *one* event by the actual treatment

PIN =
ratio between DIN and proportion of catchment population with treatment indication (prevalence)

Hypothetical example:

NNT (1 yr) to prevent *one* MI in RCT = 100

In practice, only 50 % of those with treatment indication receive treatment:
DIN = 100 x 100/50 = 200

Public health effect if 5 % of population have treatment indication (prevalence):
PIN = 200 x 100/5 = 4000

This signifies that the average GP

has to treat 100 subjects with adequate indication to prevent one MI during 1 year (NNT)

has to have 200 subjects with adequate indication in his/her catchment area to prevent one MI by this treatment (DIN)

has to have 4000 subjects in his/her catchment area to prevent one MI by this treatment (PIN)

If the GP has 2000 subjects in his/her catchment area, he/she will have to be at work for 2 years to prevent one MI by the actual treatment

Real examples by application of NNT, DIN and PIN in some RCTs on prevention:

Secondary prevention of MI by simvastatin (4S):
NNT (1 year) = 37

According to the Swedish study *"Life and Health"*,
only 40 % with this indication actually get this treatment,
i.e. DIN = 37 x 100/40 = 93

According to *"Life and Health"*, 3.5 % of all adults,
i.e. all aged > 18, have this indication,
i.e. PIN = 93 x 100/3.5 = 2657

An average Swedish GP (catchment area of 2000) would have to work 1.3 years (2657/2000 x 1 year) to prevent one MI by this treatment

However, less than half of subjects on preventive drug treatment are adherent with their medication

Is adherence (compliance) important?

Degree of adherence vs therapeutic benefit in patients on routine secondary prevention of MI by simvastatin (Dundee, Scotland)

Adherence in %	*Relative risk of new MI*
0	1.0
< 40	0.59 (0.22 – 1.59)
40-79	0.51 (0.19 – 1.35)
80-100	0.19 (0.08 – 0.47)

Heart (2002); 88: 229-233

Assume that average adherence (compliance, concordance) is about 50 % (which is probably an over-estimate):

Secondary prevention of MI by simvastatin (4S):
NNT (1 year) = ~~37~~ 74

According to the Swedish study *"Life and Health"*, 40 % with this indication actually get this treatment, i.e. DIN = 74 x 100/40 = 186

According to *"Life and Health"*, 3.5 % of all adults, i.e. all aged > 18, have this indication,
i.e. PIN = 186 x 100/3.5 = 5314

An average Swedish GP (catchment area of 2000) would have to work 2.7 years (5314/2000) to prevent one MI by this treatment

Primary prevention of MI by statin (WOSCOPS):
NNT (1 year) = 208 (N.B! only middle-aged men)

According to *"Life and Health"*, 10 % of middle-aged healthy men with hypercholesterolaemia have statin treatment,
i.e. DIN = 208 x 100/10 = 2080

According to *"Life and Health"*, 17 % of all adults, i.e. all aged > 18, have this indication,
i.e. PIN = 2080 x 100/17 = 12235

The average GP would have to work 6.1 years to prevent one MI by this treatment

Primary prevention of MI by statin (WOSCOPS):
NNT (1 year) = ~~208~~ 416 (N.B! only middle-aged men)

According to *"Life and Health"*, 10 % of middle-aged healthy men with hypercholesterolaemia have statin treatment,
i.e. DIN = 416 x 100/10 = 4160 (men)

According to *"Life and Health"*, 17 % of all adults, i.e. all aged > 18, have this indication, i.e.
PIN = 4160 x 100/17 = 24470

The average GP would have to work 12.2 years to prevent one MI by this treatment

One-year statin drug costs in Sweden to prevent *one* MI in a middle-aged subject based on the NNT of secondary (4S) and primary (WOSCOPS) prevention (assuming that non-compliant subjects took no doses)

	secondary (NNT= 37)	*primary (NNT = 208)*
simvastatin (20 mg)	1,020 €	5,736 €
pravastatin (40 mg)	20,933 €	117,676 €
atorvastatin (10 mg)	13,505 €	75,920 €

NNT in subjects with high-risk and low-risk hypertension

High-risk subjects

Elderly subjects with
SBP > 160 mm Hg
as in the SHEP study

NNT = 167

Low-risk subjects

Middle-aged subjects with
DBP 90 – 99 mm Hg
as in the MRFIT study

NNT = 1667

One-year drug costs (€) in Sweden to protect *one* elderly subject with SBP > 160 mm Hg from a stroke or *one* middle-aged subject with DBP 90-99 mm Hg from MI based upon the NNT of *SHEP* and *MRFIT*, respectively

SHEP (SBP > 160 mm) NNT (stroke) = 167	
	€
hydrochlorothiazide	6,095
enalapril (gen.)	7,315
atenolol (gen.)	10,294
amlodipine	35,557
losartan	51,567

MRFIT (DBP 90-99 mm) NNT (MI) = 1667	
	€
hydrochlorothiazide	60,845
enalapril (gen.)	73,015
atenolol (gen.)	102,761
amlodipine	354,932
losartan	511,718

Secondary prevention by drug therapy, such as a statin vs MI, or high-risk prevention such as an antihypertensive vs stroke in elderly with SBP > 160 mm Hg, may be medically and economically effective in practice (”real life”), provided that

1) the indication is appropriate

2) the best documented and also cheapest drugs (simvastatin and low-dose thiazide) are employed

3) major efforts are made to keep the patients adherent with the medication

Primary prevention by drug therapy, such as statins vs non-FI hypercholesterolæmia, or low-risk prevention such as antihypertensives vs MI in mild, uncomplicated hypertension (DBP 90 – 99 mm Hg) does not seem effective in practice (”real life”), whether from a medical or an economic point of view

Accordingly, *general* screening for hypercholesterolæmia or hypertension does not seem rational