The Concept of Risk When Time is a Crucial Factor: How to Understand and How to Communicate? Theoretical Considerations and Empirical Findings

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Some current projects

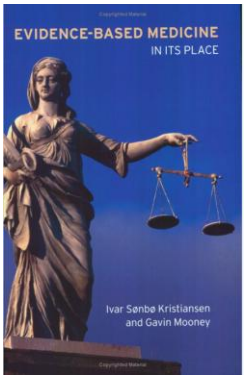
- Societal value of orphan drugs: as for other therapies
- Cost-effectiveness of intensive lifestyle intervention for type 2 diabetes: not cost-effective
- Cost-effectiveness of screening for cervical cancer: HPV-testing is cost-effective
- Cardiovascular modeling: – the NORCAD model
- US and UK EQ-5D tariffs: handle with care
- Influenza modeling: school closure may not be cost-effective
- Women's preferences for cesarean section: strong determinant of elective as well as acute cesarean
- Rheumatoid arthritis: Cost-effectiveness of biologics

Deadline for abstracts: 15 Feb 2012
www.smdm2012.com

Number needed to treat - NNT

- ”Easily understood”
- ”Intuitively meaningful”

(N Engl J Med 1988;318: 1728–33; Ann Intern Med 1997;126:712–20)



(Routledge 2004)

Cost and health consequences of reducing the population intake of salt

Increase in life expectancy: Females 1.4 months, Males 1.8 months

Odense Risk Group, Denmark

- Palle Mark Christensen, GP
- Arthur Elstein (US), psychologist
- Dorte Gyrd-Hansen, economist
- Peder Halvorsen (Norway), GP
- Jørgen Nexøe, GP
- Jesper Bo Nielsen, environmental biologist
- Henrik Støvring, statistician
- Torbjørn Wisløff (Norway), statistician
- Ivar Sønbø Kristiansen, epidemiologist (?)

Outline

- Chronic diseases
- Measures of prognosis and effectiveness
- The distribution problem
- How to express effectiveness?
- The valuation problem
- My concept of risk
- Conclusions

Chronic diseases

Background

- Chronic disease processes cause the majority of deaths in industrialized countries: acute myocardial infarction (heart attack), stroke, diabetic complications, cancer, osteoporosis, *etc.*
- Considerable proportions of health care resources are devoted to prevention and treatment of chronic diseases
- Uncertainty about the effectiveness of interventions and how intervention effects should be expressed

Christensen, Vaupel *et al*
Lancet 3 Oct 2009

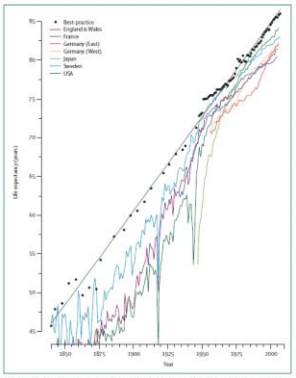
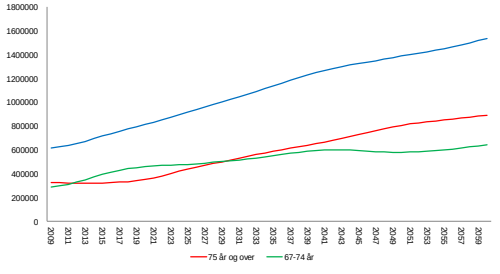


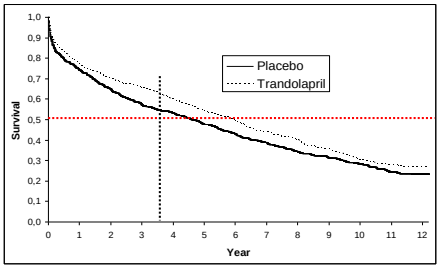
Figure 1: Best-practice life expectancy and life expectancy for women in selected countries from 1840 to 2007
Linear regression trend depicted by solid grey line with a slope of 0·24 per year. Data from supplementary material of reference 12 and the Human Mortality Database.

The age ~~wave~~ landslide



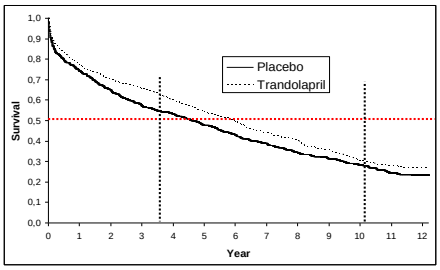
Measures of Effectiveness in the Context of Chronic Diseases

Trandolapril versus placebo



Eur Heart J 2005; 26: 145-52

Trandolapril versus placebo



Eur Heart J 2005; 26: 145-52

Effectiveness measures

Horisontal:

- Increase in 50-percentile (median) survival
- Increase in X-percentile survival

Vertical:

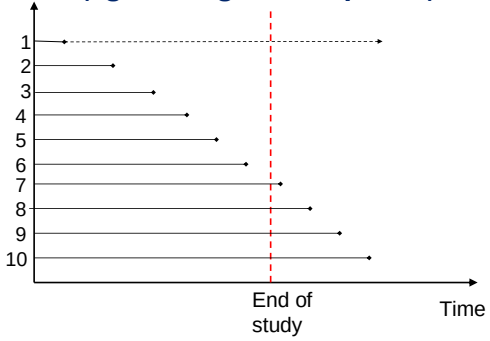
- Absolute Risk Reduction (ARR)
- Relative Risk Reduction (RRR)
- Relative Risk (RR)
- **Number-Needed-to-Treat (NNT)**
- Odds Ratio (OR) and log OR

Combined

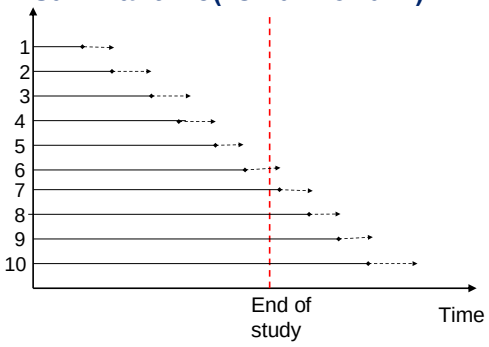
- Increase in (event-free) life expectancy. Prolongation of life (POL)

The distribution problem

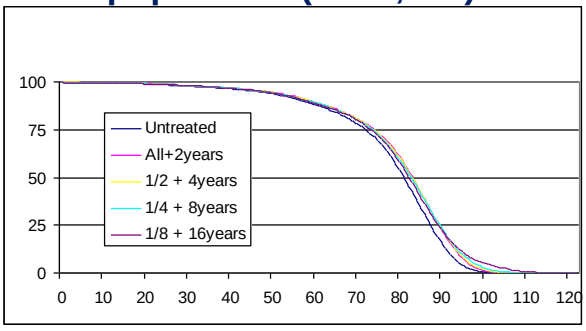
Effect of intervention on survival time ("gambling for the prize")



Effect of intervention on survival time("small for all")



Survival hypothetical population (n=44,000)



INTERPRETATION OF NNT

INCORRECT:

- "The number of patients needed to be treated for *x* years in order to prevent 1 event"

CORRECT:

- "The average number of patients needed to be treated for a time period of *x* to observe one less event at time t_x"

How to explain treatment effectiveness?

"Imagine that your doctor informs you that you are at somewhat increased risk of heart attack. You are offered a drug to be taken once daily. The drug causes few and mild side effects. You will have to see your doctor twice a year for check up, and the drug co-payment will be DKK500 ($60) per year. The doctor informs you that for every heart attack avoided, X patients will have to take the drug for 3 years. Would you choose to take such a drug?"

"Would you choose to take such a drug?" (heart attack) (n=675)

NNT	Yes	No	?
10	83%	11%	6%
25	87%	9%	4%
50	85%	10%	4%
100	85%	12%	3%
200	81%	16%	3%
400	74%	22%	4%
Total	82%	13%	4%

Kristiansen *et al* J Clin Epidemiol 2002; 55:888-92.

“Would you choose to take such a drug?” (hip fracture) (n=526)

NNT	Yes (%)	No (%)	Uncertain (%)
10	65	20	14
50	61	26	12
100	63	25	13
200	57	24	19
Total	**61**	**24**	**15**

Christensen *et al*. Clin Ther. 2003; 25: 2575-85.

“Would you choose to take such a drug?” (heart attack) (n=713)

RRR (%)	Yes	No	?
10	**48%**	**35%**	**18%**
20	**66%**	**20%**	**15%**
30	**62%**	**20%**	**18%**
40	**57%**	**27%**	**16%**
50	**60%**	**29%**	**10%**
60	**57%**	**21%**	**23%**
All	**58%**	**25%**	**17%**

BMC Med Inform Decis Mak. 2008 Jul 17;8:31

“Would you choose to take such a drug?” (heart attack) (n=1,367)

Pronlongation of life	Yes	No	?
1 month	39%	50%	12%
6 months	52%	35%	13%
12 months	56%	30%	15%
2 years	64%	25%	11%
4 years	67%	22%	11%
8 years	73%	17%	10%
Total	58%	30%	12%

BMC Med Inform Decis Mak. 2007 Mar 29;7:8.

"Would you choose to take such a drug?" (hip fracture) (n=441)

Delay	Yes	No	Uncertain
1 month	25%	66%	9%
6 months	40%	46%	14%
12 months	39%	42%	19%
4 years	53%	35%	11%
Total	40%	47%	13%

Clin Ther 2003 Oct;25: 2575-85.

MDs' recommendations CVD prevention

	NNT=50	NNT=200
Certainly or probably yes	72%	52%
Probably or certainly no	24%	45%
Missing	4%	2%
Total	100% (n=591)	100% (n=713)

(Halvorsen PA *et al.* Scand Prim Care 2003; 21: 162-6)

The Red Wine Study

- Invited: 4,000 randomly selected in Odense
- Incentives: Chocolate or red wine
- Participation rate: 37.3% ($n = 1,491$ for 24 groups)
- For 16 groups of interest: $n = 1169$

4 effectiveness levels

ARR (%)	RRR (%)	NNT	POL (months)
2	40	50	4
4	80	25	8
5	33	20	8
10	66	10	16

4 types of initial information
16 groups

Overall finding: Concordance

Format	Estimate (95% CI)
ARR	94 (91; 97)
RRR	91 (87; 94)
NNT	89 (84; 92)
PP	90 (86; 93)

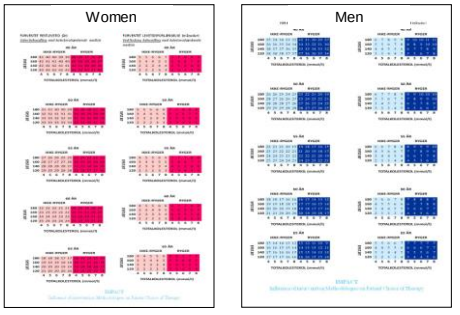
Concordance (%) between initial and final choice

Direction of discordance

	Initial choice		
Format	Accept	Decline	
ARR	92 (84; 96)	95 (91; 98)	Small change
RRR	94 (84; 98)	90 (84; 94)	Yes → No
NNT	83 (74; 90)	92 (86; 95)	Change
PP	98 (94;100)	80 (72; 86)	No → Yes

Concordance (%) between initial and final choice

Prognosis and Effectiveness Tables



(Henrik Støvring *et al* – manuscript in revision)

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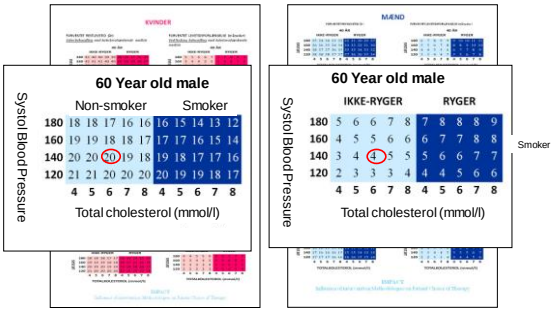
Life expectancy (yrs) Prolongation of life (mths)



Cholesterol: 6 mmol/l ~ 232 mg/dl

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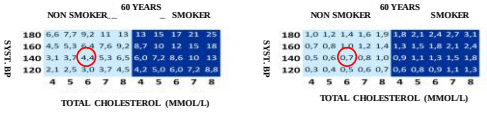
10 year all-cause mortality risk (%) without statin

Absolute risk reduction (ARR) at 10 years from simvastatin treatment



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IMPACT

- **I**nfluence of Intervention **M**ethods on **Pa**tient **C**hoice of **T**herapy
- 284 GPs invited to participate, 56 accepted, 34 recruited patients
- GPs received short course on ARR or POL and the prognosis/effectiveness table
- Patients invited into study when seeing their GP for a ”prevention talk”

Trial Registration: NCT01414751

Physicians in IMPACT

	POL (n=13)	ARR (N=21)
Female gender	39 %	33 %
Years working as GP, mean	18	15
Never used numbers to explain effectiveness	23 %	19 %
High self rated workload	58 %	80 %

Patients in IMPACT

	Prologation of Life (n=112)	Absolute Risk Reduction (=128)
Mean age (years)	57	56
Female	59 %	47 %
Daily smoker	20 %	21 %
Family history of CVD	45 %	52 %
Total cholesterol (mmol/l)	6.2	6.2

Cholesterol: 6.0 mmol/l ~ 234 mg/dl

Patient satisfaction and choices

	POL (n=112)	ARR (n=126)
Mean confidence in own decision	4.2	4.1
Mean satisfaction with own decision	4.4	4.2
Mean ease of understanding information	4.4	4.3
Mean satisfaction with information	4.4	4.3
Redeemed statin prescription	**??%**	**??%**

Patient satisfaction and choices

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Mean satisfaction with own decision	4.4	4.2
Mean ease of understanding information	4.4	4.3
Mean satisfaction with information	4.4	4.3
Redeemed statin prescription	**6%**	**25%**

The valuation problem

Preferences for postponement of fatal heart attack

		Individual		Societal
Prolongation of life (months)	n	Yes (%)	n	Yes (%)
1 for all	90	27	98	34
3 for 1/3	97	36	71	38
6 for 1/6	81	41	102	39
12 for 1/12	77	42	100	47
24 for 1/24	104	52	104	56
48 for 1/48	112	55	83	45

(Gyrd-Hansen *et al*. Health Econ. 2008; 17: 709-20)

Reasons for not taking the drug (n=117)

	%
Don't like to use drugs	23
The drug is too expensive	5
Only "1 out of 100 benefits"	30
Other reasons	14

Chistensen *et al*. Clin Ther. 2003; 25: 2575-85

Proportions accepting a treatment according to timing and magnitude of benefit

	1year into the future				10years into the future			
	Q1 (N= 550)		Q2 (N = 538)		Q3 (N = 525)		Q4 (N = 530)	
LY gain	Opening bid	Acceptance rate	Opening bid	Acceptance rate	Opening bid	Acceptance rate	Opening bid	Acceptance rate
1 w	2,500	48%						
2 w				54%	1,000	55%		
3 w							1,500	60%
1 m	10,000	55%						
2 m			20,000	59%	4,000	62%		
3 m							6,000	66%
4 m	40,000	59%						
8 m			80,000	61%	16,000	65%		
1 y							25,000	76%
p-trend		*p*<0.001		*p*=0.001		*p*<0.001		*p*<0.001

1*2500

4*2500

16*2500

(Kvamme-MK *et al*. J Health Econ 2010; 29: 541-8)

Proportions accepting a treatment according to timing and magnitude of benefit

	1year into the future				10years into the future			
	Q1 (N= 550)		Q2 (N = 538)		Q3 (N = 525)		Q4 (N = 530)	
LY gain	Opening bid	Acceptance rate	Opening bid	Acceptance rate	Opening bid	Acceptance rate	Opening bid	Acceptance rate
1 w	2,500	**48%**						
2 w			5,000	54%	1,000	**55%**		
3 w							1,500	60%
1 m	10,000	**55%**						
2 m			20,000	59%	4,000	**62%**		
3 m							6,000	66%
4 m	40,000	**59%**						
8 m			80,000	61%	16,000	**65%**		
1 y							25,000	76%
p-trend		$p<0.001$		$p=0.001$		$p<0.001$		$p=0.000$

(Kvamme-MK *et al*. J Health Econ 2010; 29: 541-8)

Distribution of the benefit

All patients gain about equal to the average ("small for all")

- Statin therapy induces wider coronary arteries in most patients (New Engl J Med 1990; 323: 1289-98)
- Bisphosphonates improve BMD in most patients (Arthritis Rheum 1999; 42: 1246-54)

A few patients achieve a big benefit ("gambling for the prize")

- Breast cancer screening
- Others

The concept of risk

The concept of risk

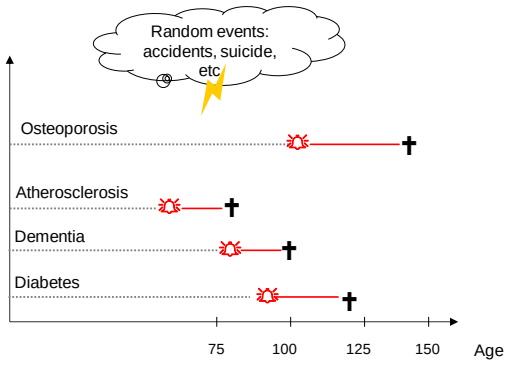
- The probability of an adverse event when there ***is no crucial time dimension***: Loosing in a Russian roulette, earn a ”1” when throwing a dice, die when having ventricular fibrillation, *etc.*
- The probability of an adverse event when there ***is a crucial time dimension***: Having a divorce when married, having an adverse outcome from a chronic disease, *etc.*

Two perspectives

- ”The governor decided that the prisoner on the death row should have a risk of death equal to 0.000023 the next month, and 1.0 the following one”

Two perspectives

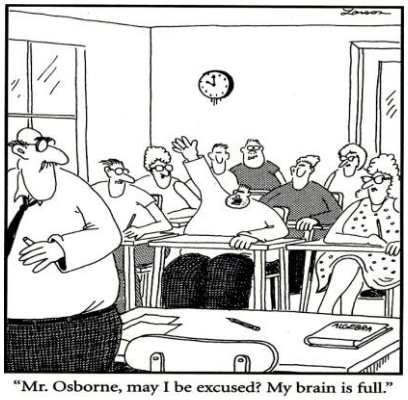
- ”The governor decided that the prisoner on the death row should have a risk of death equal to 0.000023 the next month, and 1.0 the following one”
- ”The governor granted the prisoner on the death row 1 month postponement of the capital punishment”



A deterministic ”life model”

Conclusions

- Time is the underlying phenomenon when we talk about risk in the context of chronic diseases
- Lay people have difficulties understanding levels of effectiveness when presented in terms of risk reductions
- NNT is particularly difficult to understand
- Prolongation of life may be easier to understand
- Valuation of interventions for chronic diseases is dependent upon the distribution of the benefit
- Utility may not be a linear function of time



“Mr. Osborne, may I be excused? My brain is full.”

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