Overvejelser vedr. outcomes i (farmako)epidemiologiske studier …

Kursus i basal farmakoepidemiologi 2018

Maja Hellfritzsch Poulsen

Outcome/event/udfald

Den sygdomstilstand vi ønsker at undersøge

I et kohortestudie: det vi ”måler på”
Fx selvmord /selvmordsforsøg

I et case-kontrol studie: udgangspunkt for selektion af studiepopulation
Fx colon cancer

Outcome definition/identifikation

OUTCOME	PROXY
Sygdom/tilstand	Diagnosekode
Operation	Procedurekode
Opstart af ny medicin	Receptindløsning
Ændring i biokemisk parameter	NPU-kode

Dvs. kvaliteten af vores studier afhænger (bl.a.) af om den valgte proxy er et validt udtryk for vores outcome

Er proxy'en valid?

Formår proxyen at klassificere de syge som syge og de ikke-syge som ikke-syge?

Er proxy'en valid? Eksempel

I21 (akut myokardieinfarkt)

Hvordan vil man undersøge det?

Hvordan vil man vurdere om proxy'en er valid eller ej?

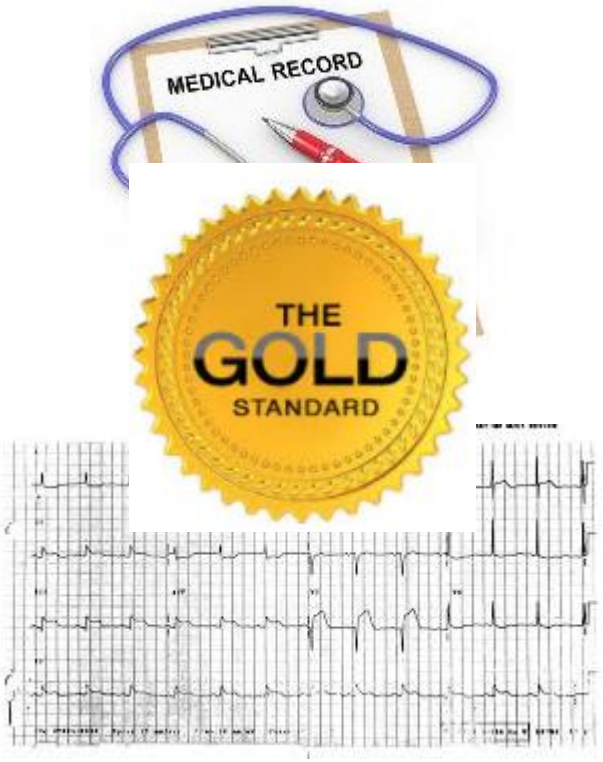
Valideringsundersøgelse

DI21 (akut myokardieinfarkt) = AMI "i virkeligheden"?

vs.

→

(←)



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BMJ Open

Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

Jens Sundbøll,[1,2] Kasper Adelborg,[1,2] Troels Munch,[1] Trine Frøslev,[1] Henrik Toft Sørensen,[1] Hans Erik Bøtker,[2] Morten Schmidt[1,3]

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ABSTRACT

Objective: The majority of cardiovascular diagnoses in the Danish National Patient Registry (DNPR) remain to be validated despite extensive use in epidemiological research. We therefore examined the positive predictive value (PPV) of cardiovascular diagnoses in the DNPR.

Design: Population-based validation study.

Setting: 1 university hospital and 2 regional hospitals in the Central Denmark Region, 2010–2012.

Participants: For each cardiovascular diagnosis, up to 100 patients from participating hospitals were randomly sampled during the study period using the DNPR.

Main outcome measure: Using medical record review as the reference standard, we examined the PPV for cardiovascular diagnoses in the DNPR, coded according to the International Classification of Diseases, 10th Revision.

Results: A total of 2153 medical records (97% of the

Strengths and limitations of this study

- This is the first validation study to include all major cardiovascular diagnoses in the Danish National Patient Registry.
- We sampled patients only from hospitals in the Central Denmark Region. However, our results are most likely generalisable to other parts of the country as the Danish healthcare system is homogeneous in structure and practice.
- We only validated patients diagnosed during 2010–2012 and therefore cannot extrapolate our results to previous periods.

INTRODUCTION

Remarkable improvements have occurred in

Valideringsundersøgelse

96 af 99 patienter med en (incident) I21 kode havde haft AMI

Virker det validt?

Mål for proxy'ens validitet

	+ Sygdom	÷ Sygdom	Total
+ Kode	Sandt pos.	Falsk pos.	
÷ Kode	Falsk neg.	Sandt neg.	
Total			

Prædiktiv værdi: evnen til at prædiktere tilstedeværelse af sygdom eller ej

Positiv prædiktiv værdi (**PPV**): sandsynlighed for sygdom ved positiv test
PPV = sandt positiv / + kode

Negativ prædiktiv værdi (**NPV**): sandsynlighed for "rask" ved negativ test
NPV = sandt negativ/ ÷ kode

Mål for proxy'ens validitet

	+ Sygdom	÷ Sygdom	Total
+ Kode	Sandt pos.	Falsk pos.	
÷ Kode	Falsk neg.	Sandt neg.	
Total			

Sensitivitet (komplethed): evnen til at identificere alle sygdomstilfælde
Sensitivitet = sandt pos. / + sygdom

Specificitet: evnen til at identificere dem uden sygdom
Specificitet = sandt neg. / ÷ sygdom

Overvejelser vedr. validitet

Udgangspunkt: PPV

Sensivitet: tror vi at alle tilfælde fanges af vores proxy?
(Er det noget man kommer på sygehuset for??)

Valideringsundersøgelse

96 af 99 patienter med en (incident) I21 kode havde haft AMI

	+ AMI	÷ AMI	Total
+ I21	Sandt +	Falsk +	
÷ I21	Sandt ÷	Falsk ÷	
Total			

Valideringsundersøgelse

96 af 99 patienter med en (incident) I21 kode havde haft AMI

	+ AMI	÷ AMI	Total
+ I21	96	3	99
÷ I21	?	?	
Total			

PPV = 96/(93+3) = 97%

Antagelser om sensitivitet?

Den perfekte outcome proxy

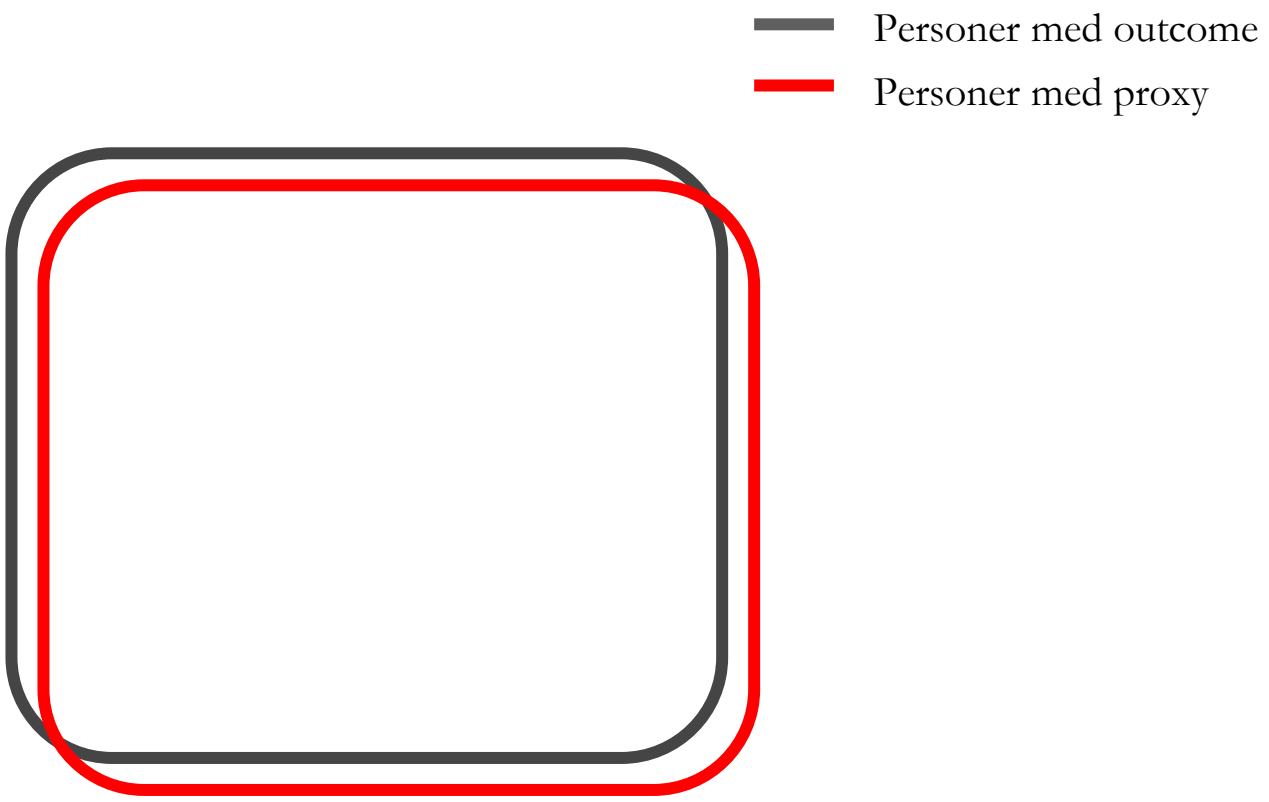
Proxyen repræsenterer altid et outcome
(Dvs. positiv prædiktiv værdi = 100%)

Et outcome vil altid resultere i en proxy
(Dvs. sensitivitet = 100%)

OBS.: I valideringsstudier vurderes ofte kun PPV

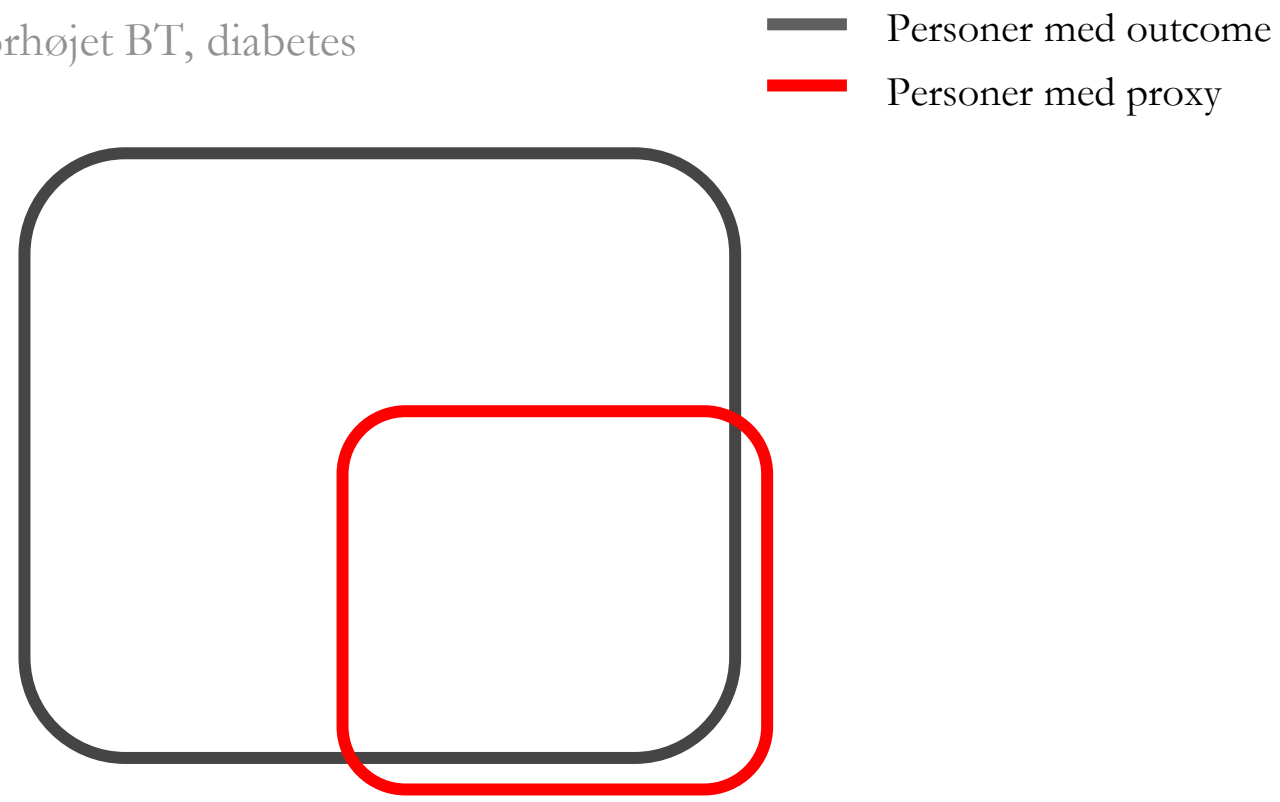
Høj PPV, høj sensitivitet

Fx. cancer



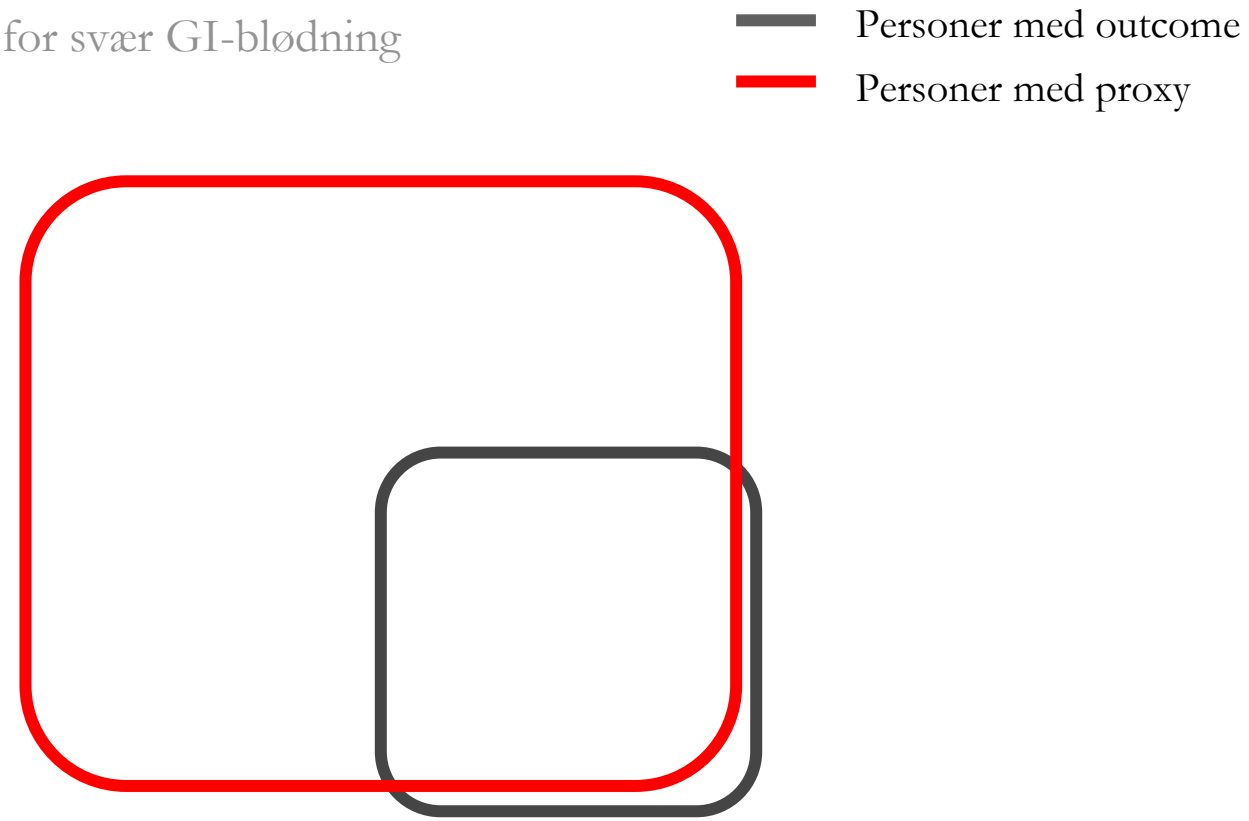
Høj PPV, lav sensitivitet

Fx diagnose for fedme, forhøjet BT, diabetes



Lav PPV, høj sensitivitet

Fx Gastroskopi som proxy for svær GI-blødning



ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 323–337

Journal of Clinical Epidemiology

REVIEW ARTICLE

A review of uses of health care utilization databases for epidemiologic research on therapeutics

Sebastian Schneeweiss*, Jerry Avorn

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street (suite 3030), Boston, MA 02120, USA

Accepted 16 October 2004

PPV > Sensitivitet

Vigtigst at de outcomes der findes rent faktisk er outcomes

Suboptimal validitet af outcome

Fører til misklassifikation af outcome status
(=informationsbias)

Lav PPV → Ikke-syge klassificeres som syge
Lav sensitivitet → Syge klassificeres som ikke-syge

Vigtigt! Så længe validiteten ikke afhænger af eksponeringsstatus er misklassifikationen non-differentieret og medfører en bias mod nul (fordi grupperne kommer til at ligne hinanden)

Non-differentieret misklassifikation

Virker det sandsynligt at validiteten af outcomet selvmord afhænger af om patienten tidligere har brugt p-piller?

Virker det sandsynligt at validiteten af outcomet colon cancer afhænger af om patienten tidligere har brugt lithium?

> diagnoses of "increased INR" and "any bleeding requiring hospitalization" in the Patient Register have not been validated. However, it seems unlikely that misclassification of the diagnoses contained in "excessive anticoagulation" would be unequally distributed between warfarin users with different exposure status.

Hellfritzsch et al. PDS 2016

Muligheder for at øge validiteten

Lav algoritmer

Validering af (alle) outcomes

Ved flere mulige koder: vælg kun dem med højeste PPV

Restriktion til: incidente outcome, primære (A) diagnoser, diagnoser stillet på bestemte afdelinger

Som primære analyse eller sensitivitetsanalyse

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Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

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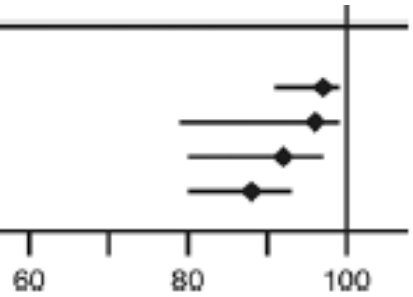
Myocardial infarction			
First-time myocardial infarction	100	96/99	97 (91-99)
First-time STEMI	23	22/23	96 (79–99)
First-time NSTEMI	39	36/39	92 (80-97)
Recurrent myocardial infarction	100	88/100	88 (80-93)



Algoritmer

Ekskluderende algoritmer (øger PPV)

Flere krav skal opfyldes for at blive klassificeret som et outcome

Fx DVT diagnose OG efterfølgende AK-behandling = DVT

Inkluderende algoritmer (øger sensitiviteten)

Flere muligheder for at blive klassificeret som et outcome

Fx diabetes diagnose EL. brug af antidiabetika = diabetes outcome

OBS. PPV af den enkelte proxy…

Outcome i "vores" studier

Suicide Attempt and Suicide

A woman was categorized as having a suicide attempt if she had a diagnosis of suicide attempt (see Table S3 in the data supplement) or a contact with a somatic or psychiatric hospital defined as "suicide attempt." Only the first suicide attempt was assessed. The Cause of Death Register provided data on suicide as defined in Table

Cases and controls. From the Danish Cancer Registry, we identified all patients (cases) in Denmark with a first time diagnosis of colorectal cancer between 2000 and 2012. We restricted the case population to histologically verified adenocarcinoma.

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REVIEW

The Danish National Patient Registry: a review of content, data quality, and research potential

Morten Schmidt[1]
Sigrun Alba Johannesdottir Schmidt[1]
Jakob Lynge Sandegaard[2]
Vera Ehrenstein[1]
Lars Pedersen[1]
Henrik Toft Sørensen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, [2]Department of Health Documentation, State Serum Institute, Copenhagen, Denmark

Background: The Danish National Patient Registry (DNPR) is one of the world's oldest nationwide hospital registries and is used extensively for research. Many studies have validated algorithms for identifying health events in the DNPR, but the reports are fragmented and no overview exists.

Objectives: To review the content, data quality, and research potential of the DNPR.

Methods: We examined the setting, history, aims, content, and classification systems of the DNPR. We searched PubMed and the *Dantsh Medtcal Journal* to create a bibliography of validation studies. We included also studies that were referenced in retrieved papers or known to us beforehand. Methodological considerations related to DNPR data were reviewed.

Results: During 1977–2012, the DNPR registered 8,085,603 persons, accounting for 7,268,857 inpatient, 5,953,405 outpatient, and 5,097,300 emergency department contacts. The DNPR provides nationwide longitudinal registration of detailed administrative and clinical data. It has recorded information on all patients discharged from Danish nonpsychiatric hospitals since 1977 and on psychiatric inpatients and emergency department and outpatient specialty clinic contacts since 1995. For each patient contact, one primary and optional secondary diagnoses are recorded according to the International Classification of Diseases. The DNPR provides a data source to identify diseases, examinations, certain in-hospital medical treatments, and

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Table S1 (*Continued*)

ICD codes[a]	Condition	Study period (contact type; diagnosis type)	ICD codes/algorithm[b]	n[c]	PPV; NPV; sensitivity; specificity[d]
I21	Acute myocardial infarction	1996–2009 (IN;* A)	I21	148	PPV =100 (97.5–100)
		1998–2007 (IN/OUT; A)	I21, I22, I23	50	PPV =98.0 (89.5–99.7)
		1993–2003 (IN/OUT/ED; A/B*)	410; I21	1,072	$PPV_{IN/OUT/ED}$ =81.9 (79.5–84.1); $PPV_{IN; A/B}$ =92.4 (90.4–93.9); $PPV_{IN; A}$ =94.4 (92.6–95.7)
		1982–1991 (IN; A/B)	410, 427.24, 427.27, 427.91, 427.97	5,022	PPV_{A} =94.3 (93.6–94.9); PPV_{A+B} =93.4 (92.6–94.0); Se_{A} =62.8 (61.7–64.0); Se_{A+B} =69.5 (68.4–70.6)
		1979–1980 (IN; A/B)	410–414	527	PPV =92.4 (89.8–94.4)
I26	PE	1994–2006 (IN/OUT/ED; A/B)	450.99; I26	353	PPV_{All} =67.4 (62.4–72.1); $PPV_{IN/OUT}$ =82.1 (77.2–86.1); PPV_{ED} =29.6 (22.0–38.5); PPV_{A} =87.0 (81.9–90.9)
	PE during pregnancy and postpartum	1980–2001 (IN;* A*)	450.00–450.99; I26.0–I26.9 + (650–666; O80–84)	22	$PPV_{preg+postpartum}$ =81.8 (59.7–94.8);[e] PPV_{preg} =63.6 (40.7–82.8)[f]
	PE after stroke	2003–2006 (IN; A/B)	I26 (after admission to stroke units and age ≥18 y)	11	PPV =90.9 (62.3–98.4); NPV =97.4 (95.8–98.4); Se =0.0 (0.0–32–4); Sp =100 (99.3–100)
I46	Cardiac arrest	1993–2003 (IN/OUT/ED; A/B*)	427.27; I46	42	$PPV_{IN/OUT/ED}$ =50.0 (35.5–64.5); PPV_{IN} =53.1 (36.5–69.1)
I48	Atrial fibrillation or flutter	1993–2009 (IN/OUT/ED; A/B)	427.93, 427.94; I48	284	PPV_{All} =92.3 (88.6–94.8); $PPV_{IN/OUT}$ =94.0 (90.5–96.3) (independent of diagnosis type and department specialty); PPV_{ED} =64.7 (41.3–82.7)
		1980–2002 (n/a; n/a)	427.93, 427.94; I48	174	PPV =98.9 (95.9–99.7)
		1980–2002 (n/a; n/a)	427.93, 427.94; I48	116	PPV =96.6 (91.5–98.7)
I48.9A	Atrial flutter	1977–1999 (IN/OUT/ED; A/B)	427.94; I48.9A	108	PPV =50.0 (40.7–59.3)
I50	Heart failure	1998–2007 (IN/OUT; A)	I50, I11.0, I13.0, I13.2	50	PPV =100 (92.9–100)

Take home message

I PE defineres outcomes langt oftest ved proxy'er

Validiteten af proxy'en er af betydning for studiets kvalitet

For det meste er det vigtigste en høj positiv prædiktiv værdi

Sensitiviteten kan godt være ringe trods en høj PPV

Der er adskillige måder at optimere validiteten af sin outcome definition på, men gør det med omtanke

SPØRGSMÅL?

Dansk Selskab for Farmakoepidemiologi / Danish Society for Pharmacoepidemiology, dsfe@dsfe.dk