Sciences Economiques & Sociales de la Santé
& Traitement de l'Information Médicale

www.sesstim-orspaca.org

Samy SUISSA

Professor of Epidemiology and Biostatistics, McGill University, Montréal, Canada
Director, Centre for Clinical Epidemiology, Jewish General Hospital, Montréal, Canada

Biais reliés au temps en pharmacoépidémiologie

avril 2016

Cliquez ici pour voir l'intégralité des ressources associées à ce document

Time-related biases in pharmacoepidemiology

Samy Suissa
Lady Davis Institute, Jewish General Hospital
McGill University
Montreal, Canada

Webinar QuanTIM,
April 15, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD

G.J. Criner, J.E. Connett, S.D. Aaron, R.K. Albert, W.C. Bailey, R. Casaburi, J.A.D. Cooper, Jr., J.L. Curtis, M.T. Dransfield, M.K. Han, B. Make, N. Marchetti, F.J. Martinez, D.E. Niewoehner, P.D. Scanlon, F.C. Sciurba, S.M. Scharf, D.D. Sin, H. Voelker, G.R. Washko, P.G. Woodruff, and S.C. Lazarus, for the COPD Clinical Research Network and the Canadian Institutes of Health Research

BACKGROUND

Retrospective studies have shown that statins decrease the rate and severity of exacerbations, the rate of hospitalization, and mortality in chronic obstructive pulmonary disease (COPD). We prospectively studied the efficacy of simvastatin in preventing exacerbations in a large, multicenter, randomized trial.

Articles

Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial

Sil Kordes, Michael N Pollak, Aeilko H Zwinderman, Ron A Mathôt, Mariëtte J Weterman, Aart Beeker, Cornelis J Punt, Dick J Richel, Johanna W Wilmink

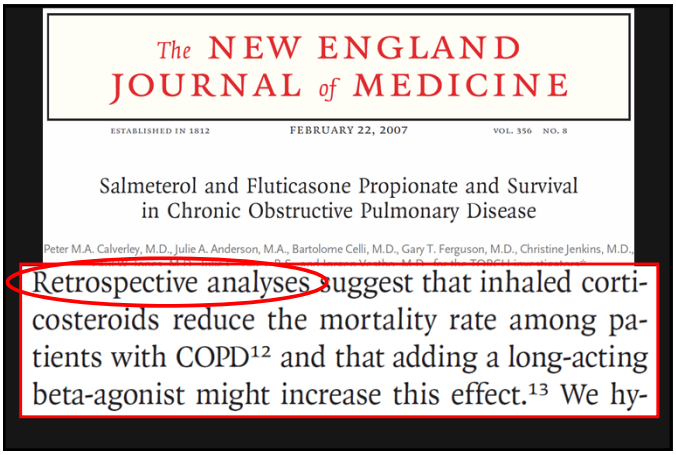
Many retrospective pharmacoepidemiological studies have suggested that patients with diabetes treated with metformin have a reduced cancer risk, an improved cancer prognosis, or improved survival.[3–5] However, the methods

THIS TALK

- Immortal time bias
- Immeasurable time bias
- Importance ?

Immortal time bias:

Inhaled corticosteroids in COPD



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D.,

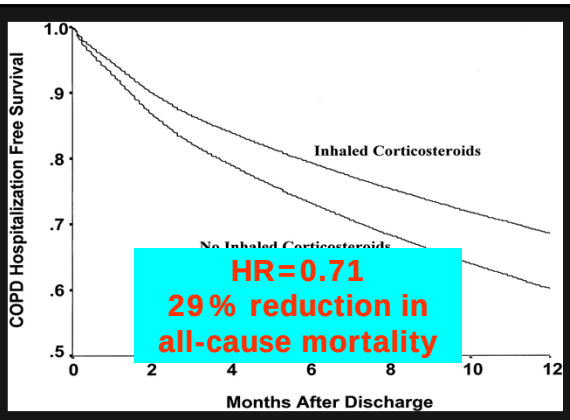
Retrospective analyses suggest that inhaled corticosteroids reduce the mortality rate among patients with COPD[12] and that adding a long-acting beta-agonist might increase this effect.[13] We hy-

Inhaled Corticosteroids and the Risk of Mortality and Readmission In Elderly Patients with Chronic Obstructive Pulmonary Disease

DON D. SIN and JACK V. TU

The Institute for Clinical Evaluative Sciences (ICES) and The Department of Medicine, Sunnybrook and Women's College Health Science Center, University of Toronto, Toronto, Ontario; and Department of Medicine, University of Alberta, Alberta, Canada

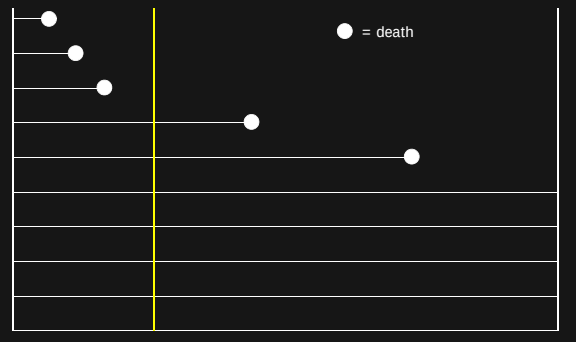
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 164 2001



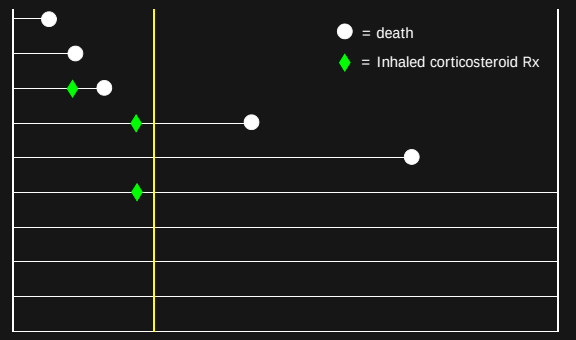
Ontario Study

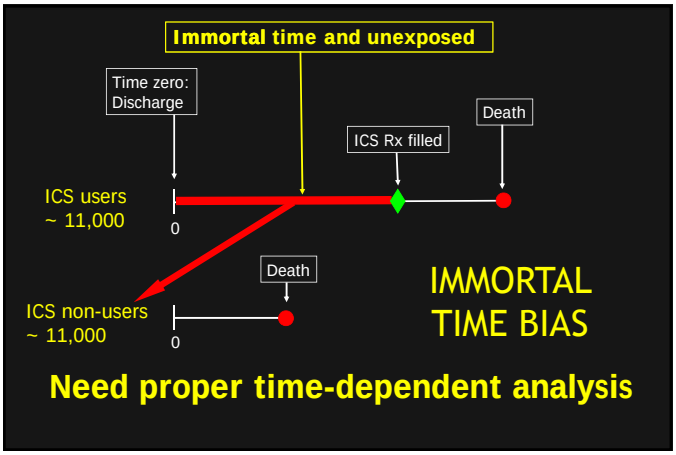
- Cohort study of 22,620 patients hospitalised for COPD (Ontario databases, 1992-97)
- One year follow-up
- 25% readmitted for COPD, 11% died
- 51% received an ICS *within 90 days after discharge*
- Data analysis by "intent-to-treat" approach using Cox's proportional hazards model, adjusting for many covariates

Ontario Study: Design



Ontario Study: Design





Effectiveness of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

Immortal Time Bias in Observational Studies

Samy Suissa

Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University Health Centre; and the Departments of Epidemiology and Biostatistics and Medicine, McGill University, Montreal, Quebec, Canada

Am J Respir Crit Care Med Vol 168. pp 49–53, 2003
Originally Published in Press as DOI: 10.1164/rccm.200210-1231OC on March 27, 2003
Internet address: www.atsjournals.org

Immortal time bias:
Replication of Ontario COPD study

		Crude		Adjusted*	
	Percent Exposed	Rate Ratio	95% Confidence Interval	Rate Ratio	95% Confidence Interval
Inhaled corticosteroids					
Time-fixed analysis†	39.1	0.68	0.55–0.84	0.69	0.55–0.86

Suissa, *AJRCCM* 2003;168:49-53

Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice

J.B. Soriano*,+ , J. Vestbo§, N.B. Pride[f], V. Kiri[#], C. Maden¶, W.C. Maier*

Eur Respir J 2002; 20: 819–825

Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

Results from Two Observational Designs Free of Immortal Time Bias

Victor A. Kiri, Neil B. Pride, Joan B. Soriano, and Jørgen Vestbo

Inhaled corticosteroids and survival in chronic obstructive pulmonary disease: does the dose matter?

D.D. Sin*,†, S.F.P. Man*

Respiratory Medicine (2009) 103, 85–90

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

ELSEVIER

Survival of COPD patients using inhaled corticosteroids and long-acting beta agonists

Douglas W. Mapel[a,b,*], Judith S. Hurley[b], Douglas Roblin[c], Melissa Roberts[b], Kourtney J. Davis[b], Robert Schreiner[c], Floyd J. Frost[b]

Inhaled corticosteroids and risk of lung cancer among COPD patients who quit smoking

Victor A. Kiri [a,*,e], Leonardo M. Fabbri [b], Kourtney J. Davis [c], Joan B. Soriano [d]

Inhaled corticosteroids and survival in COPD patients receiving long-term home oxygen therapy ☆

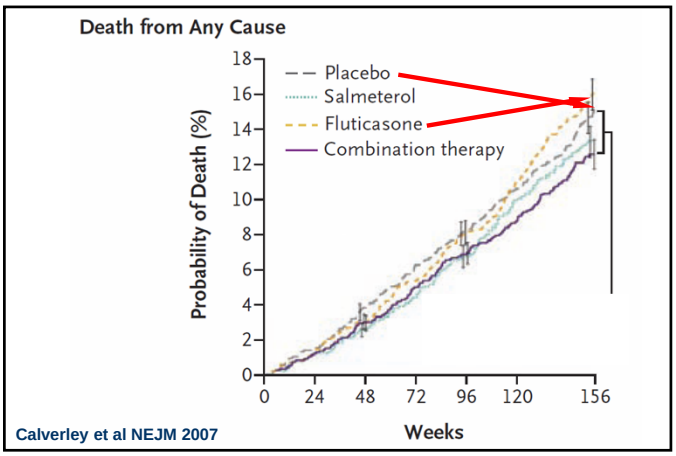
R. Tkacova[a,b,*], S. Toth[a,b], D.D. Sin[c]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*



Calverley et al NEJM 2007

Numerical example:

Metformin and cancer

REVIEW ARTICLE

Metformin and the Risk of Cancer

Time-related biases in observational studies

Samy Suissa, PHD[1,2]
Laurent Azoulay, PHD[1,3]

Diabetes Care, volume 35, December 2012

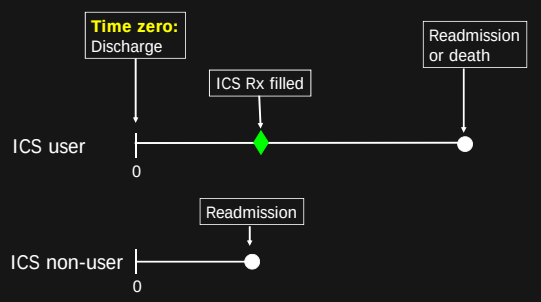
Bias (author [reference])	Study design	Outcome	Relative risk[a] (95% CI)
Immortal time bias			
[illegible] et al. (15)	Cohort	Cancer mortality	0.8 (0.6–0.9)
Bowker et al. (16)	Cohort	Cancer mortality	0.80 (0.65–0.98)
Currie et al. (17)	Cohort	Any cancer	0.54 (0.43–0.66)[b]
Lee et al. (18)	Cohort	Any cancer	0.12 (0.08–0.19)
	Cohort	Colorectal cancer	0.36 (0.13–0.98)
	Cohort	Liver cancer	0.06 (0.02–0.16)
	Cohort	Pancreatic cancer	0.15 (0.03–0.79)
Buchs et al. (19)	Cohort	Any cancer	0.996 (0.994–0.998)[c]
Chen et al. (20)	Cohort	Liver cancer	0.24 (0.07–0.80)
Geraldine et al. (21)	Cohort	Any cancer	0.20 (0.03–1.64)
Yang et al. (22)	Cohort	Any cancer	0.51 (0.31–0.82)[d]
	Cohort	Any cancer	[illegible][e]
Lai et al. (23)	Cohort	Lung cancer	0.55 (0.32–0.94)
	Cohort	Liver cancer	[illegible]
He et al. (24)	Cohort	Prostate: all-cause mortality	0.55 (0.32–0.96)
Lee et al. (25)	Cohort	Colorectal: all-cause mortality	0.66 (0.45–0.98)
	Cohort	Colorectal: cancer mortality	0.66 (0.48–0.92)
He et al. (26)	Cohort	Breast: all-cause mortality	0.52 (0.28–0.97)
	Cohort	Breast: cancer mortality	0.47 (0.24–0.90)
Romero et al. (27)	Cohort	Ovary: progression	0.38 (0.16–0.90)
	Cohort	Ovary: all-cause mortality	0.43 (0.16–1.19)

Table 2—*Comparison between biased time-fixed and corrected time-dependent data analyses for the cohort study of metformin and lung cancer incidence (23)*

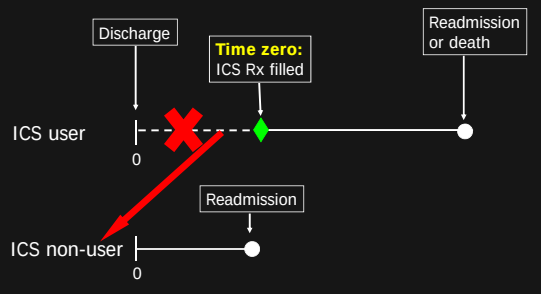
	Metformin users			Nonusers			
	Lung cancer cases (*n*)	Person-years (*n*)	Rate per 10,000 person-years	Lung cancer cases (*n*)	Person-years (*n*)	Rate per 10,000 person-years	Crude rate ratio (95% CI)
Biased time-fixed analysis							
Total	96	93,987	10.2	33	14,266	23.2	0.44 (0.29–0.63)

Alternative “new user” cohort design

Alternative “new-user” Design



Alternative “new-user” Design



Eur Respir J 2004; 23: 1–5
DOI: 10.1183/09031936.04.00062504
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Bias from unaccounted immortal time in a cohort study of the effectiveness of inhaled corticosteroids in COPD

S. Suissa

Replication of the study

	Crude RR	Adjusted# RR	95 % CI
Hierarchical intention-to-treat analysis	0.52	0.66	0.57–0.76

Suissa, *ERJ 2004*;23:391-5

Replication of the study

	Crude RR	Adjusted# RR	95 % CI
Hierarchical intention-to-treat analysis	0.52	0.66	0.57–0.76
According-to-treatment analysis	0.70	0.94	0.81–1.09

IMMORTAL TIME BIAS

Suissa, *ERJ 2004*;23:391-5

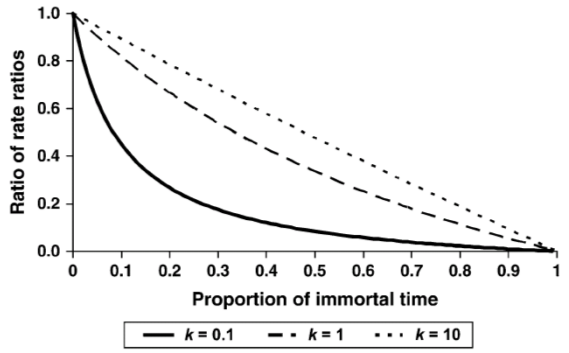
Practice of Epidemiology

Immortal Time Bias in Pharmacoepidemiology

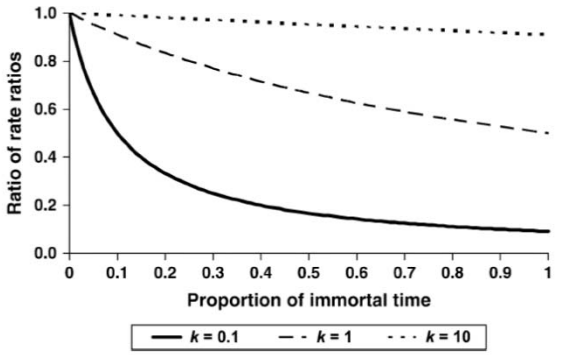
Samy Suissa

From the Department of Epidemiology and Biostatistics, and Department of Medicine, McGill University, I

Time-based and event-based cohort designs



Exposure-based cohort design



THIS TALK

- Immortal time bias
- Immeasurable time bias
- Importance ?

Immeasurable time bias: STATINS

Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis

Julia Hippisley-Cox, Carol Coupland

BMJ VOLUME 330 7 MAY 2005

Current use of studied drugs*	Cases (n=2266)	Controls (n=9064)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
None	677 (29.9)	1738 (19.2)	1.00	1.00
Statins alone	26 (1.1)	117 (1.3)	0.48 (0.31 to 0.74)	0.53 (0.33 to 0.86)
Angiotensin converting enzyme inhibitors	211 (9.3)	474 (5.2)	1.14 (0.94 to 1.37)	0.80 (0.65 to 0.99)
Aspirin alone			)	0.59 (0.50 to 0.68)
β blockers alone			)	0.81 (0.63 to 1.04)
Statins or angiotensin inhibitors			)	0.69 (0.43 to 1.12)
Statins and aspirin			)	0.39 (0.29 to 0.52)
Statins and β blockers			)	0.46 (0.26 to 0.82)
Angiotensin converting and aspirin			)	0.54 (0.45 to 0.66)
Angiotensin converting and β blockers			)	0.64 (0.43 to 0.94)
Aspirin and β blockers			)	0.38 (0.31 to 0.47)
Statins, angiotensin c inhibitors, and aspirin			)	0.29 (0.21 to 0.41)
Statins, angiotensin converting enzyme inhibitors, and β blockers	11 (0.5)	34 (0.4)	0.68 (0.34 to 1.37)	0.67 (0.30 to 1.51)
Statins, aspirin, and β blockers	45 (2.0)	622 (6.9)	0.16 (0.11 to 0.22)	0.17 (0.12 to 0.23)
Angiotensin converting enzyme inhibitors, aspirin, and β blockers	71 (3.1)	420 (4.6)	0.41 (0.31 to 0.54)	0.34 (0.26 to 0.46)
Statins, angiotensin converting enzyme inhibitors, aspirin, and β blockers	57 (2.5)	406 (4.5)	0.31 (0.23 to 0.42)	0.25 (0.18 to 0.35)

RR=0.17
83% reduction in mortality !

RCTs vs case-control study

	Total number of deaths	Rate Ratio	95% CI	Rate Reduction
Meta-analyses of RCTs				
Lancet (2005)	8,186	0.88	0.84-0.91	**12%**
JACC (2008)	Not reported	0.93	0.87-0.99	**7%**
BMJ (2009)	3,650	0.88	0.81-0.96	**12%**

RCTs vs case-control study

	Total number of deaths	Rate Ratio	95% CI	Rate Reduction
Meta-analyses of RCTs				
Lancet (2005)	8,186	0.88	0.84-0.91	**12%**
JACC (2008)	Not reported	0.93	0.87-0.99	**7%**
BMJ (2009)	3,650	0.88	0.81-0.96	**12%**
Case-control study (2005)				
-Statins alone	2,266	0.53	0.33-0.86	**47%**

RCTs vs case-control study

	Total number of deaths	Rate Ratio	95% CI	Rate Reduction
Meta-analyses of RCTs				
Lancet (2005)	8,186	0.88	0.84-0.91	**12%**
JACC (2008)	Not reported	0.93	0.87-0.99	**7%**
BMJ (2009)	3,650	0.88	0.81-0.96	**12%**
Case-control study (2005)				
-Statins alone	2,266	0.53	0.33-0.86	**47%**
-Statins, aspirin	2,266	0.39	0.29-0.52	**61%**
-Statins, aspirin, β-blockers	2,266	0.17	0.12-0.23	**83%**
-Statins, aspirin, β-blockers, ACE	2,266	0.25	0.18-0.35	**75%**

American Journal of Epidemiology

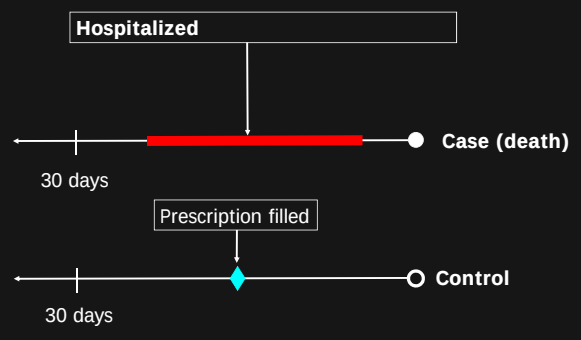
DOI: 10.

Practice of Epidemiology

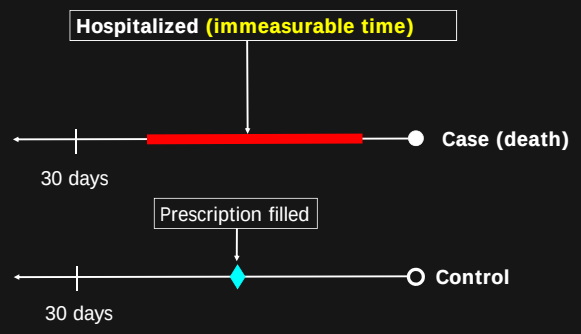
Immeasurable Time Bias in Observational Studies of Drug Effects on Mortality

Samy Suissa[1,2]

Case-control design



Case-control design



ILLUSTRATION

- Cohort of 2,049 patients hospitalised for COPD in Saskatchewan (1990-2003)
- 1313 died during follow-up (cases) matched to 1313 risk-set controls
- Exposure: Inhaled corticosteroid prescription in 30-day period prior to index date
- Data analysis done 2 ways:
  - Irrespective of immeasurable time
  - Accounting for immeasurable time

	Cases (deaths)		Controls	
	N	LOS	N	LOS
All subjects	1313	11.0	1313	2.3

	Cases (deaths)		Controls	
	N	LOS	N	LOS
All subjects	1313	11.0	1313	2.3
ICS prescription (30 days)	217	6.6	341	2.2
No ICS prescription	1,096	11.9	972	2.3

immeasurable time

Immeasurable time bias

	Cases	Controls	Crude RR	Adjusted RR (95 % CI)	
ICS Rx (last 30 days)					
No	1,096	972	1.00	1.00	Ref
Yes	217	341	0.56	0.60	0.50-0.73

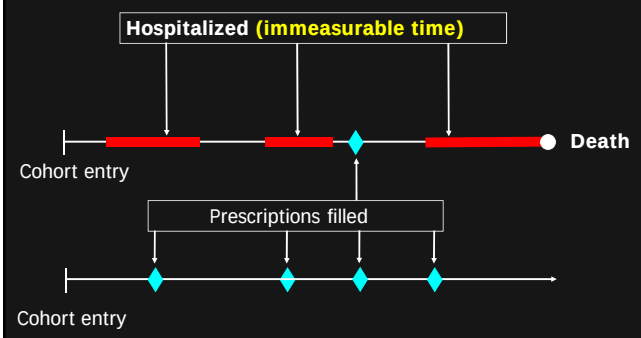
Immeasurable time bias

	Cases	Controls	Crude RR	Adjusted RR (95 % CI)	
ICS Rx (last 30 days)					
No	1,096	972	1.00	1.00	Ref
Yes	217	341	0.56	0.60	0.50-0.73
Time-adjusted 30-day ICS use	0.26	0.28	0.93	0.98	0.83-1.17

Immeasurable time bias

Inhaled corticosteroid use by method of data analysis	Cases	Controls	Crude rate ratio	Adjusted*	
				Rate ratio	95% confidence interval
No. of subjects	1,313	1,313			
Method 1—all subjects					
Use in the last 30 days	217	341	0.56	0.60	0.50, 0.73
No use in the last 30 days	1,096	972	1.00	1.00	Referent
Method 2—nonhospitalized subjects					
Use in the last 30 days	73	247	0.73	0.81	0.60, 1.10
No use in the last 30 days	290	719	1.00	1.00	Referent
Method 3—all subjects adjusted for hospitalization					
Use in the last 30 days	217	341	0.59	0.63	0.51, 0.79
No use in the last 30 days	1,096	972	1.00	1.00	Referent

Cohort design



THIS TALK

- Immortal time bias
- Immeasurable time bias
- Importance ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD

G.J. Criner, J.E. Connett, S.D. Aaron, R.K. Albert, W.C. Bailey, R. Casaburi, J.A.D. Cooper, Jr., J.L. Curtis, M.T. Dransfield, M.K. Han, B. Make, N. Marchetti, F.J. Martinez, D.E. Niewoehner, P.D. Scanlon, F.C. Sciurba, S.M. Scharf, D.D. Sin, H. Voelker, G.R. Washko, P.G. Woodruff, and S.C. Lazarus, for the COPD Clinical Research Network and the Canadian Institutes of Health Research

This article was published on May 18, 2014, at NEJM.org.

BACKGROUND

Retrospective studies have shown that statins decrease the rate and severity of exacerbations, the rate of hospitalization, and mortality in chronic obstructive pulmonary disease (COPD). We prospectively studied the efficacy of simvastatin in preventing exacerbations in a large, multicenter, randomized trial.

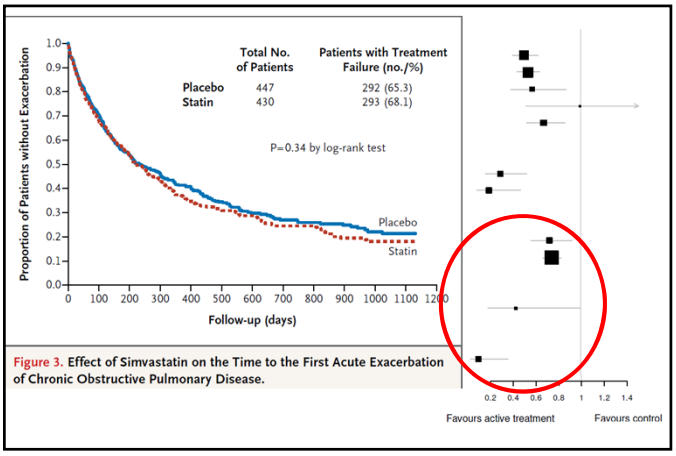


Figure 3. Effect of Simvastatin on the Time to the First Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

Simvastatin in Moderate-to-Severe COPD

The NEW ENGLAND JOURNAL of MEDICINE

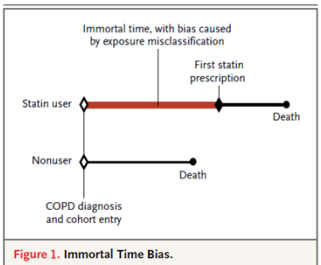


Figure 1. Immortal Time Bias.

5. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012;35:2665-73.

DOI: 10.1056/NEJMc1408400

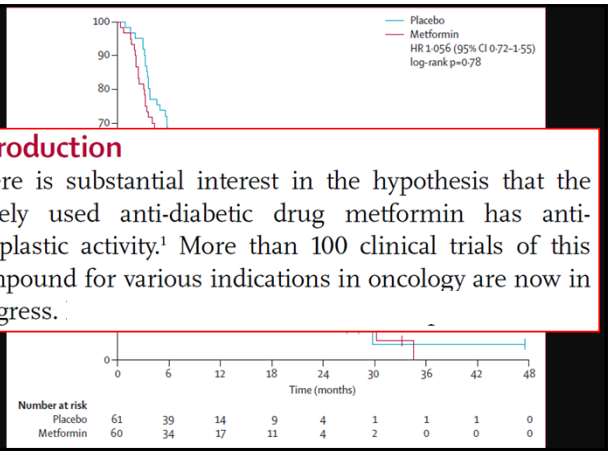
Lancet Oncol 2015 **Articles**

Published Online
June 9, 2015

Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial

Sil Kordes, Michael N Pollak, Aeilko H Zwinderman, Ron A Mathôt, Mariette J Weterman, Aart Beeker, Cornelis J Punt, Dick J Richel, Johanna W Wilmink

Many retrospective pharmacoepidemiological studies have suggested that patients with diabetes treated with metformin have a reduced cancer risk, an improved cancer prognosis, or improved survival.[3–5] However, the methods



Introduction

There is substantial interest in the hypothesis that the widely used anti-diabetic drug metformin has anti-neoplastic activity.[1] More than 100 clinical trials of this compound for various indications in oncology are now in progress.