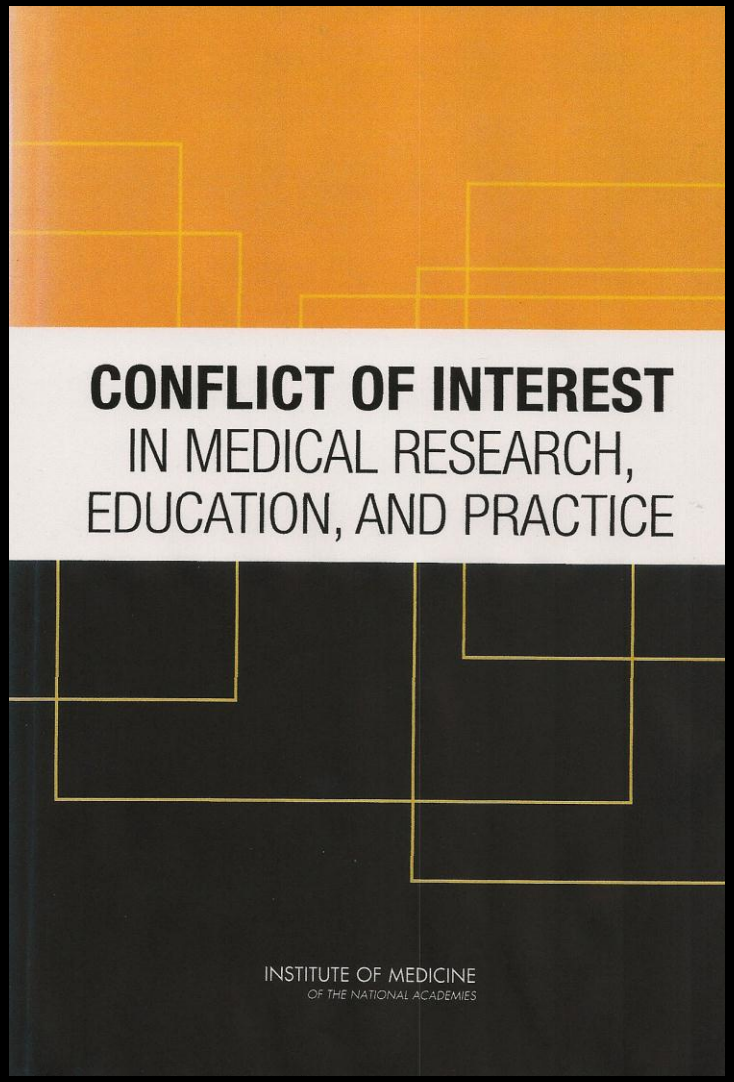
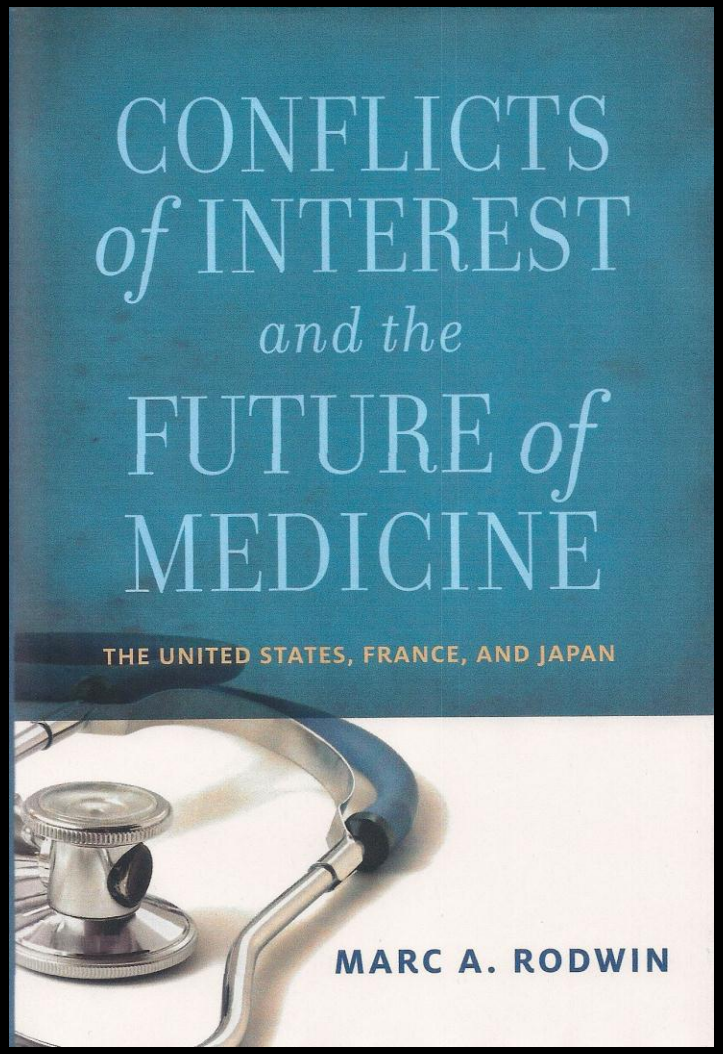
Conflits d'intérêts académiques

Pr Francois Lemaire

IMR 18-11-2011

DRCD de l'AP-HP, Saint-Louis


CONFLICT OF INTEREST
IN MEDICAL RESEARCH,
EDUCATION, AND PRACTICE
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES


CONFLICTS
of INTEREST
and the
FUTURE of
MEDICINE
THE UNITED STATES, FRANCE, AND JAPAN
MARC A. RODWIN

Conflits d'intérêt académiques

Domaines de prédilection:

recherche

Formation

rédaction de recommandations

Conflits d'intérêt académiques

Conflits d'intérêt non financiers

- Promotion académique
- Notoriété
- Curiosité intellectuelle (« intellectual passion » : Uniform requirements for manuscripts submitted to BM journals ; ICMJE 1983)

Conflits d'intérêt financiers

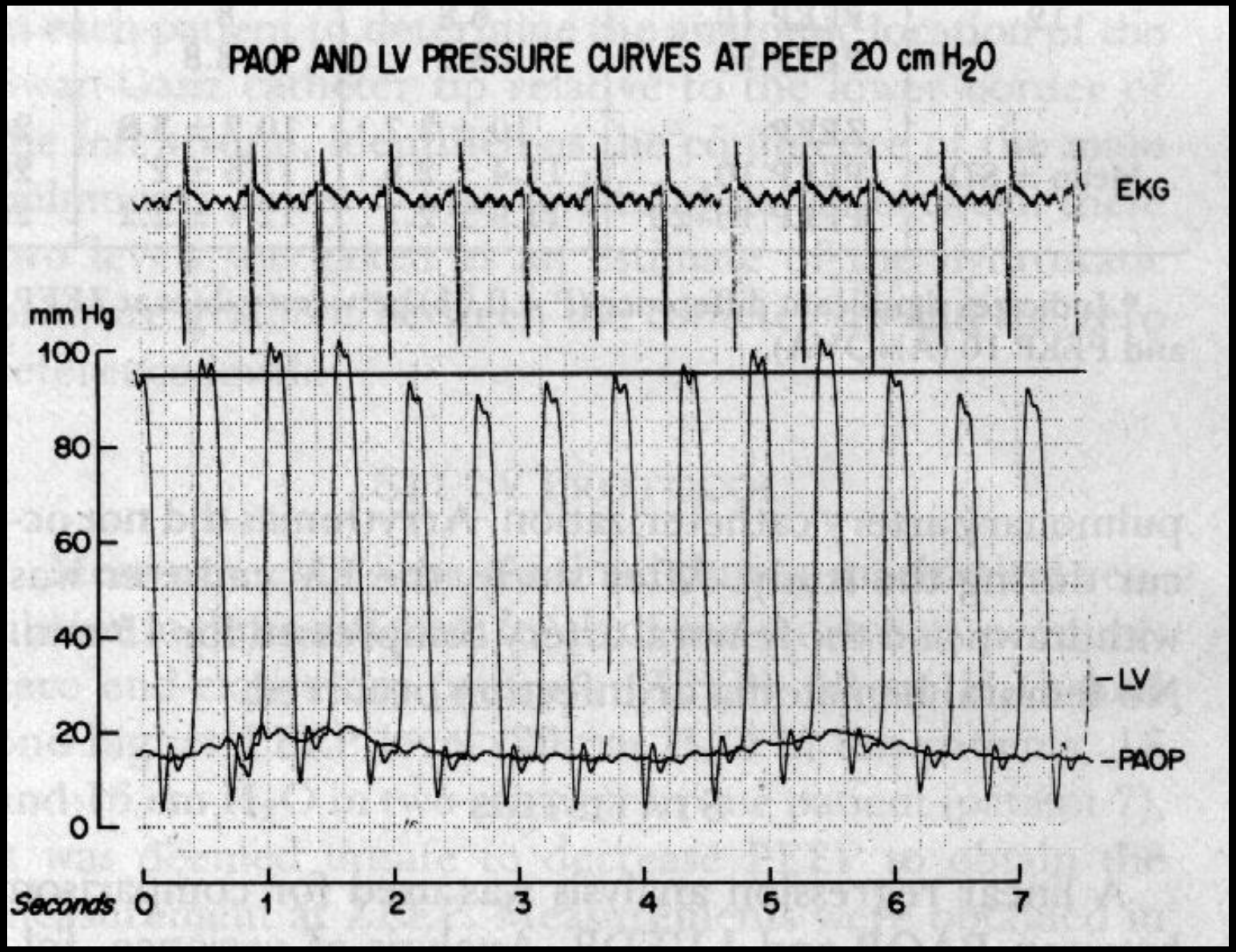
- Direct : inclusions ds les essais; consultants ind pharma
- Indirect

Non financial conflicts of interest in research

NG Levinsky NEJM 2002; 347:759

« In 1963, I was a young academic physician studying the regulation of sodium excretion…
My primary motive was academic – the desire to advance knowledge about important physiological mechanisms…
A potent secondary motive was to advance my career by publishing the results of the research and maintaining grant support- academic currency that buys prestige and promotion. »

Teboul, Lemaire et al Anesthesiology 1988)

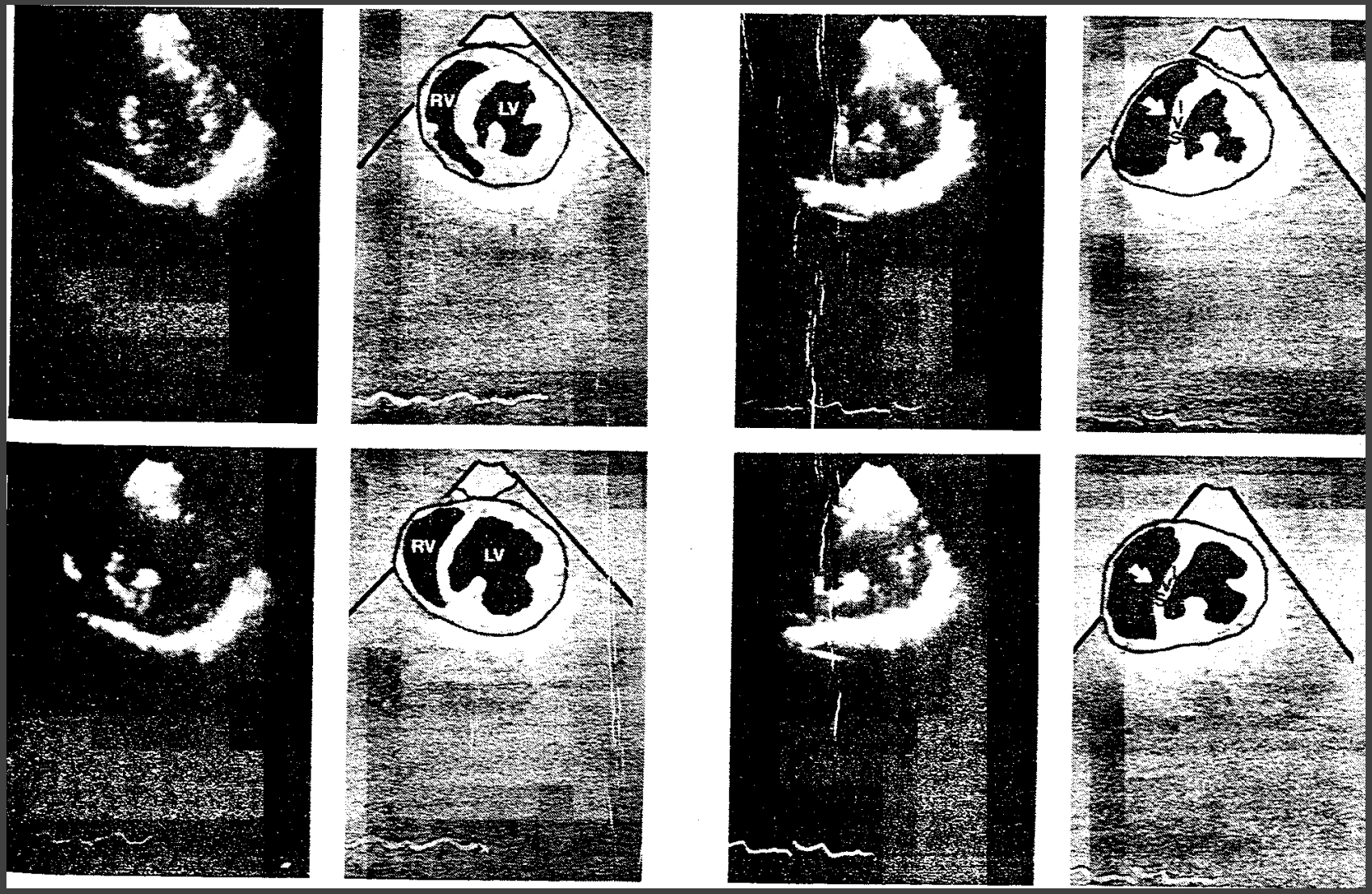


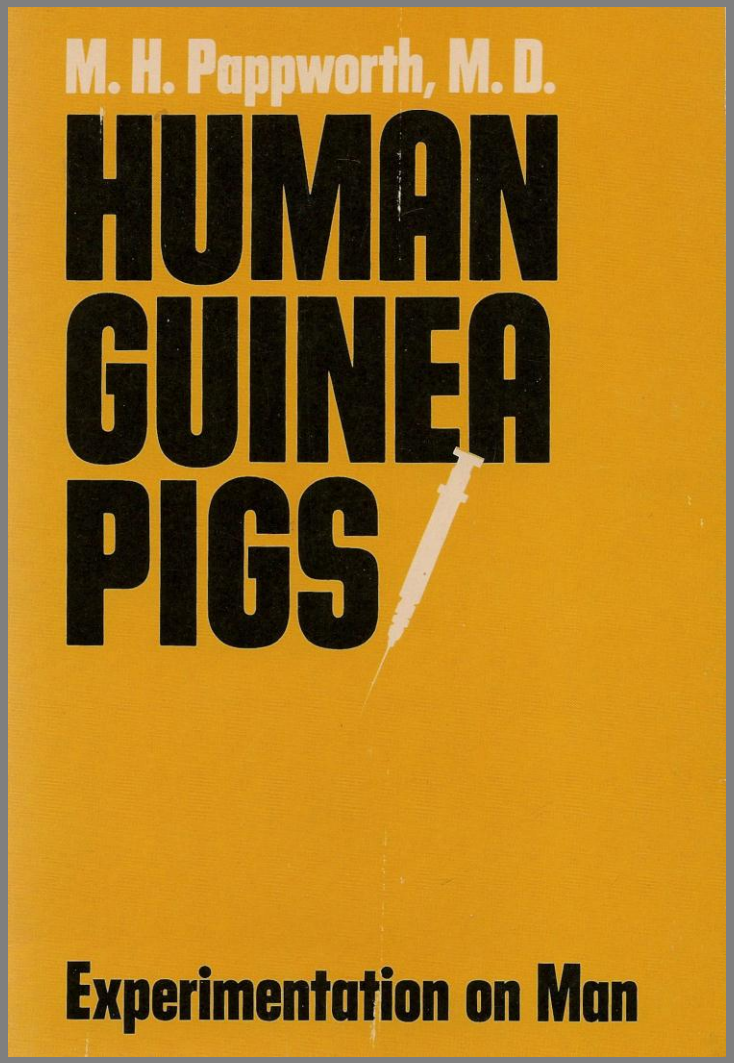
F Jardin (NEJM 1981; 304: 387)

ZEEP PEEP 30

ES

ED





Réponse du Lancet à MH Pappworth : *« I Know there are times when good comes of speaking strongly…to what appear to be public scandals : but you haven't persuaded us that this is one of those occasions »*

Ethics and clinical research, by HK Beecher NEJM; 1966; 274:1354

HK Beecher

HK Beecher

Ethics and clinical research, by HK Beecher NEJM; 1966; 274:1354

Une liste de (50) études (publiées) "non éthiques"

- Injection IM de virus vivants à des enfants mentalt déficients
- Patients hospitalisés: Injection of cellules cancereuses
- Greffe d'un mélanome d'une fille à sa mère
- Cathéterisme OG transbronchique

Commentaires

- la pression sur les jeunes investigateurs ("publish or perish")

Ethics and clincal research by HK Beecher NEJM 1966 ; 274 : 1354

"… Medical schools and universities are increasingly dominated by investigators. Every young man knows that he will never be promoted to a tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator. …one can see how great the pressures are on ambitious young physicians.
…one can therefore anticipate an increase in experimentation; and the newly developed concept of clinical research as a profession can lead to infortunate separation between the interest of science and the interests of patients."

1970-1990: l'âge d'or de la recherche clinique

D'Oxford à Créteil, du chien à l'homme, une expérimentation sur la vaso-constriction hypoxique en 1983-6

Conflits d'intérêt non financiers
L'exemple d'Ellen Roche

Conflits d'intérêt non financier Ellen Roche (1)

-NEJM 2002 (346: 716) Protecting research subjects : the crisis at Johns Hopkins
- Lancet 2001 357 : 2067 Improving the safety of patients during clinical research
- & 358: 213 news: Hopkins takes responsability for volunteer death
- BMJ 2001 (357: 2114) : healthy volunteer dies in US physiology study
& (328: 531) : Hopkins faces further criticism over experiments
- NYT : 27-07-2001

Conflits d'intérêt non financier Ellen Roche (1)

- E Roche, 24 ans, technicienne de laboratoire à J Hopkins
- volontaire dans un essai physiopath du NIH; investigateur: Dr A Togias
- inhalation Hexamethonium (bloqueur sympathique) le 4 mai 2002
- décès un mois plus tard, le 2 juin dans un tableau d' ARDS
-Suspension de l'essai, puis de la totalité de la recherche clinique à Hopkins par l'OHRP (19-07-01)
- quatre inspections séparées (OHRP), incluant la revue par l'Université (IRB) de 2600 protocoles !
- redémarrage complet en janvier 2002

Conflits d'intérêt non financier Ellen Roche (2)

Réaction immédiate de l'Université:

« …We find it dificult to understand why a relatively new agency would take these draconins measures in an institution that has cared for for thousands of people in clinical trials…
We have done clinical trials here at Hopkins for over a hundred of years… »

Conflits d'intérêt non financier Ellen Roche (3)

Mise en évidence de nombreuses dysfonctions concernant l'essai du Dr Togias :

- Hexaméthonium : un produit ancien, retiré du marché depuis 50 ans, non déclaré à la FDA comme IND
- accidents anciens non connus des investigateurs
- EIG antérieurs non détectés, non pris en compte
- notice information trompeuse

Graves anomalies dans l'organisation et le contrôle de la recherche clinique à Hopkins par son IRB :

- analyse des protocoles insuffisante: pas d'examen individuel, en séance plénière;
- un seul comité, 800 nouveaux protocoles par an
- pas de compte rendus des séances

Rapport du Comité d'audit externe

Culture of Possible Coercion

There appears to be an informal culture within the Asthma and Allergy Center that raises questions of subtle coercive pressures as well as a more casual approach to safety in research using normal volunteers. It was often the practice of the staff of the Center to participate in Center studies. The investigators carefully followed the restriction forbidding direct staff solicitation but signs were posted soliciting volunteers throughout the center and many staff members participated. In fact, a registry of former participants in trials was maintained as a source for recruitment to new studies. We were told that the majority of the registrants were Asthma Center staff. Ellen Roche herself had participated in a number of previous studies. As far as we can tell, not only were the volunteers compensated, but they also were given time off during the working day to participate. We believe that Hopkins should consider the possibility that these factors might be coercive and prohibit the participation of research subjects from the unit (broadly interpreted) in which he/she is employed.

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN- OUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

ABSTRACT

Background Drotrecogin alfa (activated), or recombinant human activated protein C, has antithrombotic, antiinflammatory, and profibrinolytic properties. In a previous study, drotrecogin alfa activated produced dose-dependent reductions in the levels of markers of coagulation and inflammation in patients with severe sepsis. In this phase 3 trial, we assessed whether treatment with drotrecogin alfa activated reduced the rate of death from any cause among patients with severe sepsis.

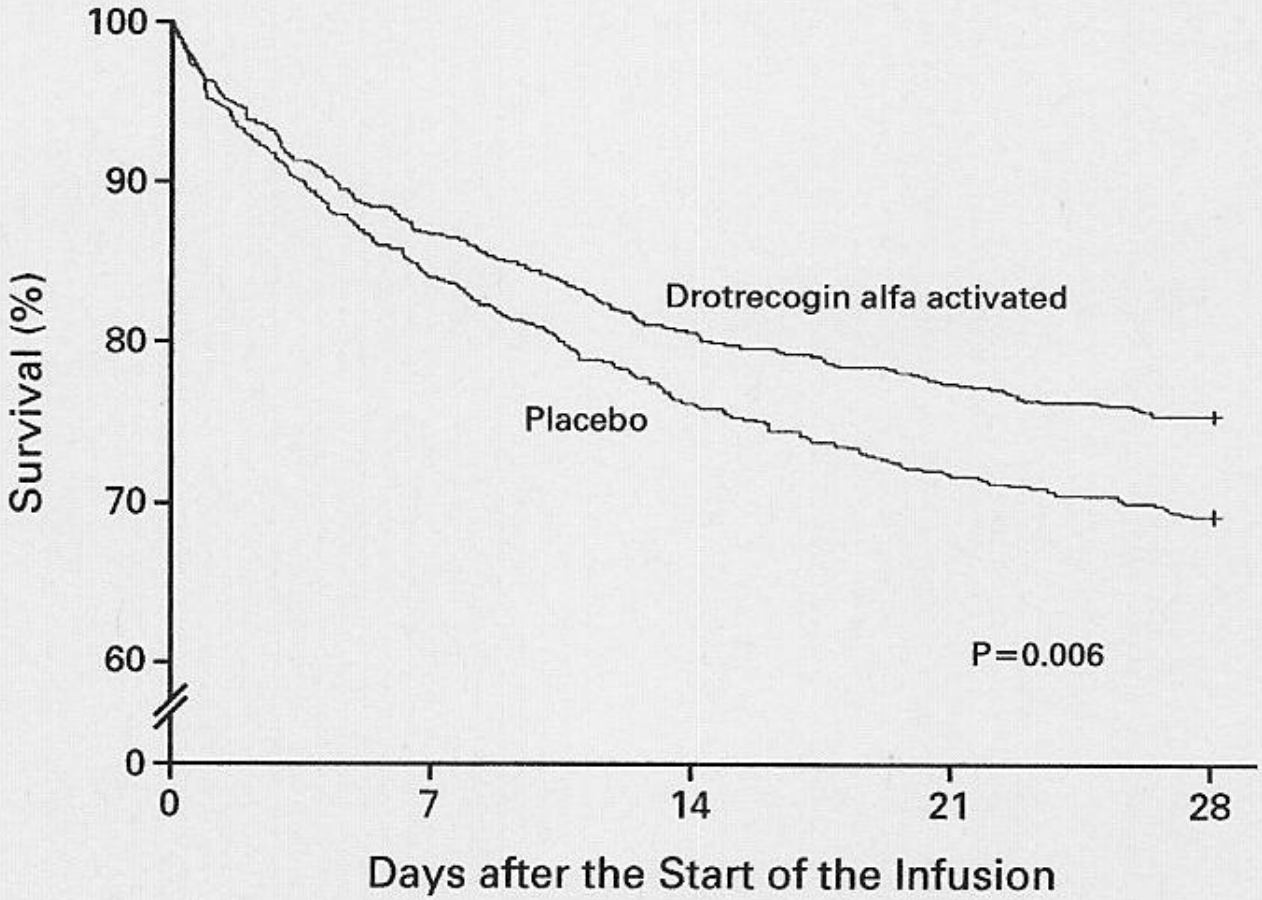
Methods We conducted a randomized, double-blind, placebo-controlled, multicenter trial. Patients with systemic inflammation and organ failure due to acute infection were enrolled and assigned to receive an intravenous infusion of either placebo or drotrecogin alfa activated (24 μg per kilogram of body weight per hour)

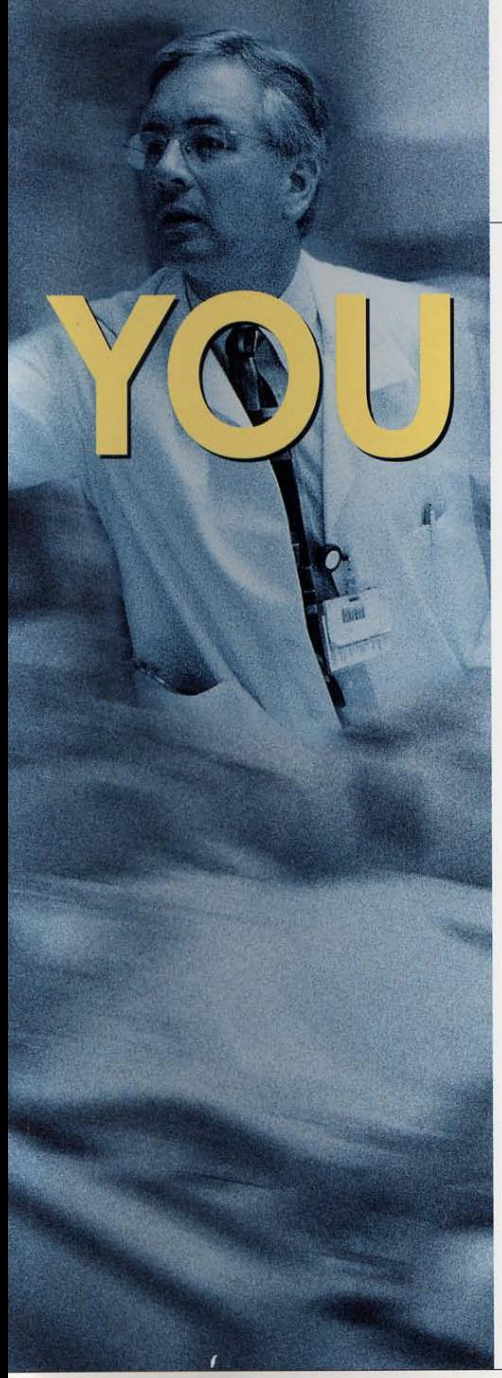
SEVERE sepsis, defined as sepsis associated with acute organ dysfunction, results from a generalized inflammatory and procoagulant response to an infection.[1] The rate of death from severe sepsis ranges from 30 to 50 percent despite advances in critical care.[2-5] In the United States, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal.[6]

The inflammatory and procoagulant host responses to infection are closely related.[7] Inflammatory cytokines, including tumor necrosis factor α, interleukin-1β, and interleukin-6, are capable of activating coagulation and inhibiting fibrinolysis, whereas the procoagulant thrombin is capable of stimulating multiple inflammatory pathways.[7-11] The end result may be diffuse endovascular injury, multiorgan dysfunction

G Bernard et al NEJM 2001

G. Bernard et al NEJM 2001





Xigris®
drotrecogin alfa (activated)

CAN INCREASE THEIR ODDS OF SURVIVAL.

In high-risk severe sepsis, Xigris works.

Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (eg, as determined by APACHE II*). Efficacy has not been established in adult patients with severe sepsis and lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis.

Bleeding is the most common adverse reaction associated with Xigris therapy. In the Phase 3 study, serious bleeding events were observed during the 28-day study period in 3.5% of Xigris-treated and 2.0% of placebo-treated patients. The difference in serious bleeding occurred primarily during infusion. The incidence of intracranial hemorrhage (ICH) was 0.2% for Xigris-treated and 0.1% for placebo-treated patients. ICH has been reported in Xigris-treated patients in non-placebo controlled trials with an incidence of approximately 1% during infusion. The risk of ICH may be increased in patients with risk factors for bleeding such as severe coagulopathy and severe thrombocytopenia. Should clinically important bleeding occur, immediately stop the Xigris infusion.

* APACHE (Acute Physiology And Chronic Health Evaluation). For more information on using the APACHE II scoring system, please see http://www.sfar.org/scores2/scores2.html

Please see brief summary on adjacent page for Contraindications, Warnings, and other Important Safety Information.

Lilly

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2011
EMA/856472/2011
Press Office

Press release

Xigris (drotrecogin alfa (activated)) to be withdrawn due to lack of efficacy

PROWESS-SHOCK study shows no gain in 28-day survival of septic shock patients

The European Medicines Agency has been informed of Eli Lilly's decision to withdraw Xigris from the market worldwide further to the 28-day mortality results from the PROWESS-SHOCK study. Eli Lilly has also decided to discontinue all other ongoing clinical trials.

Xigris ®

- 2001: publication dans le NEJM d'une étude montrant l'intérêt du Xigris® dans les états septiques graves
- autorisation par la FDA dans la foulée ; mais réserves +++; demande d' études additionnelles : essais ADRESS, RESOLVE…études qui seront négatives
- 2002: autorisation par l'EMEA « under exceptional circumstances »
- 2002: réévaluation par l'EMEA ; demande d'un essai de confirmation contre placebo (PROWESS-shock)
- octobre 2011: Eli Lily annonce l'absence d'efficacité, retrait de l'autorisation par l'EMA

Xigris ®

Une autre histoire
racontée par :

- **Marcia Angell (2004) Random House Publisher NY**
- **Heichacker et Natanson NEJM 2010**
- **Ch Wiedermann (2005) Wien Klin Wochensherift**
- **Wall Street J (2003)**

Xigris ® (2)

- **Suite aux réserves de la FDA, de l'EMEA et des critiques de nombreux médecins, les ventes de Xigris sont décevantes**
- **Eli Lilly consulte une agence de communication (Belsito et Co)**

Le programme de marketing proposé comporte :

- Créer/augmenter une sensibilisation des prescripteurs au rationnement des soins :

- Financer une Task Force « Values, Ethics and Rationing in Critical Care (VERICC) (1,8 M dollars)

- organiser des symposia sur le rationnement ("il n'est pas éthique de ne pas utiliser un medicament autorisé même s'il est cher")

CCM 2004 ; 32 : 1588

Review Article

Rationing critical care beds: A systematic review*

Tasnim Sinuff, MD; Kamyar Kahnamoui, MD; Deborah J. Cook, MD; John M. Luce, MD; Mitchell M. Levy, MD; for the Values, Ethics, & Rationing in Critical Care (VERICC) Task Force

Objective: Rationing critical care beds occurs daily in the hospital setting. The objective of this systematic review was to examine the impact of rationing intensive care unit beds on the process and outcomes of care.

Data Source: We searched MEDLINE (1966–2003), CINAHL (1982–2003), Ovid Healthstar (1975–2003), EMBASE (1980–2003), Scisearch (1980–2003), the Cochrane Library, PUBMED related articles, personal files, abstract proceedings, and reference lists.

Study Selection: We included studies of seriously ill patients considered for admission to an intensive care unit bed during periods of reduced availability. We had no restriction on study design. Studies were excluded if rationing was performed using a scoring system or protocol and if cost-effectiveness was the only outcome.

Data Extraction: In duplicate and independently, we performed data abstraction and quality assessment.

Data Synthesis: We included ten observational studies. Hospital mortality rate was increased in patients refused intensive care unit admission vs. those admitted (odds ratio, 3.04; 95% confidence interval, 1.49–6.17). Factors associated with both intensive care unit bed refusal and increased mortality rate were increased age, severity of illness, and medical diagnosis. When intensive care unit beds were reduced, admitted patients were sicker, were less often admitted primarily for monitoring, and had a shorter intensive care unit length of stay, without other observed adverse effects.

Conclusions: These studies suggest that patients who are perceived not to benefit from critical care are more often refused intensive care unit admission; refusal is associated with an increased risk of hospital death. During times of decreased critical bed availability, several factors, including age, illness severity, and medical diagnosis, are used to triage patients, although their relative importance is uncertain. Critical care bed rationing requires further investigation. (Crit Care Med 2004; 32:1588–1597)

Key Words: ration; triage; critical care; intensive care

Xigris ® (3)

- Subventionner des recommandations de sociétés savantes (SCCM, ESICM) sur le traitement des états septiques graves « Surviving Sepsis Campaign »
    - guidelines : utiliser le Xigris (reco B)

Intensive Care Med (2004) 30:536–555
DOI 10.1007/s00134-004-2210-z

SPECIAL ARTICLE

R. Phillip Dellinger
Jean M. Carlet
Henry Masur
Herwig Gerlach
Thierry Calandra
Jonathan Cohen
Juan Gea-Banacloche
Didier Keh
John C. Marshall
Margaret M. Parker
Graham Ramsay
Janice L. Zimmerman
Jean-Louis Vincent
M. M. Levy

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

Received: 6 January 2004
Accepted: 29 January 2004
Published online: 3 March 2004
© Springer-Verlag 2004

Trzeciak, MD; Christophe Vinsonneau, MD. *Executive Committee, Surviving Sepsis Campaign. **Steering Committee, Surviving Sepsis Campaign.

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Section of Critical Care Medicine,
Cooper University Hospital,
One Cooper Plaza, 393 Dorrance, Camden,
NJ 08103, USA

ICM Sepsis campaign 2004

Acknowledgment *Founding of the Surviving Sepsis Campaign.* The ESICM, SCCM and International Sepsis Forum have established the Surviving Sepsis Campaign with the aim of improving the care of septic patients. The first phase of the Campaign was built around the Barcelona ESICM congress and included the initial Barcelona Declaration, a media campaign that identified sepsis as a killer and the need to make progress in public awareness and to reduce mortality, and two surveys performed among physicians. The cost of phase I was approximately EUR 553,227, and was supported by unrestricted educational grants from Eli Lilly (94%), Edwards (3%) and Baxter (3%). Producing the present guidelines document was the phase II of the Campaign. For this process, the sponsor companies have been entirely separated from the process by which the guidelines were developed by the many contributors, whose conflicts of interest have been collected in accordance with SCCM guidance (see document). The costs for this phase included mainly the costs of the meeting, teleconference and website update, amounted to approximately EUR 125,006, and were beared by unrestricted educational grants from Eli Lilly (90%) and Edwards (10%). Most of the expense for this effort has been time by the committee who received no reimbursement.

Conflits d'intérêt financier indirects

Serving two masters B Lo NEJM 2010

Missions of Academic Health Centers and Medical Companies.

Mission of Academic Health Center	Mission of Drug, Medical Device, or Biotech Company
Conduct basic research to understand the mechanisms of disease and human functioning	Develop new products that will generate profits for the company
Train graduate students and fellows to become independent investigators who can compete effectively for funding from the National Institutes of Health	Encourage graduate students and fellows to carry out research on the company's promising products for development
Promote evidence-based medicine and independent critical judgment by physicians	Develop marketing strategies to improve sales and profits
Provide cost-effective care to patients and achieve a profit margin from clinical care that can be used to subsidize other activities	Increase profits through increased sales of products
Improve public health, global health, and care for orphan diseases for which patients seek care at the hospital	Work on issues of public health and global health and on treatments for orphan diseases if it fits the company's business model or plan for charitable giving or enhances its reputation

The New York Times

November 4, 2000

Penn Settles Suit On Genetic Test

PHILADELPHIA, Nov. 3— The family of a teen-ager who died in a gene therapy experiment has settled a wrongful-death lawsuit against his doctors and the University of Pennsylvania.

The teenager, Jesse Gelsinger, 18, of Tucson, died on Sept. 17, 1999, four days after the experiment began. His death is the first known to have been caused by gene therapy.

Terms of the settlement were not released.

Mr. Gelsinger suffered from an inherited disorder that inhibited nitrogen processing in the body. Researchers injected him with a cold virus that had been modified to carry a gene that would control the condition. But two days after the therapy began, he slipped into a coma.

Mr. Gelsinger was eventually taken off life support and died.

Science News 2005; 307 : 1028

GENE THERAPY

As Gelsinger Case Ends, Gene Therapy Suffers Another Blow

Five years after 18-year-old Jesse Gelsinger died in a gene therapy experiment, the U.S. Department of Justice has reached a settlement with the researchers and with their institutions. The department announced last week that the University of Pennsylvania (U. Penn) will pay fines of $517,496, and Children's National Medical Center in Washington, D.C., will pay $514,622. The settlement also restricts the clinical research of the three investigators.

The Department of Justice alleged that toxic reactions in humans should have halted the trial earlier and that the lead investigators misrepresented clinical findings to the study's overseers, such as the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). James Wilson of U. Penn, who had a financial interest in a company that stood to profit if the trial was successful, has agreed not to lead any FDA-regulated clinical trials for 5 years and be monitored for 3 years. Steven Raper of U. Penn and Mark Batshaw of Children's face less severe restrictions. Under the agreement, the scientists do not admit responsibility for Gelsinger's death. "Outrageous," responds Gelsinger family attorney Alan Milstein, who said the family had hoped for a formal apology and the release of the clinical trial documents.

While the Gelsinger case drew to a close, the field of gene therapy suffered another setback last month: A third child in a French trial for X-linked severe combined immunodeficiency (X-SCID) developed leukemia, French authorities reported on 24 January. Seventeen children have been successfully treated for SCID using gene therapy, making it the field's bright spot. But two patients in the French trial developed leukemia in late 2002 after a vector inserted near an oncogene; one child died last October. In response to the third leukemia case, the French trial has been halted again and FDA has suspended three U.S. SCID trials, but a trial in Britain continues.

The two previous leukemia cases in France occurred in infants treated at 3 months of age or less, which led to speculation that cells with the oncogene insertion proliferate more readily in very young children. But the third child was treated at 9 months, suggesting that older children may also be at risk, says Harry Malech of NIH, who heads one of the U.S. trials. Experts expect to discuss the case when FDA's gene therapy advisory committee and NIH's Recombinant DNA Advisory Committee meet in March.

—JENNIFER COUZIN AND JOCELYN KAISER

CREDIT: UNIVERSITY COLLEGE LONDON

Published by AAAS

Conflits d'intérêt académiques
Solutions ?

1. **Recherche clinique :**
   - la réglementation actuelle
   - les CER (France CPP)

2. **Les relations avec l'industrie : d'innombrables articles, recommandations**
   - (US) Institute of Medicine (NEJM 2009; 360 : 2160) : interdire la participation des médecins ayany des conflits d'intérêts pour la rédaction des recommandations

➔ Déclarations des conflits d'intérêts (uniquement financiers)

ICM 2008
Sepsis Campaign

J. Author Disclosure Information 2006–2007

Dr. Dellinger has consulted for AstraZeneca, Talecris, and B Braun. He has received honoraria from Eli Lilly (2), Brahms (2), INO Therapeutics (1), Pulsion (1), and bioMerieux (1). He has also received grant support from AstraZeneca and Artisan.

Dr. Levy has received honoraria from Eli Lilly and Edwards Lifesciences. He has also received grant support from Phillips Medical Systems, Edwards Lifesciences, Phillips Medical Systems, Novartis, Biosite, and Eisai.

Diagnostic
Dr. Ra
Maquet ar
Eli Lilly.
Draeger, a
Dr. Ra
and Respir
Dr. Sev
of interest.
Dr. The
AstraZene
NIH for a

ICM 2008
Sepsis Campaign

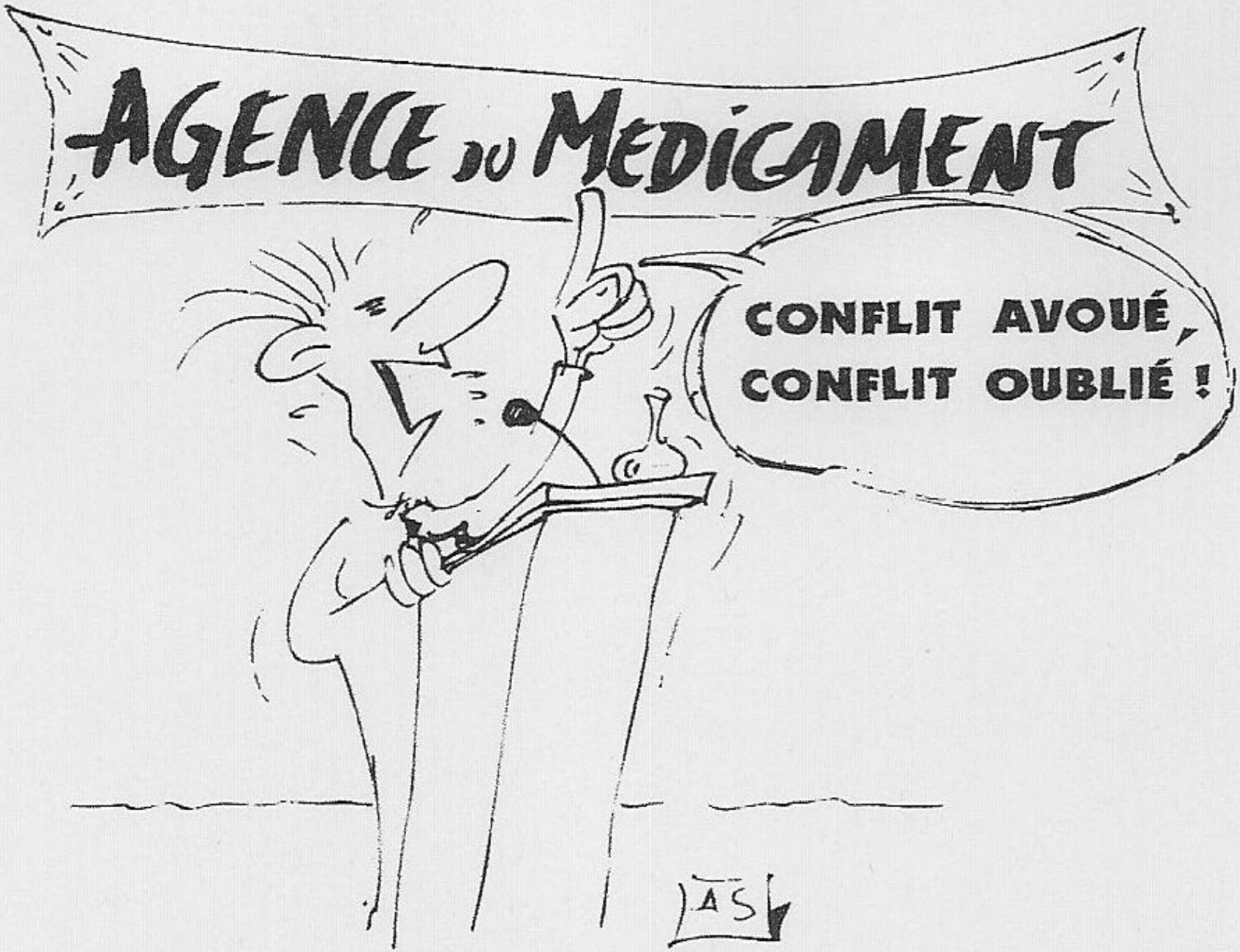
Dr. Angus has consulted for or received speaking fees from AstraZeneca, Brahms Diagnostica, Eisai, Eli Lilly, GlaxoSmithKline, OrthoBiotech, Takeda, and Wyeth-Ayerst. He has also received grant support from GlaxoSmithKline, OrthoBiotech, and Amgen.

Dr. Brun-Buisson has not disclosed any potential conflicts of interest.

Dr. Beale has received honoraria from Eisai and speaking fees (paid to university) from Lilly UK, Philips, Lidco, and Chiron.

ICM 2008
Sepsis Campaign

Dr. Vincent has consulted for AstraZeneca, Biosite, bioMerieux, Edwards Lifesciences, Eli Lilly Eisai, Ferring, GlaxoSmithKline, Intercell, Merck, Novartis, NovoNordisk, Organon, Pfizer, Phillips Medical Systems, Roche Diagnostics, Spectral Diagnostics, Takeda, and WyethLederle. He has also received honoraria from Eli Lilly, Edwards Lifesciences, Eisai, GlaxoSmithKline, Novartis, NovoNordisk, and Pfizer.


AGENCE DU MEDICAMENT
CONFLIT AVOUÉ,
CONFLIT OUBLIÉ !
AS

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: A multicenter prospective study (the FIBROSTIC study)

Francoise Degos[1,*], Paul Perez[2], Bruno Roche[3], Amel Mahmoudi[4], Julien Asselineau[2], Hélène Voitot[5], Pierre Bedossa[6], for the FIBROSTIC study group[†]

[1]*APHP, Hôpital Beaujon, Hepatology Dept., INSERM U 773, Clichy, France;* [2]*CHU de Bordeaux, Clinical Epidemiology Unit & CIC-EC7, Bordeaux, France;* [3]*APHP, CHB, Hôpital Paul Brousse, INSERM Paris Sud U 785, Villejuif, France;* [4]*APHP, Hôpital Jean Verdier, Bondy, France;* [5]*APHP, Hôpital Beaujon, Biochemistry Dept., Clichy, France;* [6]*APHP, Hôpital Beaujon, Pathology Dept., INSERM U 773, Clichy, France*

Background & Aims: The diagnostic accuracy of non-invasive liver fibrosis tests that may replace liver biopsy in patients with chronic hepatitis remains controversial.

We assessed and compared the accuracy of FibroScan® and that of the main biomarkers used for predicting cirrhosis and significant fibrosis (METAVIR ⩾ F2) in patients with chronic viral hepatitis.

Methods: A multicenter prospective cross-sectional diagnostic accuracy study was conducted in the Hepatology departments of 23 French university hospitals. Index tests and reference standard (METAVIR fibrosis score on liver biopsy) were measured on the same day and interpreted blindly. Consecutive patients with chronic viral hepatitis (hepatitis B or C virus, including possible Human Immunodeficiency Virus co-infection) requiring liver biopsy were recruited in the study.

Results: The analysis was first conducted on the total population (1839 patients), and after excluding 532 protocol deviations, on 1307 patients (non-compliant FibroScan® examinations). The overall accuracy of FibroScan® was high (AUROC 0.89 and 0.90, respectively) and significantly higher than that of biomarkers in predicting cirrhosis (AUROC 0.77–0.86). All non-invasive methods had a moderate accuracy in predicting significant fibrosis (AUROC 0.72–0.78). Based on multilevel likelihood ratios, non-

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Introduction

Diagnosis and treatment of patients with chronic hepatitis mostly rely on the staging of liver fibrosis. Antiviral therapy is proposed if moderate to severe (METAVIR stages F2 and F3) [1] fibrosis is present. If cirrhosis is present, specific surveillance is initiated, in particular for the early detection of hepatocellular carcinoma. Despite its limitations, liver biopsy is the usual procedure for staging fibrosis and is recommended by the international guidelines [2,3].

Non-invasive procedures such as transient elastography (FibroScan®, Echosens, Paris, France) and serum biomarkers (particularly Fibrometre®, Fibrotest®, Hepascore and APRI) have been developed in order to avoid biopsy. Transient elastography is a new imaging technique measuring liver stiffness, i.e. its elasticity. As highlighted by recent meta-analyses [4], its diagnostic accuracy is difficult to judge because of the small sample sizes of most published studies and because of the inter-study variability of accuracy estimates and elasticity thresholds, varying in the liter-

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

FibroStic: A large confirmatory study for non-invasive biomarkers accuracy, if correctly interpreted

To the Editor:

The article by Degos *et al.* assessing the diagnostic accuracy of Fibroscan compared to liver fibrosis biomarkers in chronic viral hepatitis is an interesting multicenter study, but several major flaws rendered the conclusions hazardous [1].

First, the design induced a high risk of selection bias. During the study inclusion period, biomarkers were already being widely used in France with an obvious selection of patients, i.e. all the patients included from our center had biopsy because of a significant discordance between FibroTest and elastography [2]. This was too late to be representative of näive patients without a selection bias. The authors compared patients with and without prior non-invasive marker use, but this was not the point. They should have identified patients who had discordance between tests or inapplicable tests leading to the indication of biopsy, in the different tertiary centers, in order to prevent the selection bias.

Second, the conclusion that "the diagnostic accuracy of non-invasive tests was high for cirrhosis but poor for significant fibrosis" is a caricature of a spectrum effect. An accuracy defined by AUROC of 0.90 for cirrhosis is mathematically equivalent to an AUROC of 0.78 for significant fibrosis [3,4]. The authors should

phy as first-line estimates of fibrosis in patients with chronic hepatitis C in December 2006 and their use by French hepatologists [2].

Disclosures

M. Munteanu is full time employee of Biopredictive, the company marketing FibroTest. T. Poynard is the inventor of FibroTest and has a capital interest in Biopredictive. The patent belongs to the public organization Assistance Publique Hôpitaux de Paris.

References

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