Nagłe zaostrzenie idiopatycznego włóknienia płuc - postępowanie

dr hab. med. Wojciech Piotrowski, prof. nadzw. UMED w Łodzi
Klinika Pneumonologii i Alergologii

Gorące Tematy Pneumonologii
Warszawa 2-3 luty 2017

Plan wykładu

* Definicja
* Epidemiologia
* Czynniki ryzyka
* Etiologia i patogeneza
* Postępowanie

Acute Exacerbation of Idiopathic Pulmonary Fibrosis

An International Working Group Report

Harold R. Collard[1], Christopher J. Ryerson[2], Tamera J. Corte[3], Gisli Jenkins[4], Yasuhiro Kondoh[5], David J. Lederer[6], Joyce S. Lee[7], Toby M. Maher[8,9], Athol U. Wells[9], Katerina M. Antoniou[10], Juergen Behr[11], Kevin K. Brown[12], Vincent Cottin[13], Kevin R. Flaherty[14], Junya Fukuoka[15], David M. Hansell[16], Takeshi Johkoh[17], Naftali Kaminski[18], Dong Soon Kim[19], Martin Kolb[20], David A. Lynch[21], Jeffrey L. Myers[22], Ganesh Raghu[23], Luca Richeldi[24], Hiroyuki Taniguchi[5], and Fernando J. Martinez[25]

[1]Department of Medicine, University of California San Francisco, San Francisco, California; [2]Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [3]Department of Respiratory Medicine, Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia; [4]Division of Respiratory Medicine, Nottingham University Hospitals, Nottingham, United Kingdom; [5]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi, Japan; [6]Department of Medicine, Columbia University, New York, New York; [7]Department of Medicine, University of Colorado Denver, Aurora, Colorado; [8]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [9]Interstitial Lung Disease Unit and [16]Department of Radiology, Royal Brompton Hospital, London, United Kingdom; [10]Department of Respiratory Medicine, Faculty of Medicine, University of Crete, Heraklion, Greece; [11]Department of Internal Medicine V, Ludwig Maximilians University, Munich, and Asklepios Clinics, Gauting, Comprehensive Pneumology Center Munich, Member of the German Center for Lung Research, Germany; [12]Department of Medicine and [21]Department of Radiology, National Jewish Health, Denver, Colorado; [13]Department of Medicine, Louis Pradel Hospital, Hospices Civils de Lyon, Claude Bernard University Lyon 1, University of Lyon, Lyon, France; [14]Department of Medicine and [22]Department of Pathology, University of Michigan, Ann Arbor, Michigan; [15]Department of Pathology, Nagasaki University, Nagasaki, Japan; [17]Department of Radiology, Kinki Central Hospital, Itami, Japan; [18]Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Yale School of Medicine, New Haven, Connecticut; [19]Department of Medicine, University of Ulsan, Seoul, South Korea; [20]Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [23]Department of Medicine, University of Washington, Seattle, Washington; [24]Academic Unit of Clinical and Experimental Sciences, University of Southampton and National Institute for Health Research Southampton Respiratory Biomedical Unit, Southampton, United Kingdom; and [25]Department of Medicine, Weill Cornell University, New York, New York

Am J Respir Crit Care Med 2016; 194 (3)

Definicja 2016

* Ostre, klinicznie istotne pogorszenie oddychania charakteryzujące się obecnością nowych rozległych zmian w pęcherzykach płucnych

Nagłe zaostrzenie IPF – kryteria 2016

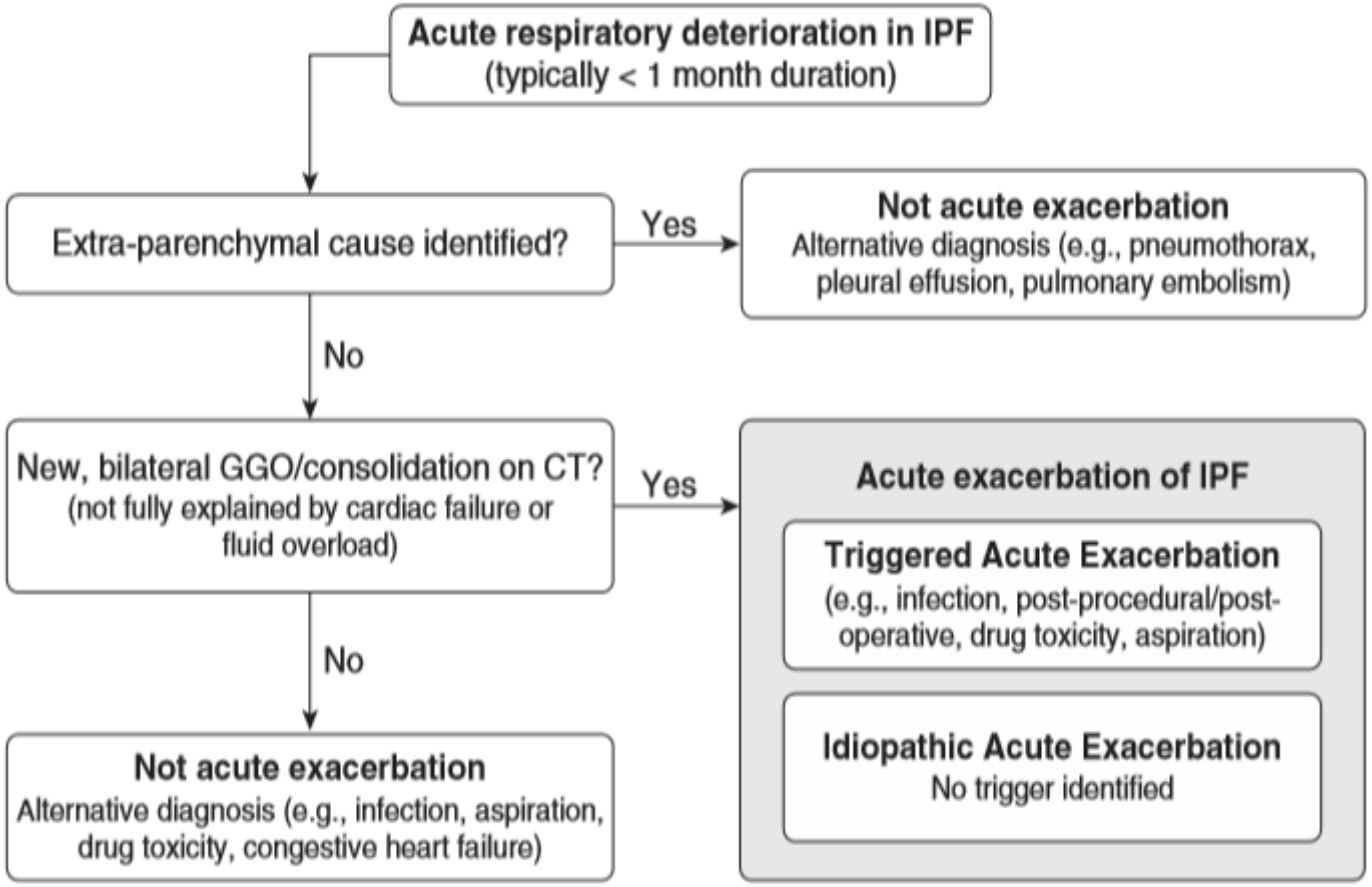
* Wcześniejsze lub nowe rozpoznanie IPF
* Niewyjaśniona duszność (nasilenie lub de novo) – typowo w okresie 1 miesiąca
* Obszary mlecznej szyby nakładające się na wzorzec UIP
* Pogorszenie, którego nie wyjaśnia niewydolność krążenia lub przewodnienie

Collard HR AJRCCM 2016

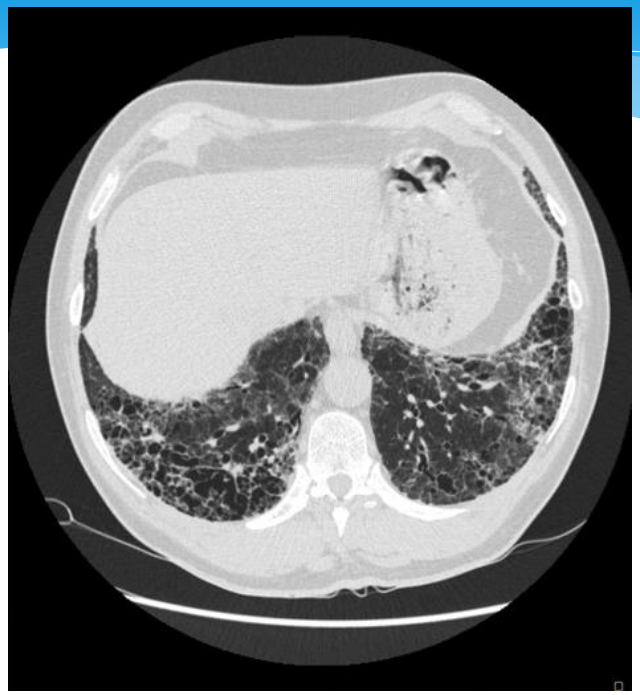
Acute Exacerbation of Idiopathic Pulmonary Fibrosis

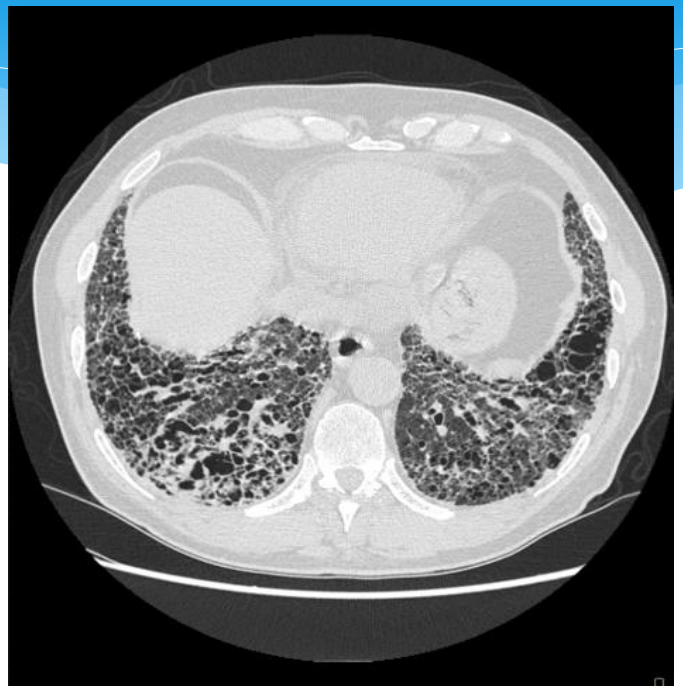
An International Working Group Report

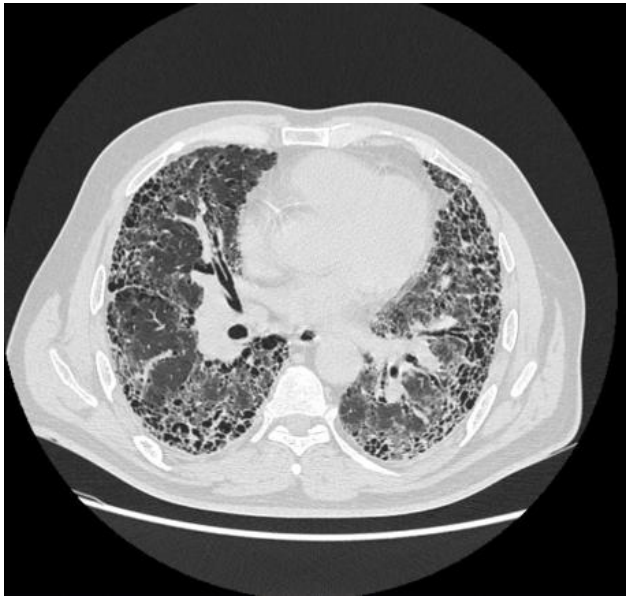
Harold R. Collard[1], Christopher J. Ryerson[2], Tamera J. Corte[3], Gisli Jenkins[4], Yasuhiro Kondoh[5], David J. Lederer[6], Joyce S. Lee[7], Toby M. Maher[8,9], Athol U. Wells[9], Katerina M. Antoniou[10], Juergen Behr[11], Kevin K. Brown[12], Vincent Cottin[13], Kevin R. Flaherty[14], Junya Fukuoka[15], David M. Hansell[16], Takeshi Johkoh[17], Naftali Kaminski[18], Dong Soon Kim[19], Martin Kolb[20], David A. Lynch[21], Jeffrey L. Myers[22], Ganesh Raghu[23], Luca Richeldi[24], Hiroyuki Taniguchi[5], and Fernando J. Martinez[25]

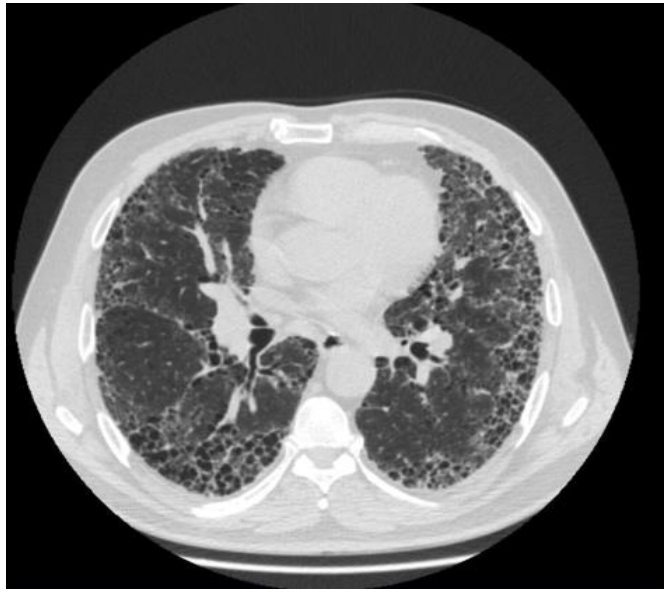


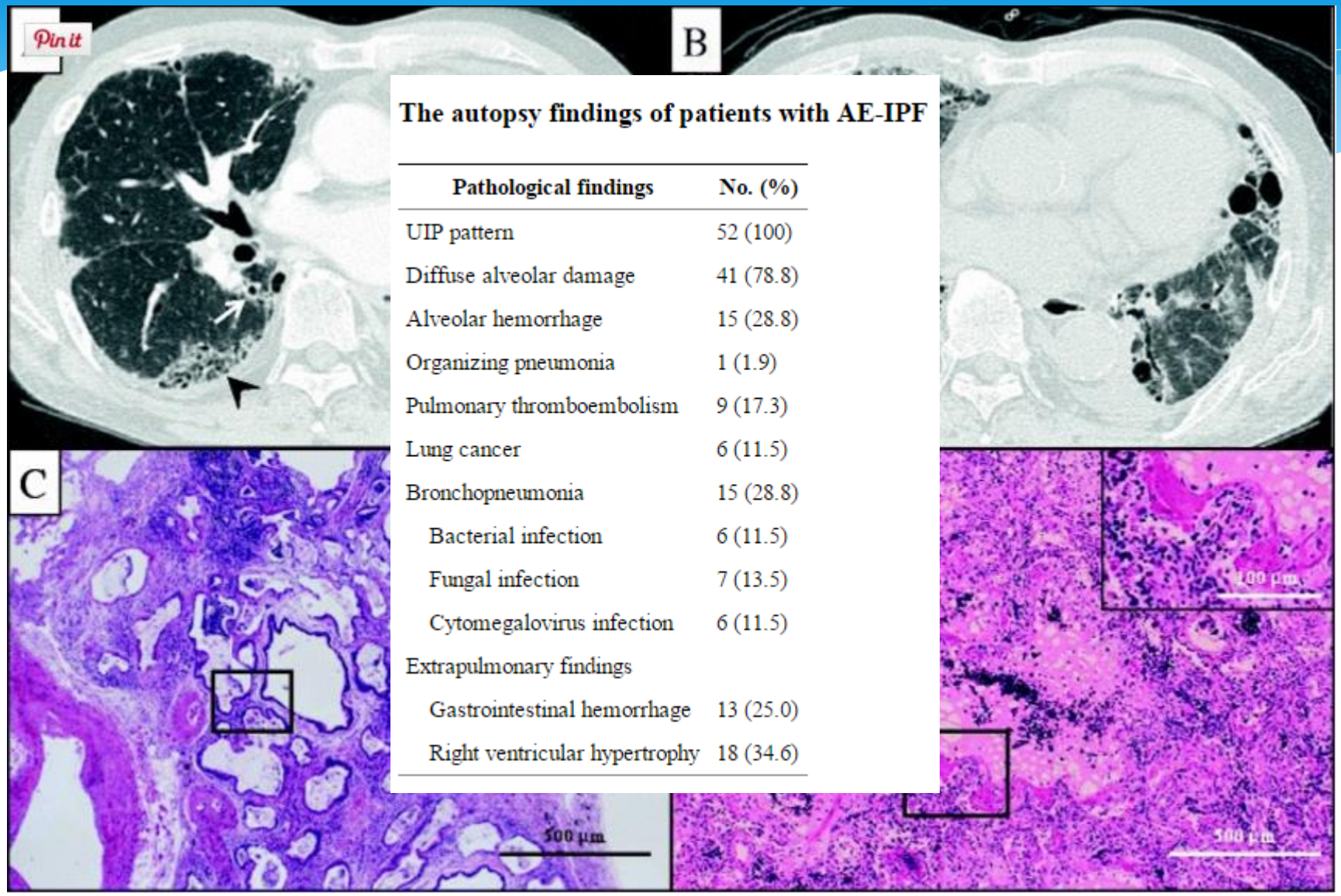
AJRCCM August 2016









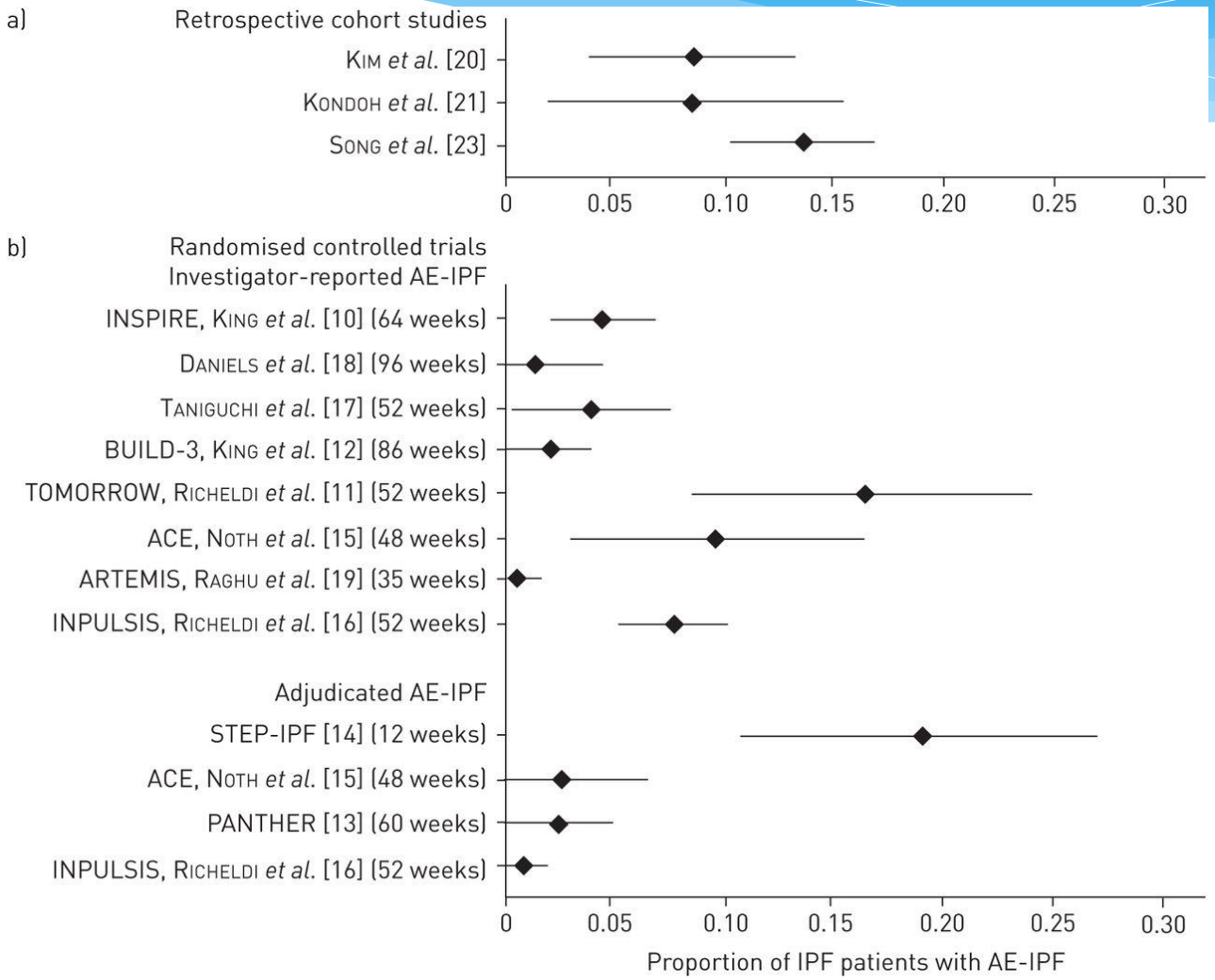


The autopsy findings of patients with AE-IPF

Pathological findings	No. (%)
UIP pattern	52 (100)
Diffuse alveolar damage	41 (78.8)
Alveolar hemorrhage	15 (28.8)
Organizing pneumonia	1 (1.9)
Pulmonary thromboembolism	9 (17.3)
Lung cancer	6 (11.5)
Bronchopneumonia	15 (28.8)
Bacterial infection	6 (11.5)
Fungal infection	7 (13.5)
Cytomegalovirus infection	6 (11.5)
Extrapulmonary findings	
Gastrointestinal hemorrhage	13 (25.0)
Right ventricular hypertrophy	18 (34.6)

Oda K et al. Autopsy analyses in acute exacerbation of idiopathic pulmonary fibrosis. Respir Res 2014; 15: 109

Annual incidence of acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) from a) cohort studies and b) placebo groups of randomised controlled trials.



Christopher J. Ryerson et al. Eur Respir J 2015;46:512-520

Czynniki ryzyka (1)

* Niskie FVC
* Niskie DLCO
* Krótki dystans w teście chodu
* Nadciśnienie płucne
* Hipoksemia
* Silna duszność
* Spadek FVC w krótkim czasie

Czynniki ryzyka (2)

* Młodszy wiek
* Współchorobowości (choroba niedokrwienna)
* Wysoka wartość BMI
* Rozedma ?
* Osoby niepalące ?

AE-IPF - rokowanie

* Najczęstsza przyczyna zgonu chorych na IPF (40-46%)
* Śmiertelność – 60% (1 m-c), 67% (3 m-ce), 90% (6 m-cy)
* Mediana przeżycia – 2-4 m-ce
* 50% chorych z AE-IPF przyjmowanych do OIOM
* 80-90% chorych przyjmowanych do OIOM z powodu AE-IPF umiera

Potencjalne czynniki spustowe

* Wirusy
* Zanieczyszczenia powietrza
* Mikroaspiracje
* Zabiegi chirurgiczne (biopsja płuca, resekcja guza)
* Inne zabiegi chirurgiczne
* Intubacja i wentylacja mechaniczna
* BAL
* Leki

RESPIRATORY INVESTIGATION 52 (2014) 65–70

Contents lists available at ScienceDirect

Respiratory Investigation

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

ELSEVIER

Original article

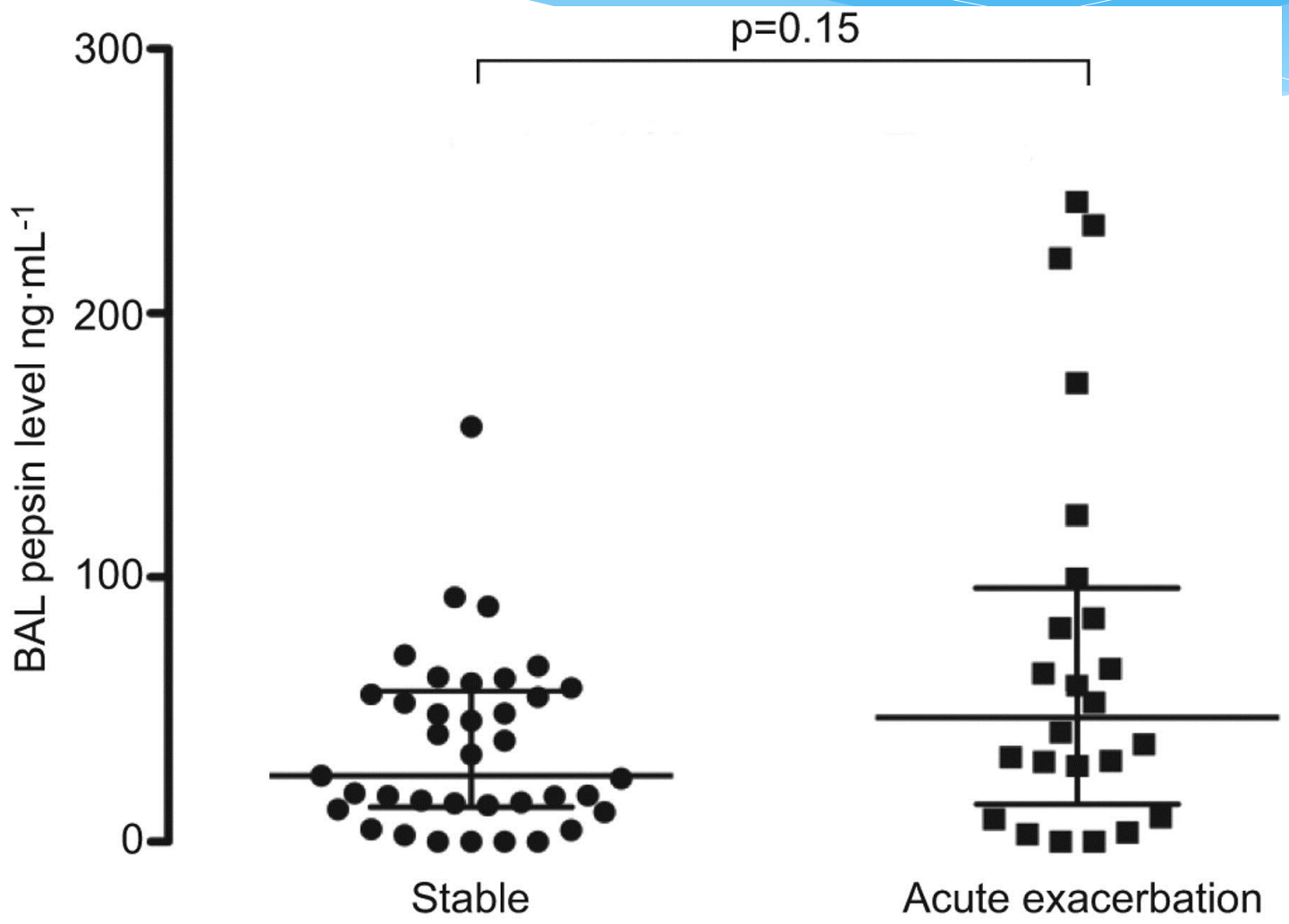
Viral infections in patients with an acute exacerbation of idiopathic interstitial pneumonia

Atsuhito Ushiki[a,*], Yoshitaka Yamazaki[b], Mineyuki Hama[a], Masanori Yasuo[c], Masayuki Hanaoka[a], Keishi Kubo[a]

hRSV A	hRSV B	hPIV 1	hPIV 2	hPIV 3	hMPV	flu A	flu B	Adeno	Boca	Rhino	CMV
0/14	0/14	0/14	0/14	0/14	0/14	0/14	0/14	0/14	0/14	0/14	2/14

CONCLUSION: viral infections do not seem to cause AE-IPF

Bronchoalveolar lavage (BAL) pepsin levels in patients with stable idiopathic pulmonary fibrosis (IPF) compared with acute exacerbation of IPF. Horizontal lines represent median, 25th percentile and 75th percentile.



J.S. Lee et al. Eur Respir J 2012;39:352-358

Biopsja chirurgiczna a zaostrzenie IPF

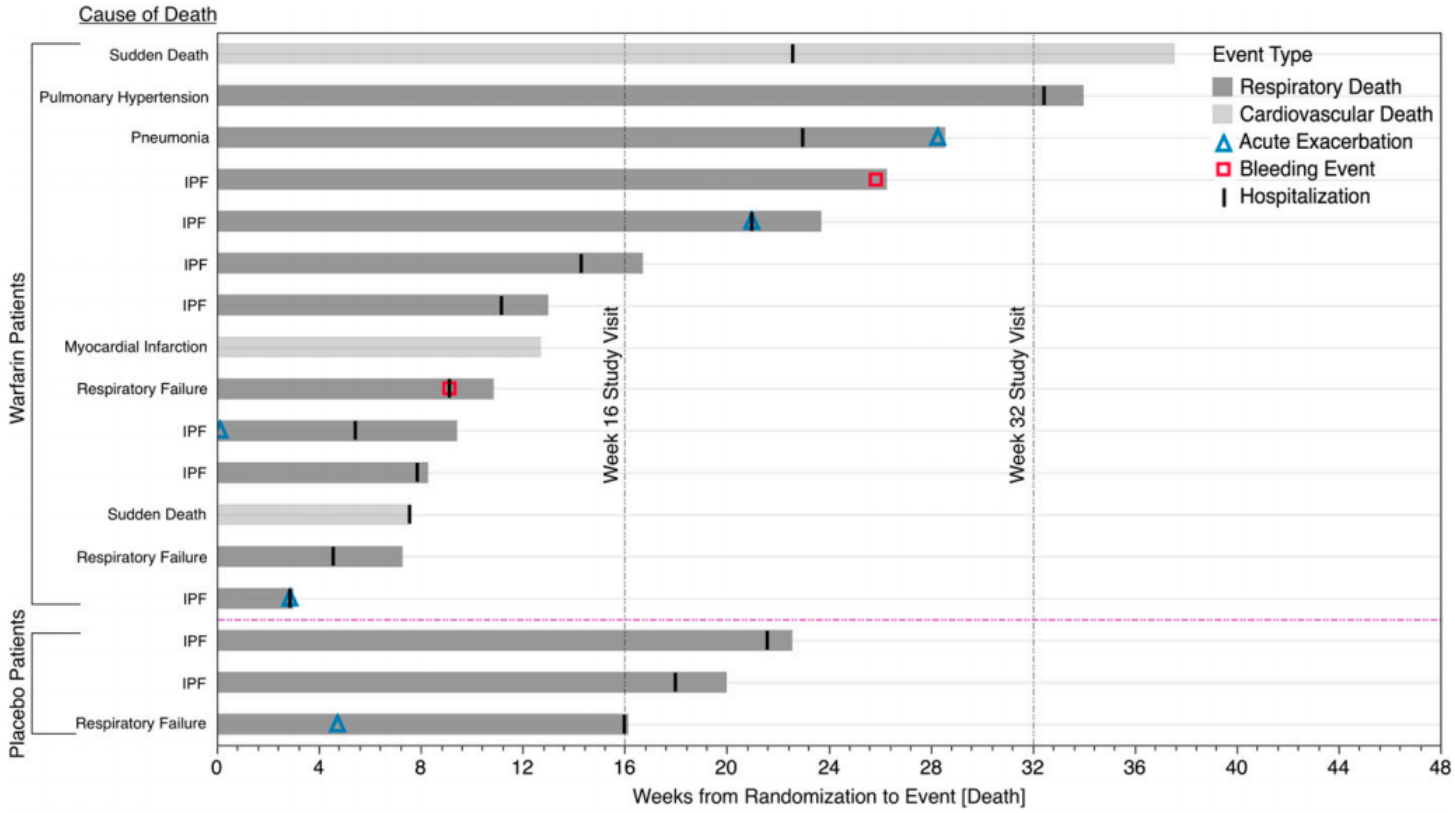
* 161 biopsji (diagnostyka ILD)
* UIP/IPF – 24,2%
* Powikłania u 19 chorych (11,8%)
* 30-dniowa śmiertelność pooperacyjna – 3,1%
* Główna przyczyna zgonu – zaostrzenie niewydolność oddechowej
* UIP/IPF –OR 5,67; 95%CI 1,27-25,25

Rotolo et al. Sarcoidosis Vasc Diffuse Lung Dis 2015

A Placebo-Controlled Randomized Trial of Warfarin in Idiopathic Pulmonary Fibrosis

Imre Noth[1], Kevin J. Anstrom[2], Sara Bristol Calvert[2], Joao de Andrade[3], Kevin R. Flaherty[4], Craig Glazer[5], Robert J. Kaner[6], and Mitchell A. Olman[7]; for the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet)*

[1]University of Chicago, Chicago, Illinois; [2]Duke Clinical Research Institute, Durham, North Carolina; [3]University of Alabama, Birmingham, Alabama; [4]National Jewish Medical Center, Denver, Colorado; [5]University of Texas Southwestern, Dallas, Texas; [6]Weill Cornell Medical College, New York, New York; and [7]Cleveland Clinic, Cleveland, Ohio



AJRCCM 2012

Published in final edited form as:
N Engl J Med. 2012 May 24; 366(21): 1968–1977. doi:10.1056/NEJMoa1113354.

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

End Point	Combination Therapy (N = 77)	Placebo (N = 78)	Hazard Ratio	P Value
Death — no. (%)				
From any cause	8 (10)	1 (1)		0.01
From respiratory causes	7 (9)	1 (1)		0.02
Hospitalization for any cause — no. (%)	23 (30)	7 (9)		<0.001
Acute exacerbation — no. (%)	5 (6)	0		0.03
Serious adverse event — no. (%)	24 (31)	8 (10)		0.001
Based on Kaplan–Meier estimate at 60 wk — % (95% CI)				
Death from any cause	19.8 (9.9–37.2)	2.0 (0.3–13.6)	9.26 (1.16–74.1)	0.01
Death from any cause or hospitalization	43.6 (30.7–59.0)	16.9 (8.7–31.5)	3.74 (1.68–8.34)	<0.001
Death from any cause or ≥10% decline in FVC	36.3 (23.7–53.0)	32.4 (19.7–50.3)	1.46 (0.70–3.05)	0.30

Raghu G et al..

Profilaktyka i leczenie

Double-blind, Placebo-controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Arata Azuma, Toshihiro Nukiwa, Eiyasu Tsuboi, Moritaka Suga, Shosaku Abe, Koichiro Nakata, Yoshio Taguchi, Sonoko Nagai, Harumi Itoh, Motoharu Ohi, Atsuhiko Sato, and Shoji Kudoh for the members of the Research Group for Diffuse Lung Diseases in Japan; and Ganesh Raghu

Fourth Department of Internal Medicine, Nippon Medical School; Division of Respiratory Disease, Toranomon Hospital, Tokyo; Department of Respiratory Oncology and Molecular Medicine Division of Cancer Control Institute of Development, Aging, and Cancer, Tohoku University, Sendai; Department of Respiratory Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto; Third Department of Internal Medicine and Department of Biochemistry, Sapporo Medical University School of Medicine, Sapporo; Department of Respiratory Medicine, Tenri Hospital, Tenri; Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University; Kyoto Preventive Medical Center, Kyoto; Department of Radiology, Fukui Medical School, Fukui; Sleep Medical Center, Osaka Kaisei Hospital, Osaka, Japan; and University of Washington Medical Center, Seattle, Washington

Am J Respir Crit Care Med. 2005

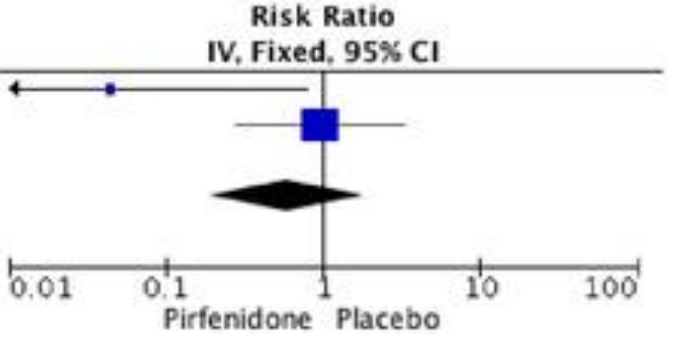
* Brak poprawy saturacji w 6MWT
* spadek FVC 130 vs 30 ml
* AE-IPF 9 vs 0

The influence of Pirfenidone treatment on AE-IPF

Study or Subgroup	Pirfenidone Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
SP2 2005	0	72	5	35	15.8%	0.04 [0.00, 0.79]
SP3 2010	6	163	4	104	84.2%	0.96 [0.28, 3.31]
Total (95% CI)		**235**		**139**	**100.0%**	**0.59 [0.19, 1.84]**
Total events	6		9			

Heterogeneity: $Chi^2 = 3.69$, df = 1 (P = 0.05); $I^2 = 73\%$

Test for overall effect: Z = 0.91 (P = 0.36)



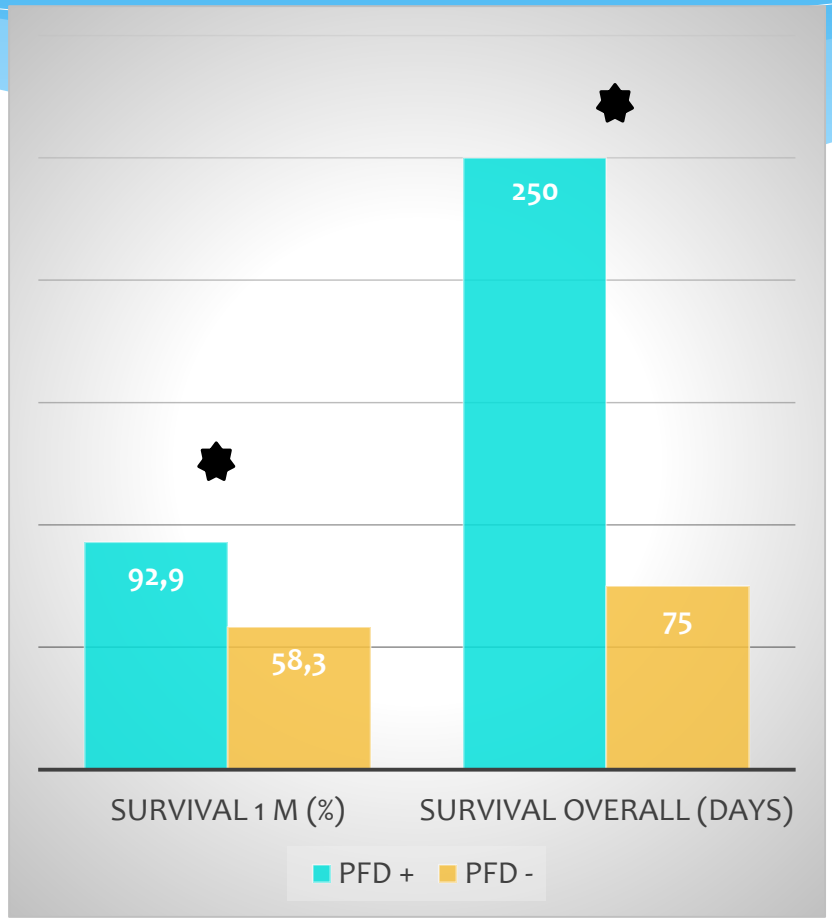
Aravena C, Labarca G, Venegas C, Arenas A, Rada G (2015) Pirfenidone for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. PLoS ONE 10(8): e0136160. doi:10.1371/journal.pone.0136160
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0136160

A2694 - Efficacy of Pirfenidone for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

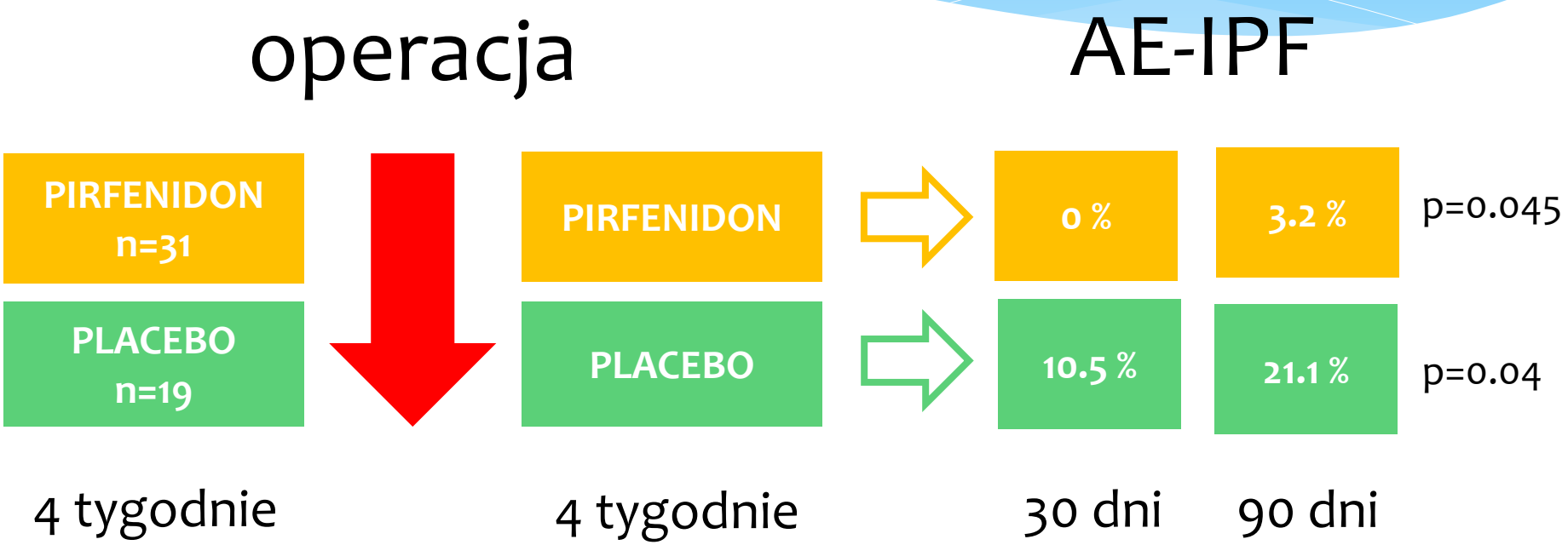
K. Furuya, Dr (Tokyoto, Japan) S. Sakamoto, Dr (Tokyoto) H. Shimizu, Dr (Tokyoto) M. Sekiya, Dr (Tokyoto) A. Kinoshita, Dr (Tokyoto) T. Isshiki, Dr (Tokyoto) K. Sugino, M.D, PhD (Tokyoto, Japan) S. Homma, MD, PhD (Tokyoto)

ATS 2016 SAN FRANCISCO

* 55 patients with AE-IPF
* 26 patients selected
* Standard treatment of AE-IPF
* 14 patients on pirfenidone 12 patients without

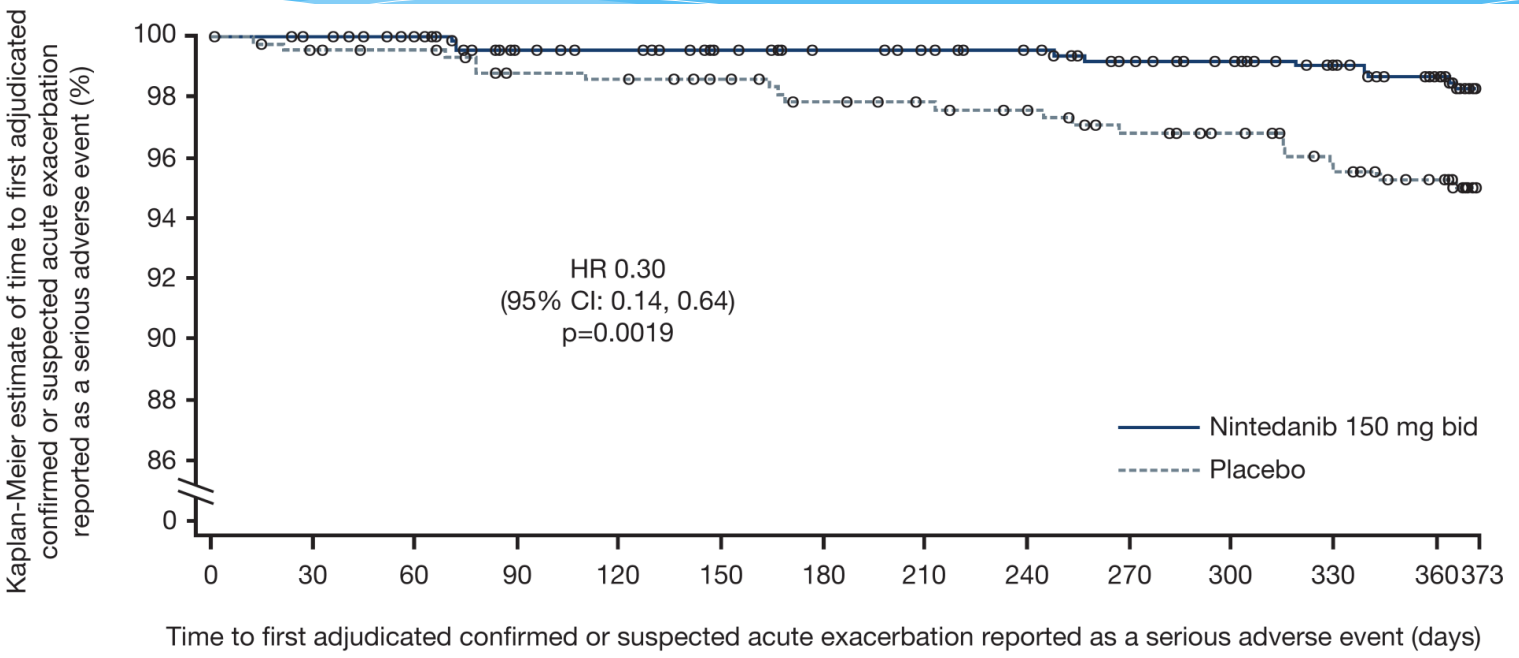


Effect of Perioperative Pirfenidone Treatment in Lung Cancer Patients With Idiopathic Pulmonary Fibrosis.



Iwata T i wsp. Ann Thorac Surg 2016

Time to first adjudicated confirmed or suspected acute exacerbation reported as a serious adverse event



No. at risk													
Nintedanib 150 mg bid	638	634	629	613	610	603	598	595	591	582	574	564	549504
Placebo	423	419	416	409	408	404	398	395	392	385	381	373	364 346

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with adjudicated confirmed or suspected acute exacerbations reported as serious adverse events, n (%)	10 (1.6)	21 (5.0)

Official Case Reports Journal of the Asian Pacific Society of Respirology

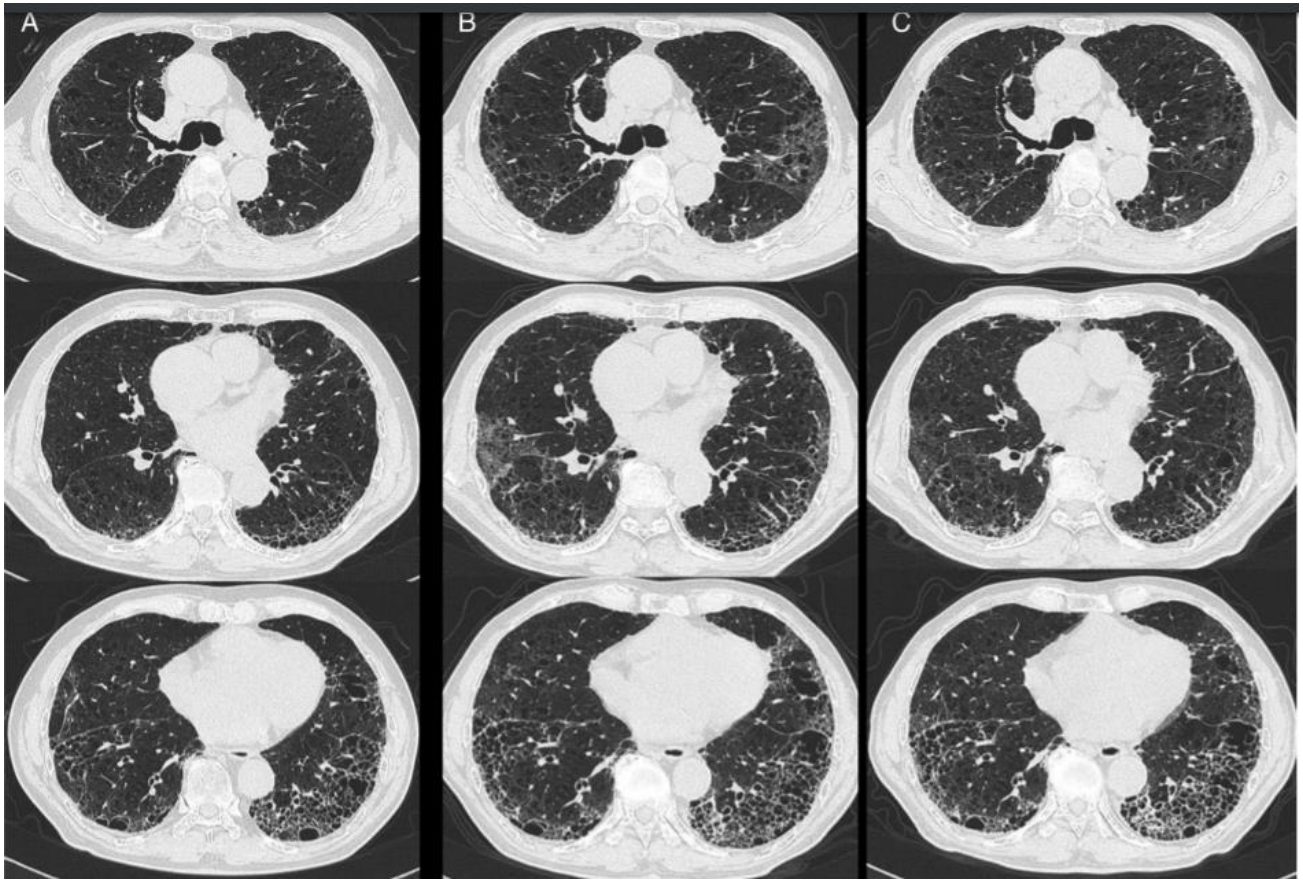
Respirology Case Reports

OPEN ACCESS

APSR

Treatment with nintedanib for acute exacerbation of idiopathic pulmonary fibrosis

Hiromi Tomioka & Hirohito Takada



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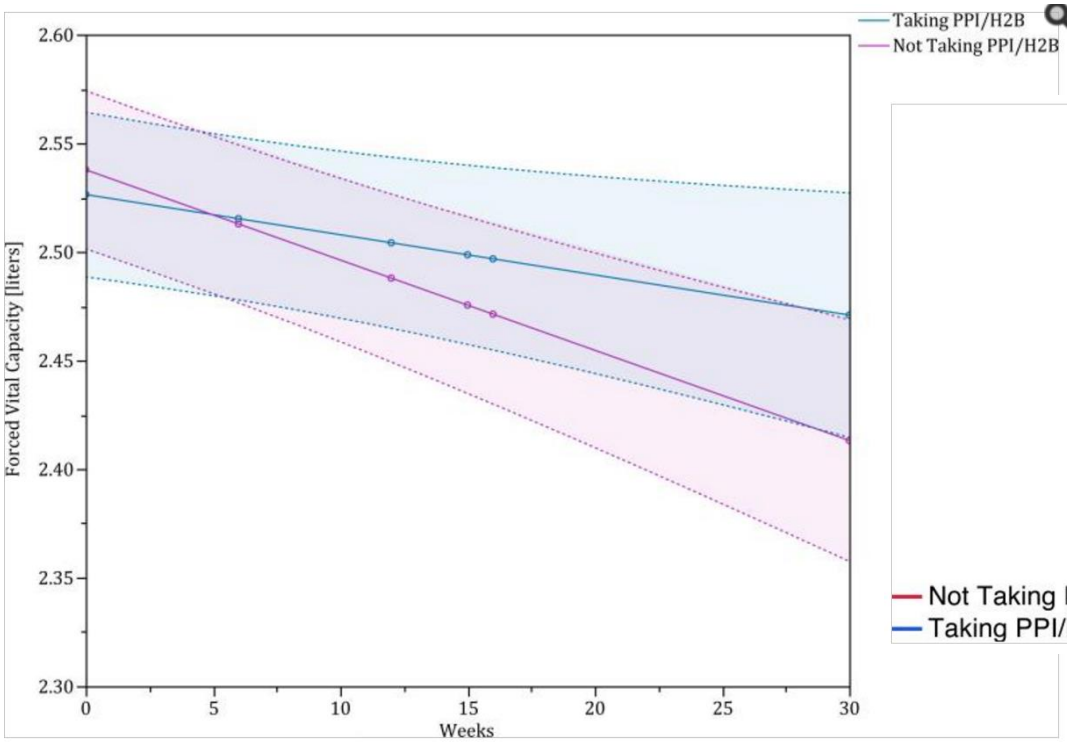
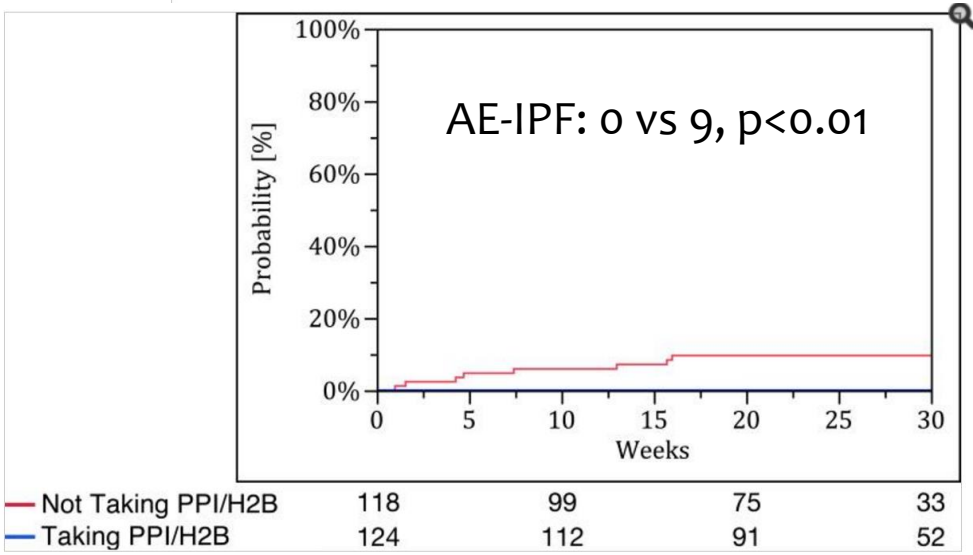
Lancet Respir Med. 2013 July ; 1(5): 369–376. doi:10.1016/S2213-2600(13)70105-X.

Anti-Acid Therapy and Disease Progression in Idiopathic Pulmonary Fibrosis: an analysis of data from three randomized controlled trials

Joyce S. Lee, MD[1], **Harold R. Collard, MD**[1], **Kevin J. Anstrom, PhD**[2], **Prof Fernando J. Martinez, MD**[3], **Prof Imre Noth, MD**[4], **Rhonda S. Roberts, MSPH**[2], **Eric Yow, MS**[2], **Prof Ganesh Raghu, MD**[5], and **the IPFnet Investigators**[6]

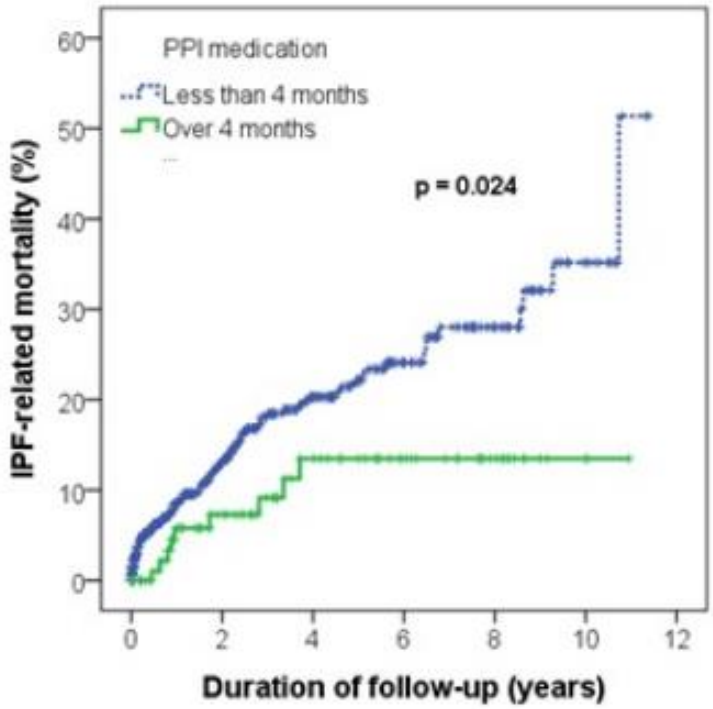




Title: Protective effect of proton pump inhibitor for survival in patients with gastroesophageal reflux disease and idiopathic pulmonary fibrosis

JNM Journal of Neurogastroenterology and Motility
2014 Impact Factor 2.296
JNM
pISSN : 2093-0879 eISSN : 2093-0887
Indexed/covered by Science Citation Index Expanded(SCIE), SCOPUS, EMBASE, EBSCO, PubMed, PubMed Central, KoreaMed, DOI/Crossref and Google Scholar.

Lee CM, et al



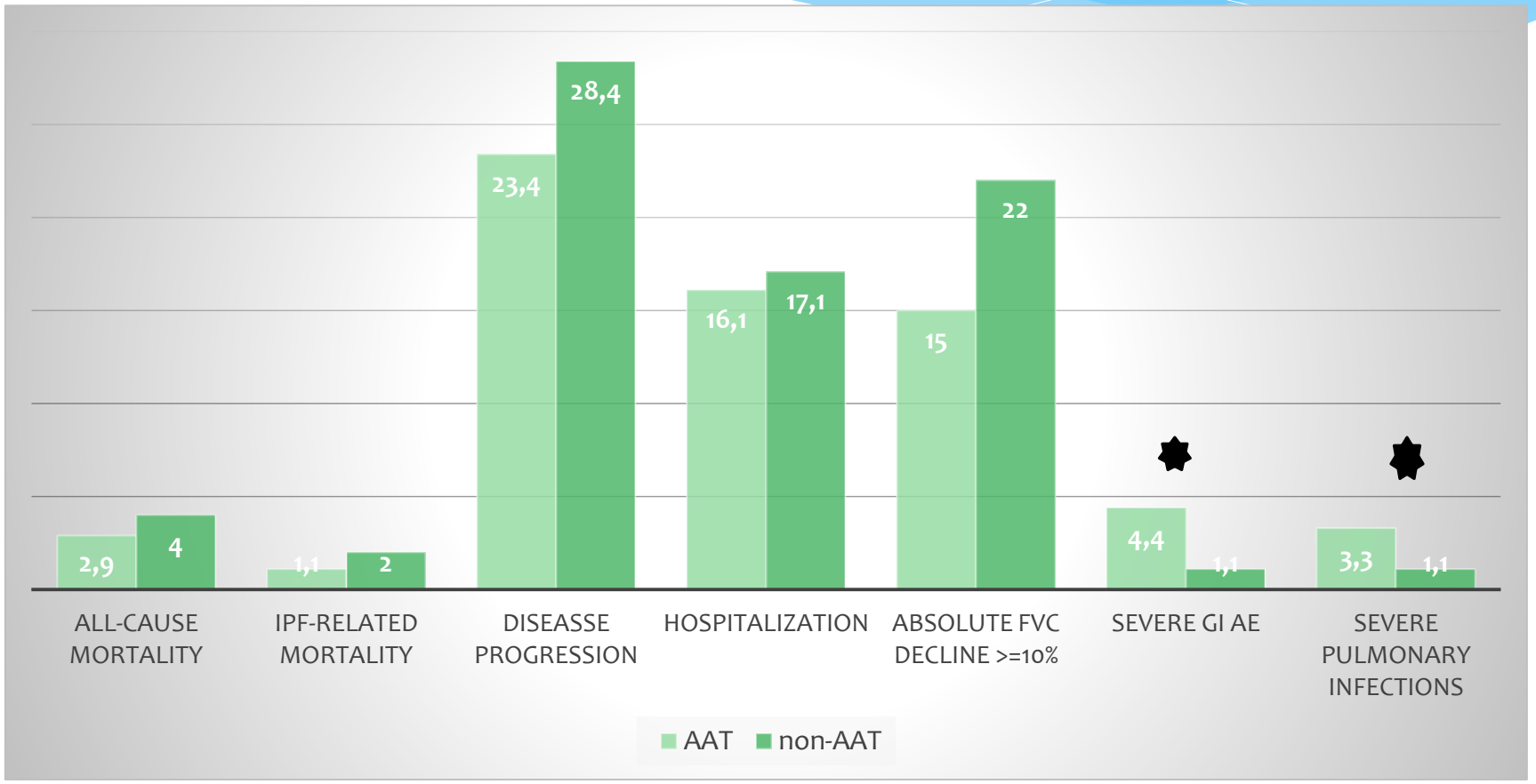
786 patients with IPF
107 with GERD (13.6%)
103 died due to IPF related causes

Chorzy na IPF którzy przyjmują IIP >4 miesiące – mniejsze ryzyko zgonu

A2689 - Antiacid Therapy and Disease Progression in Patients with Idiopathic Pulmonary Fibrosis (IPF) Under Pirfenidone Treatment

M. Kreuter, MD (Basel) P. Spagnolo, Assoc.Prof. (Basel, Switzerland) W. Wuyts, MD (Basel, Belgium) E. Renzoni, MD (Basel) D. Koschel, MD (Basel) T. M. Maher, MD (Basel) M. Kolb, MD, PhD (Basel) D. Weycker, PhD (Basel) K. Kirchgaessler, MD (Basel) U. Costabel, MD, PhD (Basel)

ATS 2016 SAN FRANCISCO



American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

- ***Question*:** Should patients with acute exacerbation of IPF be treated with corticosteroids?

  Although high-dose corticosteroids are commonly prescribed for the treatment of acute exacerbation of IPF (143, 144, 147–149, 152, 153, 155, 157, 300), there are no controlled trials on which to judge efficacy. Cyclosporin A and anticoagulation have also been used without conclusive results (152, 241, 301).

  Recommendation: The majority of patients with acute exacerbation of IPF should be treated with corticosteroids, but corticosteroids may not be reasonable in a minority (weak recommendation, very low-quality evidence).Values: This recommendation places a high value on anecdotal reports of benefit and the high mortality of acute exacerbation of IPF.

  Remarks: Specific recommendations regarding the dose, route, and duration of corticosteroid therapy cannot be made. Intravenous corticosteroids up to a gram per day have been reported in a few case series. There was consensus that supportive care is the mainstay of therapy for acute exacerbation of IPF. (Vote: 14 for use, 5 against use, 1 abstention, 11 absent.)

Praktyka

* sGKS pulses iv 500-1000 mg/day
* sGKS + Cyclofosfamid iv 500 mg/m^2 every 3 weeks

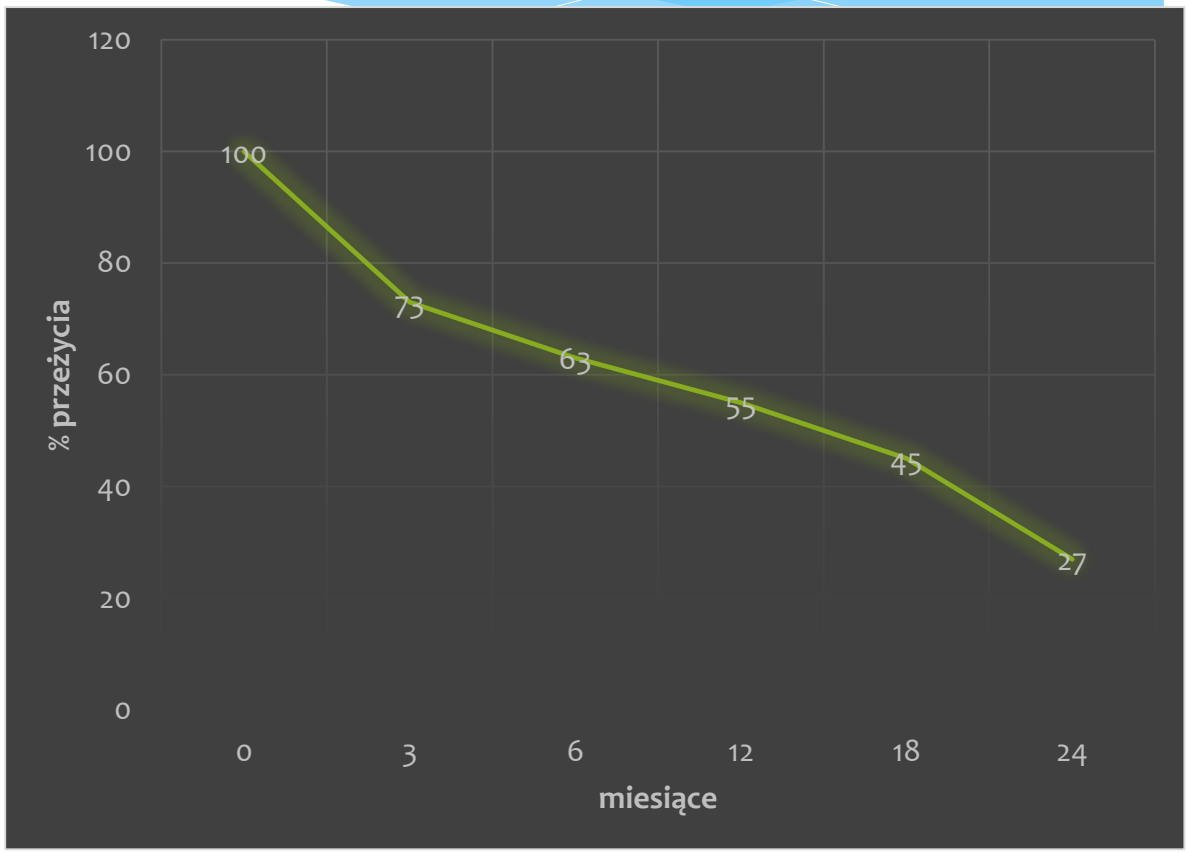
* sGKS + Cyclosporine A
* sKGS + Tacrolimus
* sGKS + Azathioprine

Corticosteroid and cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: a single center experience and literature review.

AE-IPF
n=11

Metylprednizolon 1000 mg 3x

CYC 1x w miesiącu maks. 6x



Novelli L i wsp. Sarcoidosis Vasc Diffuse Lung Dis 2016 [31]

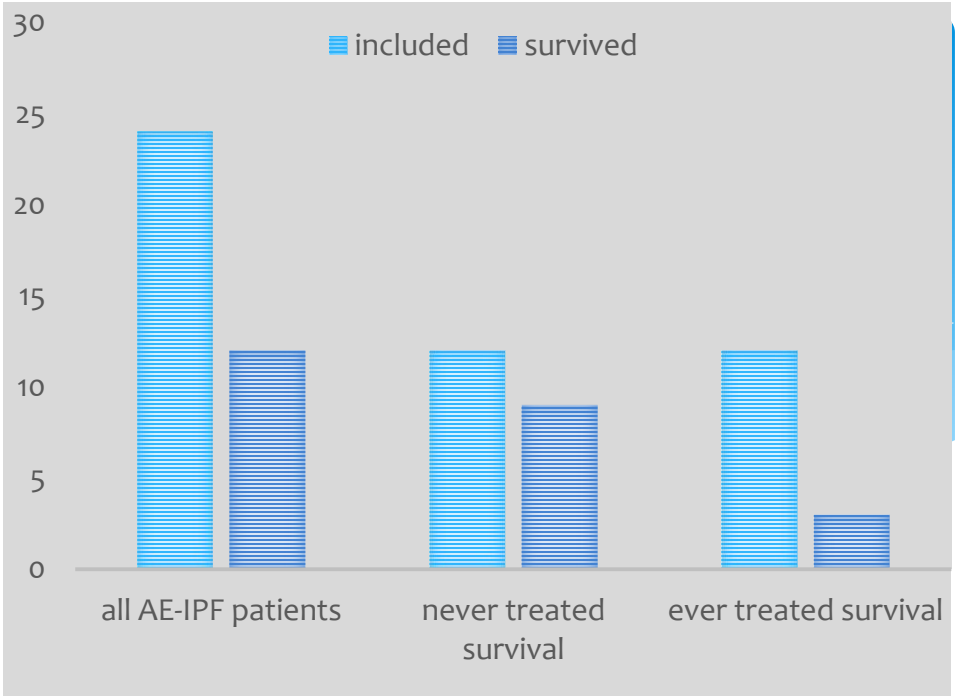
Papiris et al. BMC Pulmonary Medicine (2015) 15:162
DOI 10.1186/s12890-015-0146-4

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Survival in Idiopathic pulmonary fibrosis acute exacerbations: the non-steroid approach

Spyros A Papiris[1*†], Konstantinos Kagouridis[1†], Likurgos Kolilekas[2], Andriana I Papaioannou[1], Aneza Roussou[1], Christina Triantafillidou[3], Katerina Baou[4], Katerina Malagari[5], Stylianos Argentos[1], Anastasia Kotanidou[6], Anna Karakatsani[1] and Effrosyni D Manali[1]



- **Immediate cessation of IS**
- **Best supportive care**
- **Broad spectrum antimicrobials**
- **Recognize and treat reversible causes**

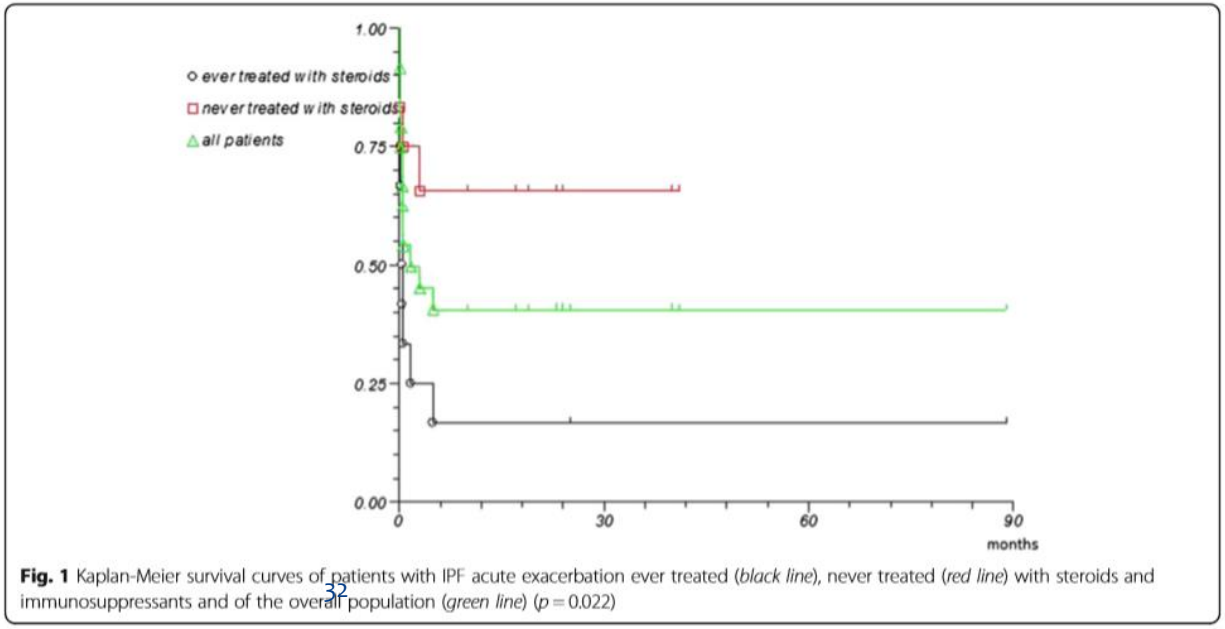


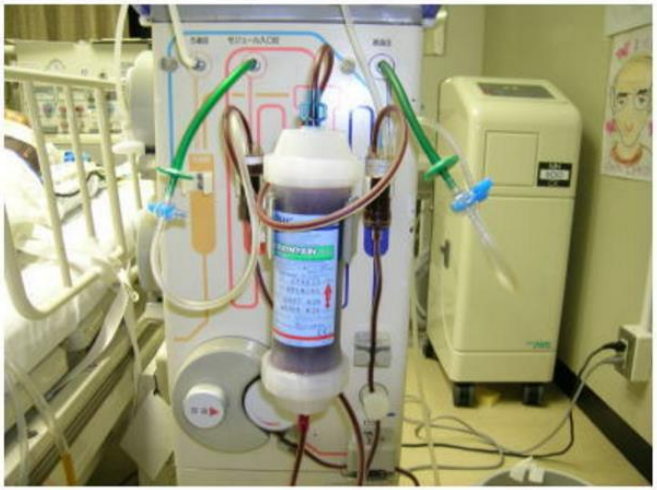
Fig. 1 Kaplan-Meier survival curves of patients with IPF acute exacerbation ever treated (*black line*), never treated (*red line*) with steroids and immunosuppressants and of the overall population (*green line*) ($p = 0.022$)

Nowe metody

* Recombinant human thrombomodulin (rhTM)
  * Modifies coagulation cascade by binding to thrombin and activation of protein C
  * Improves survival (Kataoka 2015, Isshiki 2015, Abe 2015)

* Direct hemoperfusion with polymyxin B-immobilized fiber column
  * Improves survival (Takada 2015, Enomoto 2015)

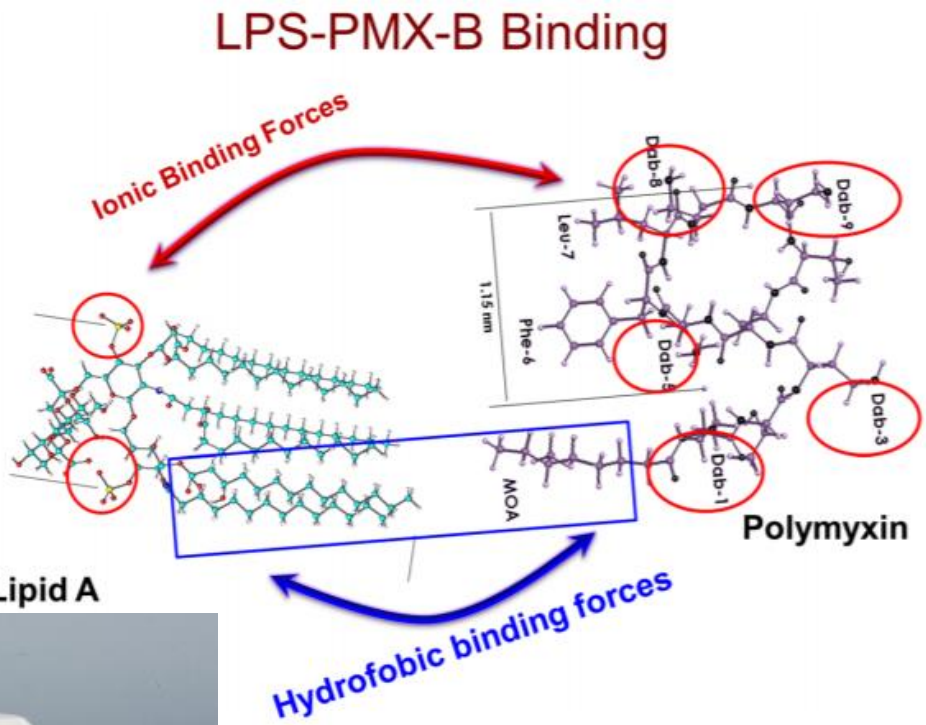
Direct hemoperfusion with polymyxin B-immobilized fiber column



エンドトキシン吸着療法

(PMX-Direct Hemo Perfusion : PMX－DHP)

エンドトキシン活性の主役であるリピドAと抗生物質であるポリミキシンBが結合することで、エンドトキシン活性を中和するエンドトキシン吸着カラム（トレミキシン）を用いて、エンドトキシンの吸着を行う治療法



Ronco & Klein 2014

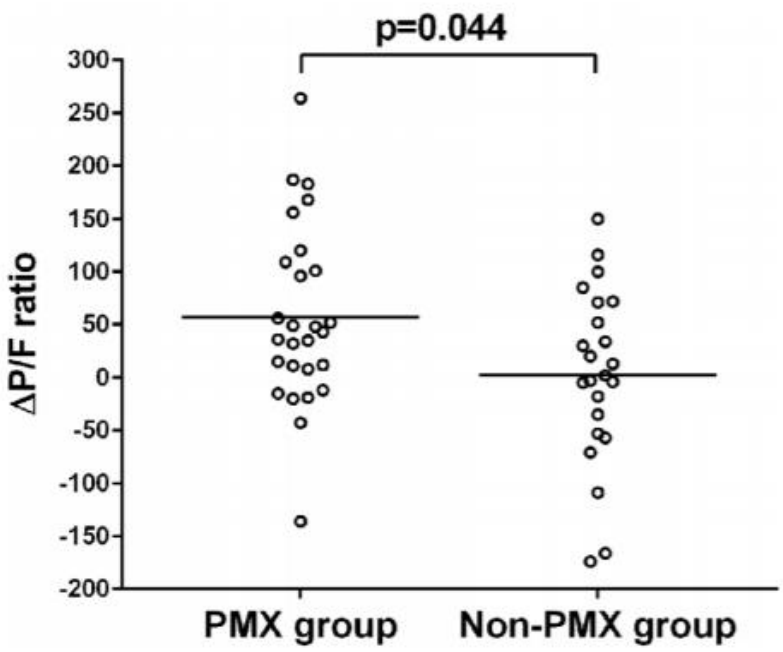
http://www.tangohp.com/about/section/dialysis2.html

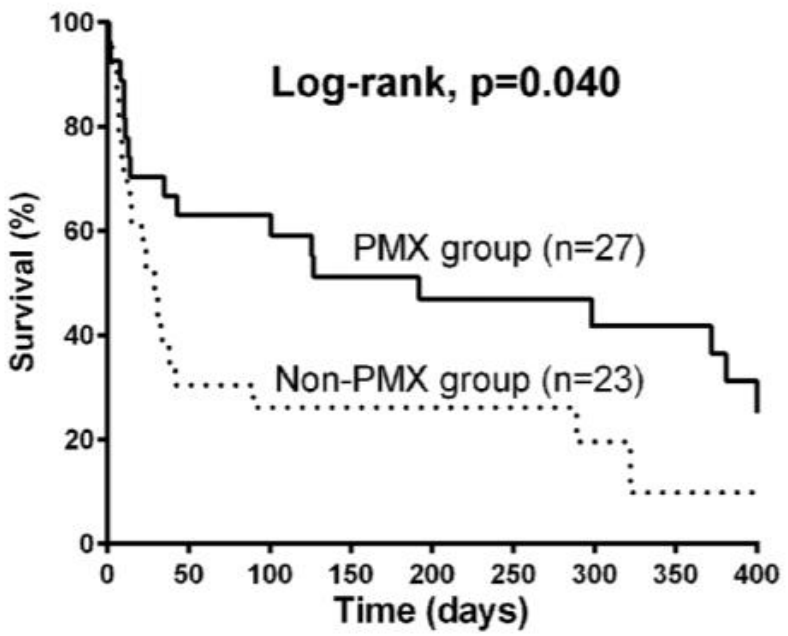
INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

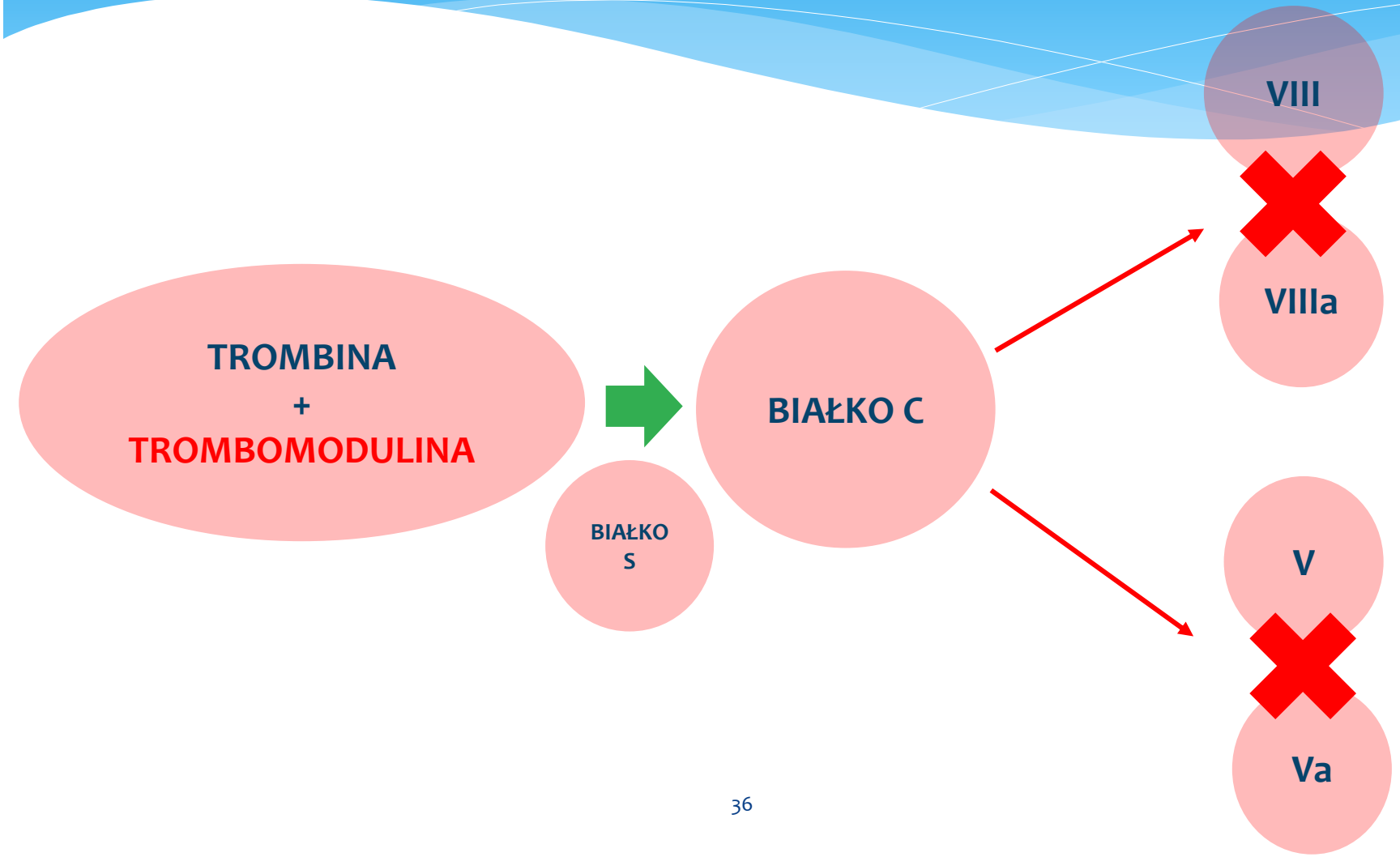
Survival from an Acute Exacerbation of Idiopathic Pulmonary Fibrosis with or without Direct Hemoperfusion with a Polymyxin B-immobilized Fiber Column: A Retrospective Analysis

Keiji Oishi[1,2], Keisuke Aoe[1,2], Yusuke Mimura[2], Yoriyuki Murata[1,2], Kenji Sakamoto[1], Wataru Koutoku[1], Tsuneo Matsumoto[1], Hiroshi Ueoka[1] and Masafumi Yano[3]





trombomodulina



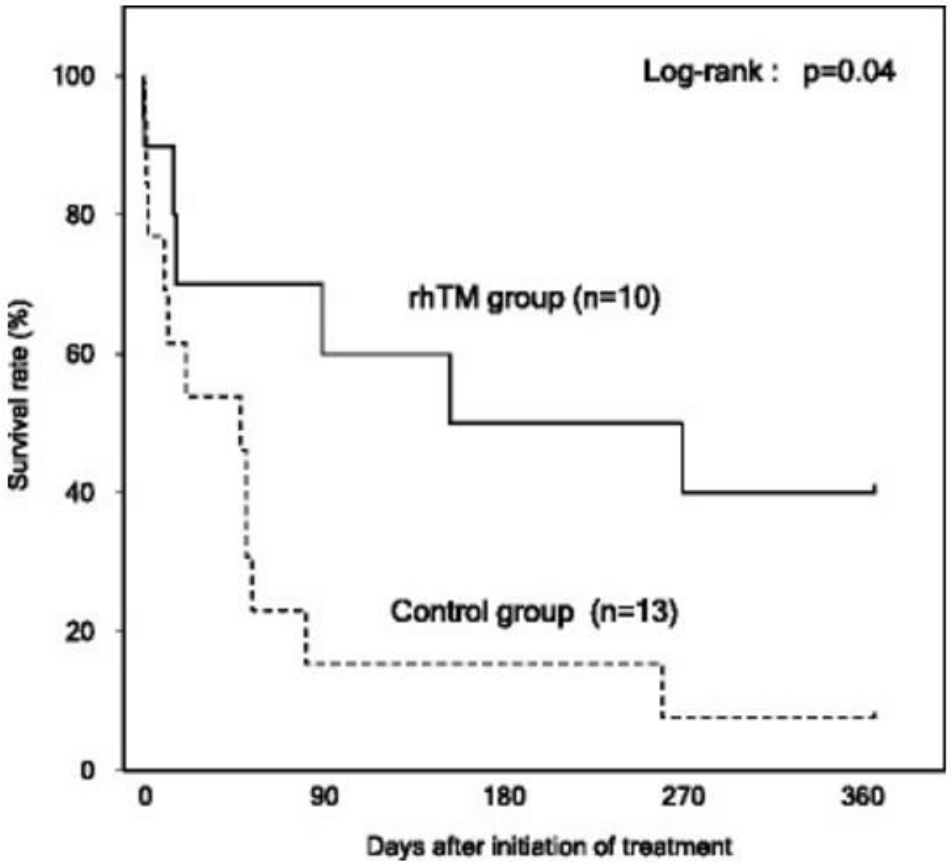
Hayakawa *et al. Multidisciplinary Respiratory Medicine* (2016) 11:38
DOI 10.1186/s40248-016-0074-z

Multidisciplinary Respiratory Medicine

ORIGINAL RESEARCH ARTICLE Open Access

Efficacy of recombinant human soluble thrombomodulin for the treatment of acute exacerbation of idiopathic pulmonary fibrosis: a single arm, non-randomized prospective clinical trial

Sho Hayakawa, Yasuo Matsuzawa*, Tamako Irie, Hagino Rikitake, Noriaki Okada and Yasuo Suzuki



* Utlenowanie P/F - ↑ NS
* Biomarkery - ↓ NS
* Wykrzepianie - ↓ NS
* Intubacja - ↓ NS

PLOS ONE

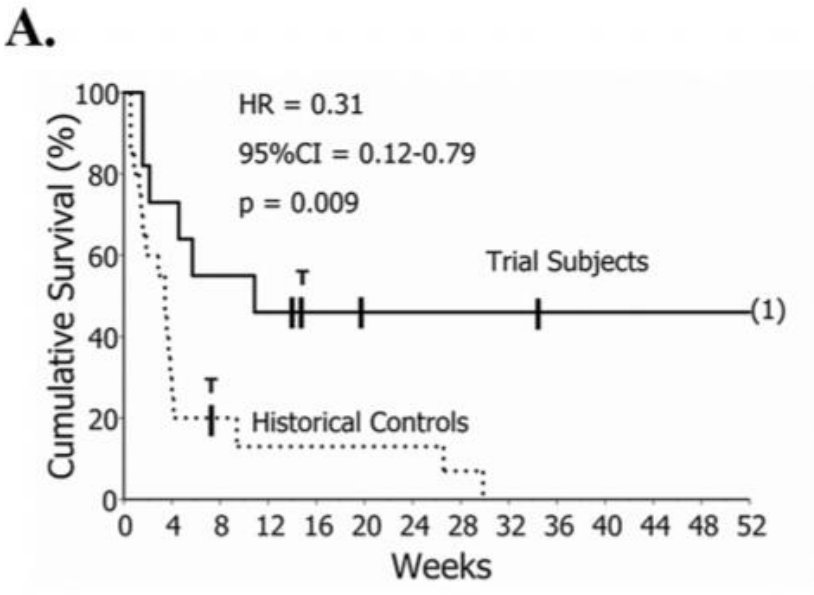
RESEARCH ARTICLE

Autoantibody-Targeted Treatments for Acute Exacerbations of Idiopathic Pulmonary Fibrosis

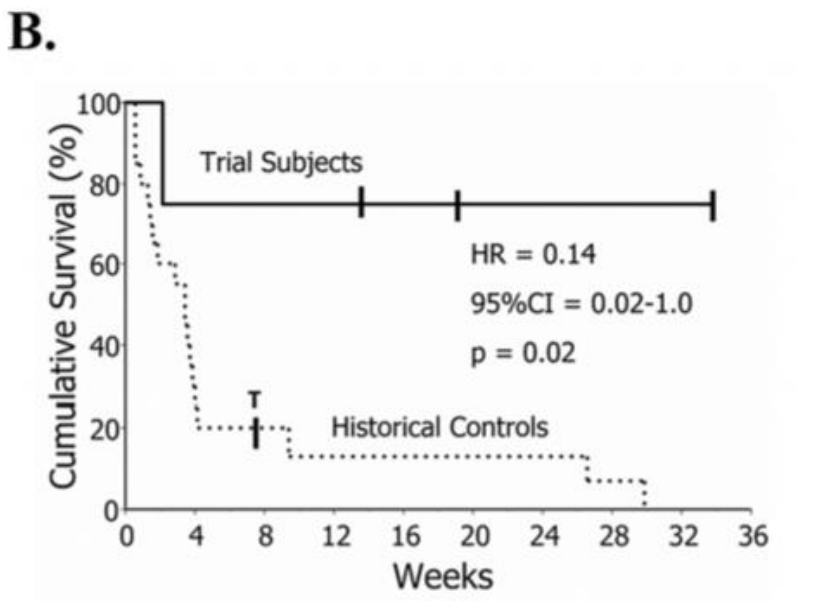
Michael Donahoe[1], Vincent G. Valentine[2], Nydia Chien[1], Kevin F. Gibson[1], Jay S. Raval[3], Melissa Saul[4], Jianmin Xue[1], Yingze Zhang[1], Steven R. Duncan[1]*

2015

Plazmafereza x5
Rituximab x2



Plazmafereza x9
Rituximab x2
IVIG 0.5 mg/kg/dzień



podsumowanie

* Zaostrzenia IPF mogą być wywołane przez znane czynniki (infekcje, aspiracje, inne) lub mogą być idiopatyczne
* Mamy do czynienia z procesem zapalnym nakładającym się na dokonane włóknienie
* Wystąpienie zaostrzenia wiąże się ze znacznym ryzykiem zgonu
* Leki przeciwfibrotyczne i terapia p-refluksowa prawdopodobnie zmniejsza ryzyko AE-IPF
* Nie wypracowano dotychczas optymalnego sposobu leczenia AE-IPF