Fondazione Umberto Veronesi – per il progresso delle scienze

RICERCATORI IN CLASSE

LA SCIENZA E LA RICERCA INCONTRANO I GIOVANI

Liceo Scientifico Galileo Galilei

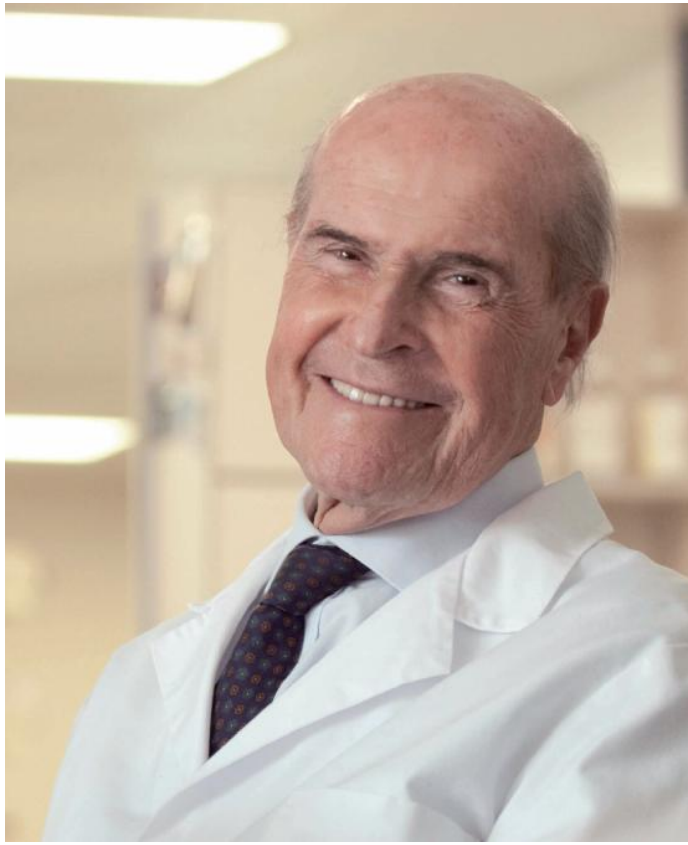
/14 Maggio 2020 / Pescara

ESTER SARA DI FILIPPO

Ricercatore Fondazione Umberto Veronesi 2020

Umberto Veronesi - un grande uomo di scienza

È stata una figura di riferimento per la lotta contro il cancro e per la cultura scientifica internazionale: ha dato impulso e innovazione alla ricerca medica italiana e ha rivoluzionato la percezione della stessa malattia oncologica.



Umberto Veronesi è stato:

- un **grande medico**
- uno **scienziato illuminato**
- impegnato in molte **battaglie sociali**

Umberto Veronesi ha partecipato a oltre **800 pubblicazioni scientifiche**, ha ricevuto **14 lauree Honoris Causa**, ha ricoperto incarichi pubblici di prestigio: dal 2000 al 2001, è stato **Ministro della Sanità della Repubblica Italiana**; dal 2008 al 2011 è stato **membro del Senato** italiano durante la 16a Legislatura.

Fondazione Umberto Veronesi – per il progresso delle scienze

Fondazione Umberto Veronesi

Per promuovere il progresso delle scienze nel 2003 il Professor Veronesi ha creato Fondazione Umberto Veronesi che oggi porta avanti il suo pensiero, i suoi obiettivi, i suoi valori con impegno e passione.

Fondazione Umberto Veronesi opera sostenendo il lavoro di centinaia di ricercatori di eccellenza e diffondendo la cultura della salute e della prevenzione.

"La fiducia nella possibilità di migliorare il mondo attraverso l'uso della ragione e della scienza ha guidato la mia vita di medico e di ricercatore, ed è alle origini di questa Fondazione"

Fondazione Umberto Veronesi – per il progresso delle scienze

Fondazione Umberto Veronesi

1. Sostegno alla ricerca

- Borse post-dottorato (**1762** dal 2003, 166 nel solo 2020!)
- Progetti di ricerca (**119** dal 2003)
- Scuola Europea di Medicina Molecolare (SEMM)

2. Divulgazione scientifica

- Progetti con le scuole
- Conferenze internazionali
- Attività editoriali
- www.fondazioneveronesi.it

Fondazione Umberto Veronesi
–per il progresso delle scienze

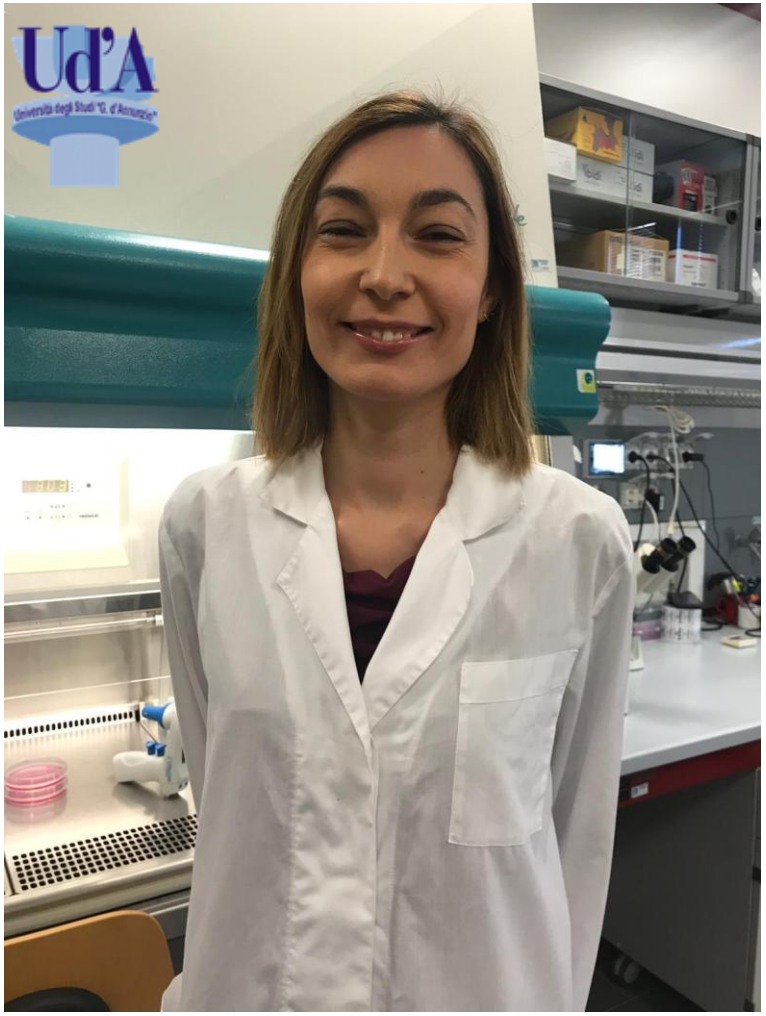
Fondazione Umberto Veronesi

La Fondazione sostiene ricercatori che lavorano nelle seguenti aree:

- Oncologia
- Cardiologia
- Neuroscienze
- Nutrigenomica
  e prevenzione delle malattie

Fondazione
Umberto Veronesi
–per il progresso
delle scienze

Perché è importante sostenere la ricerca scientifica?



Ricercatrice presso l'Università degli Studi "G. d'Annunzio" di Chieti sostenuta dalla FUV

Vivo a Fossacesia

Ho 35 anni

Maturità Classica nel 2003 presso il Liceo Classico "Vittorio Emanuele II" - Lanciano

Laurea in Farmacia nel 2009 presso l'Università degli Studi "G. d'Annunzio" - Chieti

Dottore di Ricerca nel 2015 presso l'Università degli Studi "G. d'Annunzio" - Chieti

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ESPERIENZE ALL'ESTERO

Gennaio 2018 **postdoc ospite** Institut de Myologie, **Francia**

Luglio 2017 – Agosto 2017 **postdoc ospite researcher MyoGravity team member in the laboratory of NASA, at Kennedy Space Center, Cape Canaveral, Florida**

Luglio 2016 – Agosto 2016 e Giugno 2015 – Dicembre 2015
postdoc ospite KU Leuven, Belgio

Febbraio 2014 – Marzo 2014
Studente PhD ospite presso l' **Università degli Studi di Perugia**

Aprile 2012 – Dicembre 2012 **Studente PhD ospite**
KU Leuven, Belgio

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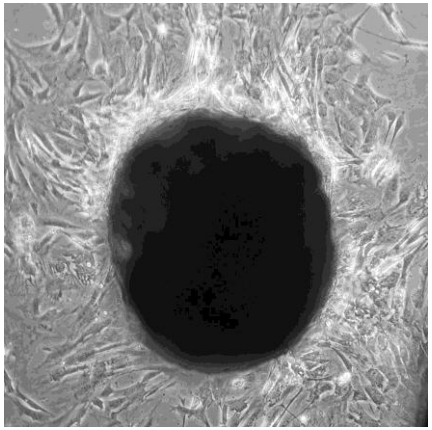
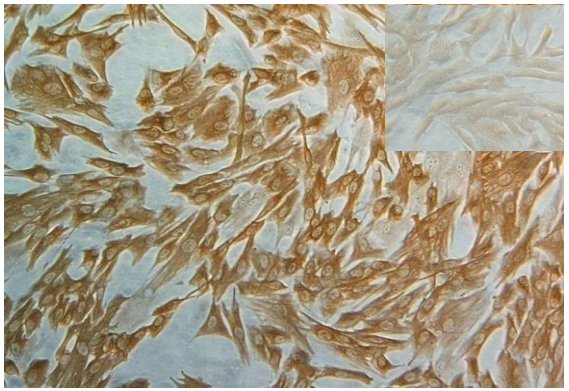
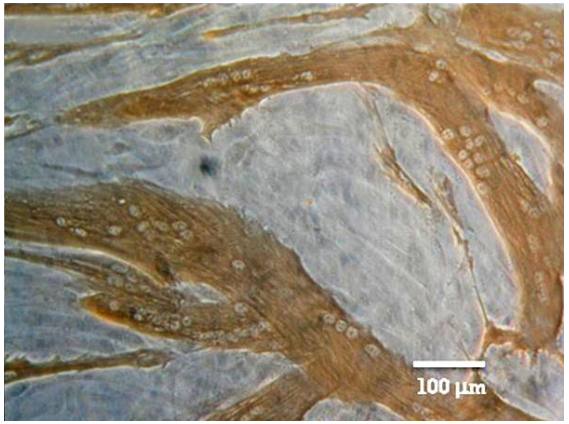
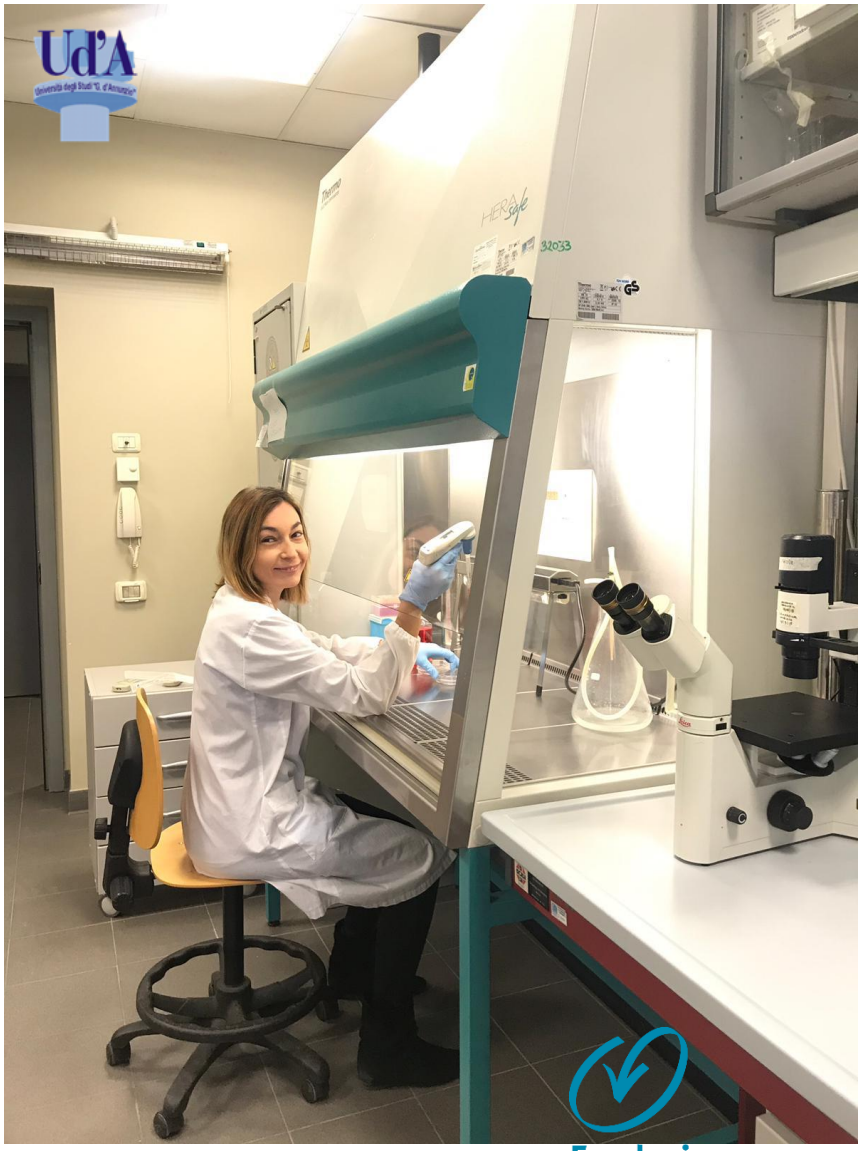
La giornata tipo di un ricercatore









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Gioie e dolori del lavoro del ricercatore

Aspetti più belli :

- SCOPRIRE
- DINAMICITA'
- CREATIVITÀ
- INTERAZIONE, lavoro di squadra
- VIAGGIARE

Aspetti più faticosi :

-PUBBLICARE
-FINANZIAMENTI

Fondazione Umberto Veronesi – per il progresso delle scienze

La pubblicazione scientifica

Scritto redatto in modo oggettivo, ovvero evidenziando in maniera trasparente e verificabile metodo e risultati, da parte di scienziati o tecnici, su un argomento scientifico, pubblicato attraverso i canali di comunicazione della comunità scientifica, tipicamente su riviste accademiche, una volta validata secondo le regole della revisione paritaria, entrando di diritto a far parte della letteratura scientifica

Principale forma di comunicazione della comunità scientifica

La pubblicazione scientifica

Portare a conoscenza della comunità scientifica il risultato di una ricerca, che potrà essere usato come base per ulteriori studi o sfruttato per applicazioni pratiche

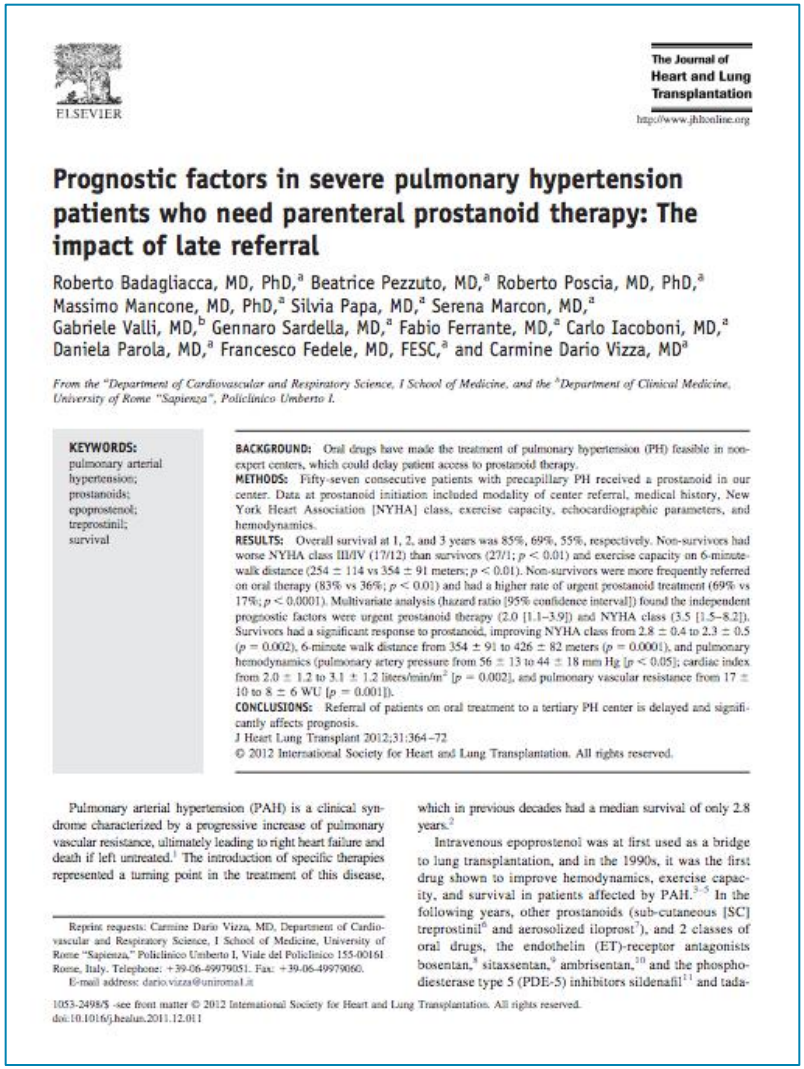
Descrivere dettagliatamente non solo il risultato stesso, ma anche tutte le procedure e le informazioni che sono state necessarie per ottenerlo

→ Verificare e riprodurre l'operato degli autori → "Validazione" del risultato

Certificare l'importanza del contributo dato dagli autori ai risultati pubblicati

La pubblicazione scientifica

Inglese scientifico



ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

Prognostic factors in severe pulmonary hypertension patients who need parenteral prostanoid therapy: The impact of late referral

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KEYWORDS: pulmonary arterial hypertension; prostanoids; epoprostenol; treprostinil; survival

BACKGROUND: Oral drugs have made the treatment of pulmonary hypertension (PH) feasible in non-expert centers, which could delay patient access to prostanoid therapy.
METHODS: Fifty-seven consecutive patients with precapillary PH received a prostanoid in our center. Data at prostanoid initiation included modality of center referral, medical history, New York Heart Association [NYHA] class, exercise capacity, echocardiographic parameters, and hemodynamics.
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CONCLUSIONS: Referral of patients on oral treatment to a tertiary PH center is delayed and significantly affects prognosis.
J Heart Lung Transplant 2012;31:364–72
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Reprint requests: Carmine Dario Vizza, MD, Department of Cardiovascular and Respiratory Science, I School of Medicine, University of Rome "Sapienza," Policlinico Umberto I, Viale del Policlinico 155-00161 Rome, Italy. Telephone: +39-06-49979051. Fax: +39-06-49979060.
E-mail address: dario.vizza@uniroma1.it

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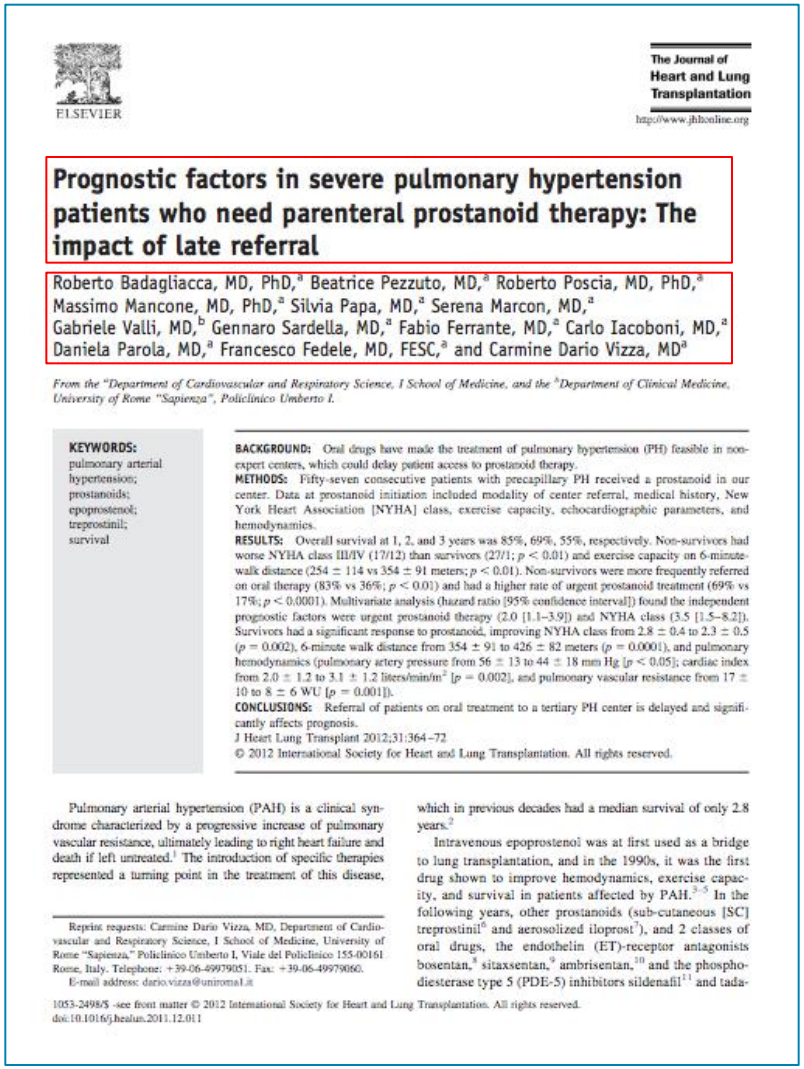
Fondazione Umberto Veronesi – per il progresso delle scienze

La pubblicazione scientifica

Titolo

Nomi degli autori



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Titolo

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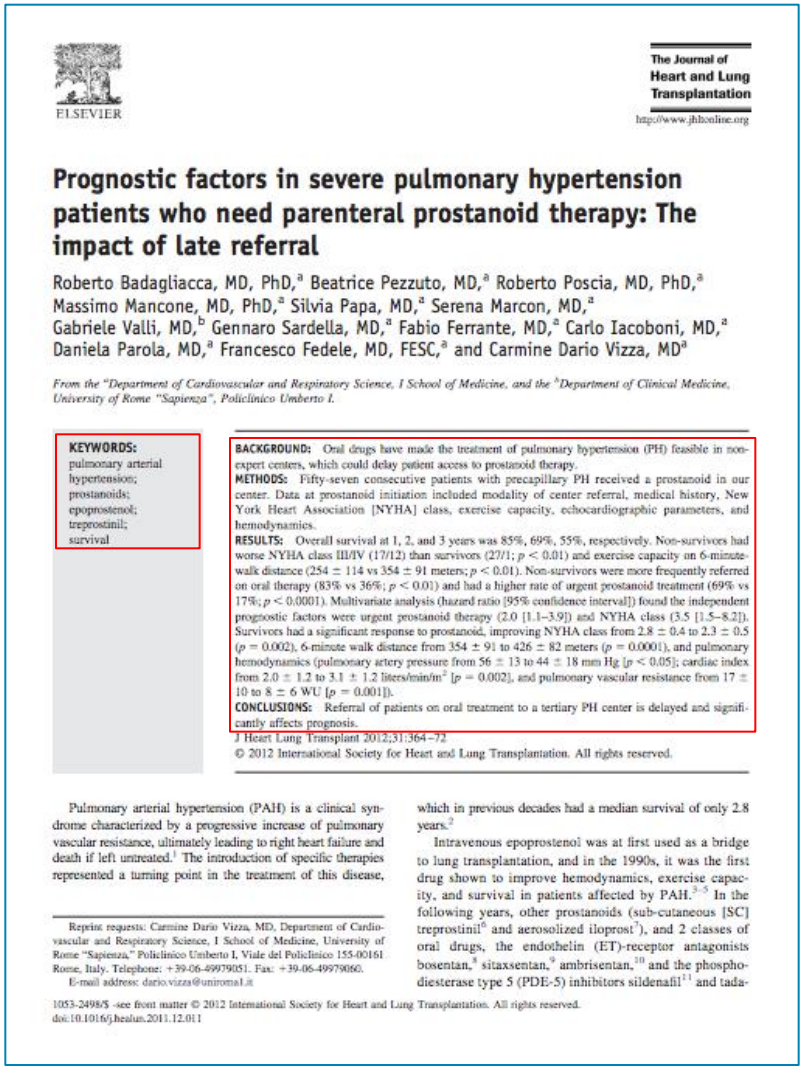
Abstract

Parole chiave



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- Titolo
- Nomi degli autori
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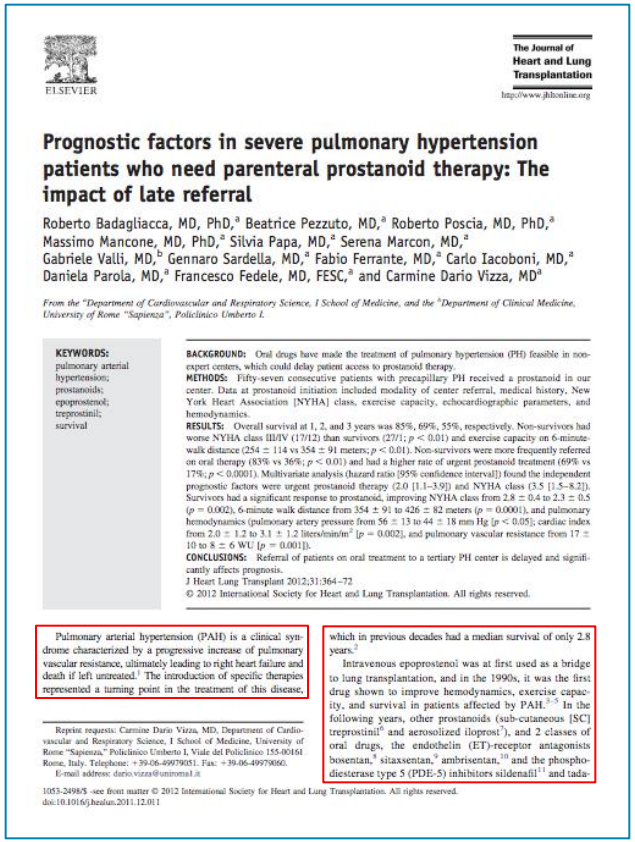
- Introduzione



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Despite these achievements, several studies proved that after an initial period of improvement, clinical worsening is a common experience among patients treated with oral drugs,[10,13–16] leading to a clinical need for parenteral prostanoid as an add-on therapy. In this perspective, timing for parenteral prostanoid therapy becomes a critical challenge. The aim of this study was to retrospectively evaluate if the late referral to a tertiary PH center may influence the clinical course of patients treated with prostanoids in any phase of their clinical history and the long-term effects in survivors.

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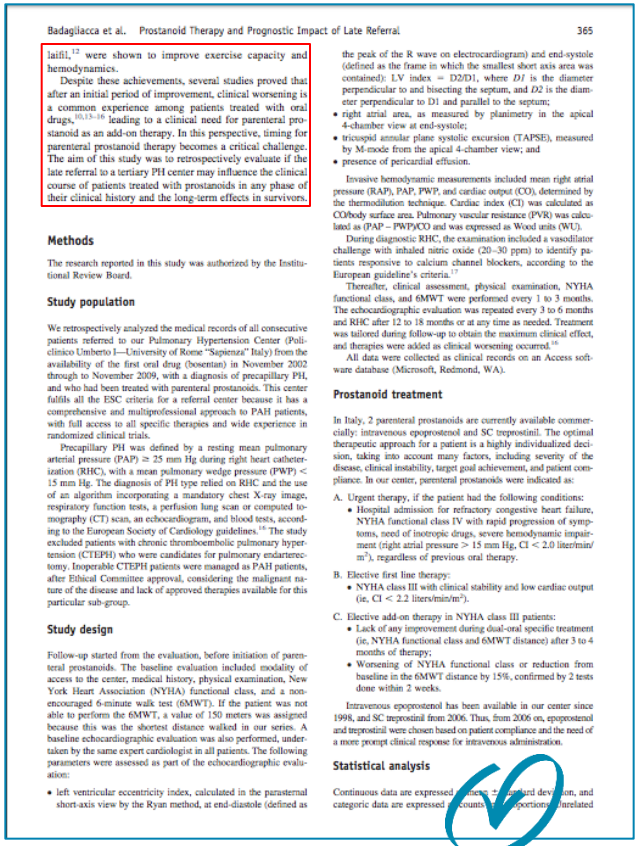

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Methods

The research reported in this study was authorized by the Institutional Review Board.

Study population

We retrospectively analyzed the medical records of all consecutive patients referred to our Pulmonary Hypertension Center (Policlinico Umberto I—University of Rome "Sapienza" Italy) from the availability of the first oral drug (bosentan) in November 2002 through to November 2009, with a diagnosis of precapillary PH, and who had been treated with parenteral prostanoids. This center fulfils all the ESC criteria for a referral center because it has a comprehensive and multiprofessional approach to PAH patients, with full access to all specific therapies and wide experience in randomized clinical trials.

Precapillary PH was defined by a resting mean pulmonary arterial pressure (PAP) ≥ 25 mm Hg during right heart catheterization (RHC), with a mean pulmonary wedge pressure (PWP) < 15 mm Hg. The diagnosis of PH type relied on RHC and the use of an algorithm incorporating a mandatory chest X-ray image, respiratory function tests, a perfusion lung scan or computed tomography (CT) scan, an echocardiogram, and blood tests, according to the European Society of Cardiology guidelines.[16] The study excluded patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were candidates for pulmonary endarterectomy. Inoperable CTEPH patients were managed as PAH patients, after Ethical Committee approval, considering the malignant nature of the disease and lack of approved therapies available for this particular sub-group.

Study design

Follow-up started from the evaluation, before initiation of parenteral prostanoids. The baseline evaluation included modality of access to the center, medical history, physical examination, New York Heart Association (NYHA) functional class, and a non-encouraged 6-minute walk test (6MWT). If the patient was not able to perform the 6MWT, a value of 150 meters was assigned because this was the shortest distance walked in our series. A baseline echocardiographic evaluation was also performed, undertaken by the same expert cardiologist in all patients. The following parameters were assessed as part of the echocardiographic evaluation:

- left ventricular eccentricity index, calculated in the parasternal short-axis view by the Ryan method, at end-diastole (defined as the peak of the R wave on electrocardiogram) and end-systole (defined as the frame in which the smallest short axis area was contained): LV index = D2/D1, where *D1* is the diameter perpendicular to and bisecting the septum, and *D2* is the diameter perpendicular to D1 and parallel to the septum;
- right atrial area, as measured by planimetry in the apical 4-chamber view at end-systole;
- tricuspid annular plane systolic excursion (TAPSE), measured by M-mode from the apical 4-chamber view; and
- presence of pericardial effusion.

Invasive hemodynamic measurements included mean right atrial pressure (RAP), PAP, PWP, and cardiac output (CO), determined by the thermodilution technique. Cardiac index (CI) was calculated as CO/body surface area. Pulmonary vascular resistance (PVR) was calculated as (PAP − PWP)/CO and was expressed as Wood units (WU).

During diagnostic RHC, the examination included a vasodilator challenge with inhaled nitric oxide (20–30 ppm) to identify patients responsive to calcium channel blockers, according to the European guideline's criteria.[17]

Thereafter, clinical assessment, physical examination, NYHA functional class, and 6MWT were performed every 1 to 3 months. The echocardiographic evaluation was repeated every 3 to 6 months and RHC after 12 to 18 months or at any time as needed. Treatment was tailored during follow-up to obtain the maximum clinical effect, and therapies were added as clinical worsening occurred.[16]

All data were collected as clinical records on an Access software database (Microsoft, Redmond, WA).

Prostanoid treatment

In Italy, 2 parenteral prostanoids are currently available commercially: intravenous epoprostenol and SC treprostinil. The optimal therapeutic approach for a patient is a highly individualized decision, taking into account many factors, including severity of the disease, clinical instability, target goal achievement, and patient compliance. In our center, parenteral prostanoids were indicated as:

A. Urgent therapy, if the patient had the following conditions:
- Hospital admission for refractory congestive heart failure, NYHA functional class IV with rapid progression of symptoms, need of inotropic drugs, severe hemodynamic impairment (right atrial pressure > 15 mm Hg, CI < 2.0 liter/min/m^2), regardless of previous oral therapy.

B. Elective first line therapy:
- NYHA class III with clinical stability and low cardiac output (ie, CI < 2.2 liters/min/m^2).

C. Elective add-on therapy in NYHA class III patients:
- Lack of any improvement during dual-oral specific treatment (ie, NYHA functional class and 6MWT distance) after 3 to 4 months of therapy;
- Worsening of NYHA functional class or reduction from baseline in the 6MWT distance by 15%, confirmed by 2 tests done within 2 weeks.

Intravenous epoprostenol has been available in our center since 1998, and SC treprostinil from 2006. Thus, from 2006 on, epoprostenol and treprostinil were chosen based on patient compliance and the need of a more prompt clinical response for intravenous administration.

Statistical analysis

Continuous data are expressed [illegible] standard deviation, and categoric data are expressed [illegible] proportions. Unrelated

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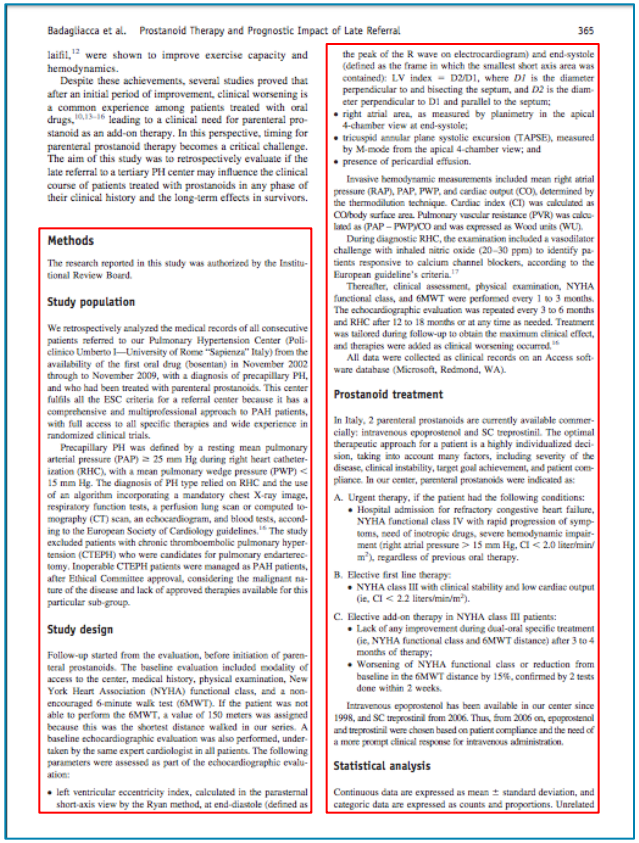

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laifil,[12] were shown to improve exercise capacity and hemodynamics.

Despite these achievements, several studies proved that after an initial period of improvement, clinical worsening is a common experience among patients treated with oral drugs,[10,13–16] leading to a clinical need for parenteral prostanoid as an add-on therapy. In this perspective, timing for parenteral prostanoid therapy becomes a critical challenge. The aim of this study was to retrospectively evaluate if the late referral to a tertiary PH center may influence the clinical course of patients treated with prostanoids in any phase of their clinical history and the long-term effects in survivors.

Methods

The research reported in this study was authorized by the Institutional Review Board.

Study population

We retrospectively analyzed the medical records of all consecutive patients referred to our Pulmonary Hypertension Center (Policlinico Umberto I—University of Rome "Sapienza" Italy) from the availability of the first oral drug (bosentan) in November 2002 through to November 2009, with a diagnosis of precapillary PH, and who had been treated with parenteral prostanoids. This center fulfils all the ESC criteria for a referral center because it has a comprehensive and multiprofessional approach to PAH patients, with full access to all specific therapies and wide experience in randomized clinical trials.

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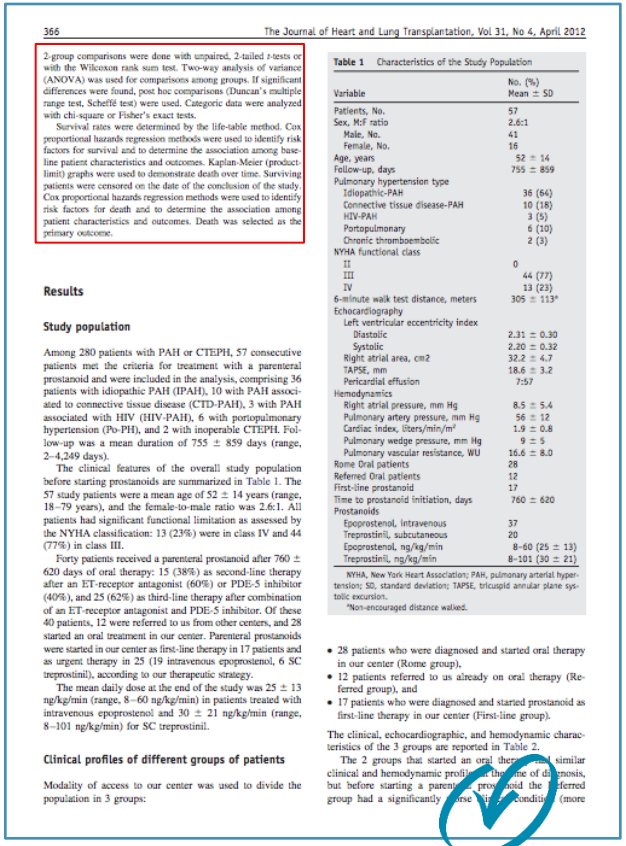

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2-group comparisons were done with unpaired, 2-tailed *t*-tests or with the Wilcoxon rank sum test. Two-way analysis of variance (ANOVA) was used for comparisons among groups. If significant differences were found, post hoc comparisons (Duncan's multiple range test, Scheffé test) were used. Categoric data were analyzed with chi-square or Fisher's exact tests.

Survival rates were determined by the life-table method. Cox proportional hazards regression methods were used to identify risk factors for survival and to determine the association among baseline patient characteristics and outcomes. Kaplan-Meier (product-limit) graphs were used to demonstrate death over time. Surviving patients were censored on the date of the conclusion of the study. Cox proportional hazards regression methods were used to identify risk factors for death and to determine the association among patient characteristics and outcomes. Death was selected as the primary outcome.

Table 1 Characteristics of the Study Population

Variable	No. (%) Mean ± SD
Patients, No.	57
Sex, M:F ratio	2.6:1
Male, No.	41
Female, No.	16
Age, years	52 ± 14
Follow-up, days	755 ± 859
Pulmonary hypertension type	
Idiopathic-PAH	36 (64)
Connective tissue disease-PAH	10 (18)
HIV-PAH	3 (5)
Portopulmonary	6 (10)
Chronic thromboembolic	2 (3)
NYHA functional class	
II	0
III	44 (77)
IV	13 (23)
6-minute walk test distance, meters	305 ± 113*
Echocardiography	
Left ventricular eccentricity index	
Diastolic	2.31 ± 0.30
Systolic	2.20 ± 0.32
Right atrial area, cm2	32.2 ± 4.7
TAPSE, mm	18.6 ± 3.2
Pericardial effusion	7:57
Hemodynamics	
Right atrial pressure, mm Hg	8.5 ± 5.4
Pulmonary artery pressure, mm Hg	56 ± 12
Cardiac index, liters/min/m^2	1.9 ± 0.8
Pulmonary wedge pressure, mm Hg	9 ± 5
Pulmonary vascular resistance, WU	16.6 ± 8.0
Rome Oral patients	28
Referred Oral patients	12
First-line prostanoid	17
Time to prostanoid initiation, days	760 ± 620
Prostanoids	
Epoprostenol, intravenous	37
Treprostinil, subcutaneous	20
Epoprostenol, ng/kg/min	8–60 (25 ± 13)
Treprostinil, ng/kg/min	8–101 (30 ± 21)

NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.
*Non-encouraged distance walked.

Results

Study population

Among 280 patients with PAH or CTEPH, 57 consecutive patients met the criteria for treatment with a parenteral prostanoid and were included in the analysis, comprising 36 patients with idiopathic PAH (IPAH), 10 with PAH associated to connective tissue disease (CTD-PAH), 3 with PAH associated with HIV (HIV-PAH), 6 with portopulmonary hypertension (Po-PH), and 2 with inoperable CTEPH. Follow-up was a mean duration of 755 ± 859 days (range, 2–4,249 days).

The clinical features of the overall study population before starting prostanoids are summarized in Table 1. The 57 study patients were a mean age of 52 ± 14 years (range, 18–79 years), and the female-to-male ratio was 2.6:1. All patients had significant functional limitation as assessed by the NYHA classification: 13 (23%) were in class IV and 44 (77%) in class III.

Forty patients received a parenteral prostanoid after 760 ± 620 days of oral therapy: 15 (38%) as second-line therapy after an ET-receptor antagonist (60%) or PDE-5 inhibitor (40%), and 25 (62%) as third-line therapy after combination of an ET-receptor antagonist and PDE-5 inhibitor. Of these 40 patients, 12 were referred to us from other centers, and 28 started an oral treatment in our center. Parenteral prostanoids were started in our center as first-line therapy in 17 patients and as urgent therapy in 25 (19 intravenous epoprostenol, 6 SC treprostinil), according to our therapeutic strategy.

The mean daily dose at the end of the study was 25 ± 13 ng/kg/min (range, 8–60 ng/kg/min) in patients treated with intravenous epoprostenol and 30 ± 21 ng/kg/min (range, 8–101 ng/kg/min) for SC treprostinil.

Clinical profiles of different groups of patients

Modality of access to our center was used to divide the population in 3 groups:

- 28 patients who were diagnosed and started oral therapy in our center (Rome group),
- 12 patients referred to us already on oral therapy (Referred group), and
- 17 patients who were diagnosed and started prostanoid as first-line therapy in our center (First-line group).

The clinical, echocardiographic, and hemodynamic characteristics of the 3 groups are reported in Table 2.

The 2 groups that started an oral therapy had similar clinical and hemodynamic profiles at the time of diagnosis, but before starting a parenteral prostanoid the Referred group had a significantly worse [illegible] condition (more

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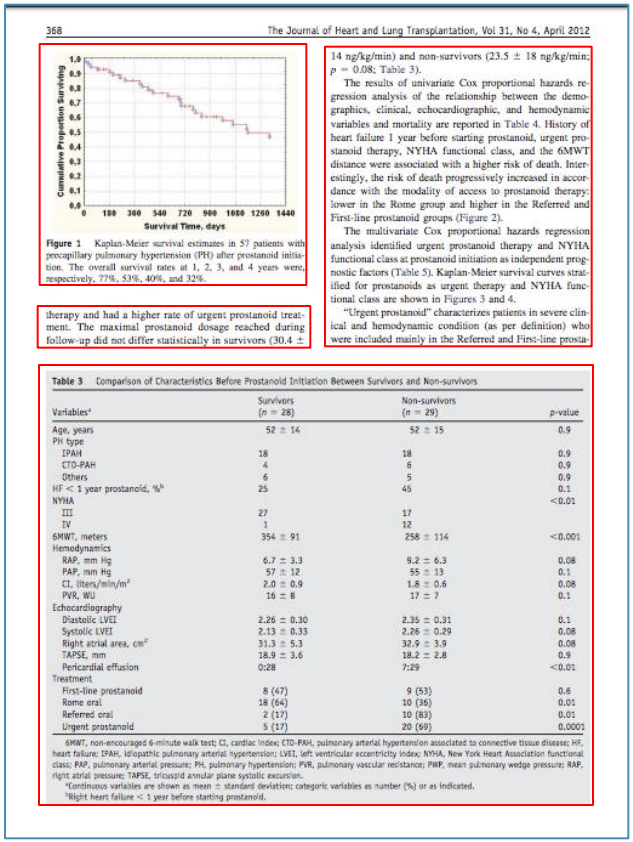

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Figure 1 Kaplan-Meier survival estimates in 57 patients with precapillary pulmonary hypertension (PH) after prostanoid initiation. The overall survival rates at 1, 2, 3, and 4 years were, respectively, 77%, 53%, 40%, and 32%.

therapy and had a higher rate of urgent prostanoid treatment. The maximal prostanoid dosage reached during follow-up did not differ statistically in survivors (30.4 ± 14 ng/kg/min) and non-survivors (23.5 ± 18 ng/kg/min; $p = 0.08$; Table 3).

The results of univariate Cox proportional hazards regression analysis of the relationship between the demographics, clinical, echocardiographic, and hemodynamic variables and mortality are reported in Table 4. History of heart failure 1 year before starting prostanoid, urgent prostanoid therapy, NYHA functional class, and the 6MWT distance were associated with a higher risk of death. Interestingly, the risk of death progressively increased in accordance with the modality of access to prostanoid therapy: lower in the Rome group and higher in the Referred and First-line prostanoid groups (Figure 2).

The multivariate Cox proportional hazards regression analysis identified urgent prostanoid therapy and NYHA functional class at prostanoid initiation as independent prognostic factors (Table 5). Kaplan-Meier survival curves stratified for prostanoids as urgent therapy and NYHA functional class are shown in Figures 3 and 4.

"Urgent prostanoid" characterizes patients in severe clinical and hemodynamic condition (as per definition) who were included mainly in the Referred and First-line prosta-

Table 3 Comparison of Characteristics Before Prostanoid Initiation Between Survivors and Non-survivors

Variables[a]	Survivors ($n = 28$)	Non-survivors ($n = 29$)	p-value
Age, years	52 ± 14	52 ± 15	0.9
PH type			
IPAH	18	18	0.9
CTD-PAH	4	6	0.9
Others	6	5	0.9
HF < 1 year prostanoid, %[b]	25	45	0.1
NYHA			<0.01
III	27	17	
IV	1	12	
6MWT, meters	354 ± 91	258 ± 114	<0.001
Hemodynamics			
RAP, mm Hg	6.7 ± 3.3	9.2 ± 6.3	0.08
PAP, mm Hg	57 ± 12	55 ± 13	0.1
CI, liters/min/m²	2.0 ± 0.9	1.8 ± 0.6	0.08
PVR, WU	16 ± 8	17 ± 7	0.1
Echocardiography			
Diastolic LVEI	2.26 ± 0.30	2.35 ± 0.31	0.1
Systolic LVEI	2.13 ± 0.33	2.26 ± 0.29	0.08
Right atrial area, cm²	31.3 ± 5.3	32.9 ± 3.9	0.08
TAPSE, mm	18.9 ± 3.6	18.2 ± 2.8	0.9
Pericardial effusion	0:28	7:29	<0.01
Treatment			
First-line prostanoid	8 (47)	9 (53)	0.6
Rome oral	18 (64)	10 (36)	0.01
Referred oral	2 (17)	10 (83)	0.01
Urgent prostanoid	5 (17)	20 (69)	0.0001

6MWT, non-encouraged 6-minute walk test; CI, cardiac index; CTD-PAH, pulmonary arterial hypertension associated to connective tissue disease; HF, heart failure; IPAH, idiopathic pulmonary arterial hypertension; LVEI, left ventricular eccentricity index; NYHA, New York Heart Association functional class; PAP, pulmonary arterial pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; PWP, mean pulmonary wedge pressure; RAP, right atrial pressure; TAPSE, tricuspid annular plane systolic excursion.
[a]Continuous variables are shown as mean ± standard deviation; categoric variables as number (%) or as indicated.
[b]Right heart failure < 1 year before starting prostanoid.

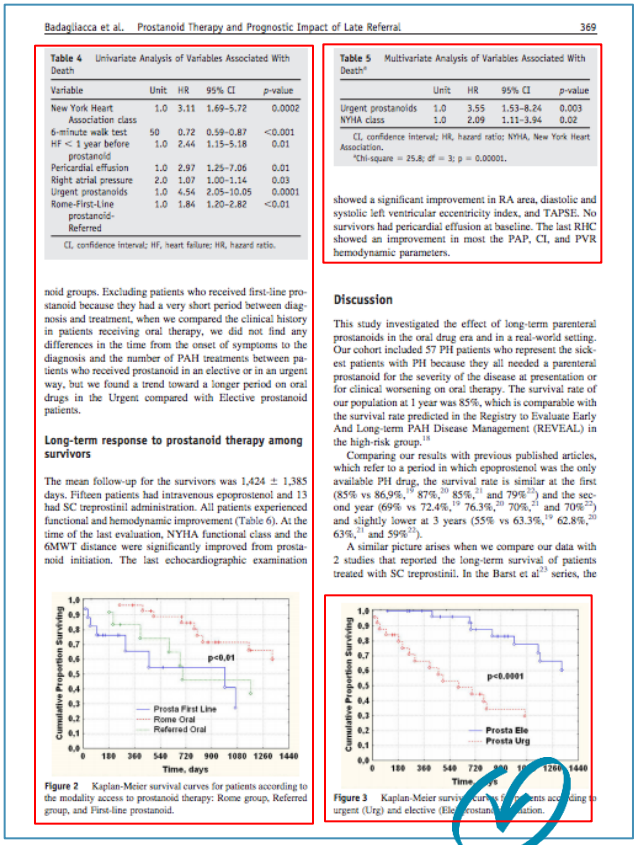

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Table 4 Univariate Analysis of Variables Associated With Death

Variable	Unit	HR	95% CI	p-value
New York Heart Association class	1.0	3.11	1.69–5.72	0.0002
6-minute walk test	50	0.72	0.59–0.87	<0.001
HF < 1 year before prostanoid	1.0	2.44	1.15–5.18	0.01
Pericardial effusion	1.0	2.97	1.25–7.06	0.01
Right atrial pressure	2.0	1.07	1.00–1.14	0.03
Urgent prostanoids	1.0	4.54	2.05–10.05	0.0001
Rome-First-Line prostanoid-Referred	1.0	1.84	1.20–2.82	<0.01

CI, confidence interval; HF, heart failure; HR, hazard ratio.

Table 5 Multivariate Analysis of Variables Associated With Death*

	Unit	HR	95% CI	p-value
Urgent prostanoids	1.0	3.55	1.53–8.24	0.003
NYHA class	1.0	2.09	1.11–3.94	0.02

CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.
*Chi-square = 25.8; df = 3; p = 0.00001.

noid groups. Excluding patients who received first-line prostanoid because they had a very short period between diagnosis and treatment, when we compared the clinical history in patients receiving oral therapy, we did not find any differences in the time from the onset of symptoms to the diagnosis and the number of PAH treatments between patients who received prostanoid in an elective or in an urgent way, but we found a trend toward a longer period on oral drugs in the Urgent compared with Elective prostanoid patients.

Long-term response to prostanoid therapy among survivors

The mean follow-up for the survivors was 1,424 ± 1,385 days. Fifteen patients had intravenous epoprostenol and 13 had SC treprostinil administration. All patients experienced functional and hemodynamic improvement (Table 6). At the time of the last evaluation, NYHA functional class and the 6MWT distance were significantly improved from prostanoid initiation. The last echocardiographic examination showed a significant improvement in RA area, diastolic and systolic left ventricular eccentricity index, and TAPSE. No survivors had pericardial effusion at baseline. The last RHC showed an improvement in most the PAP, CI, and PVR hemodynamic parameters.

Discussion

This study investigated the effect of long-term parenteral prostanoids in the oral drug era and in a real-world setting. Our cohort included 57 PH patients who represent the sickest patients with PH because they all needed a parenteral prostanoid for the severity of the disease at presentation or for clinical worsening on oral therapy. The survival rate of our population at 1 year was 85%, which is comparable with the survival rate predicted in the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) in the high-risk group.[18]

Comparing our results with previous published articles, which refer to a period in which epoprostenol was the only available PH drug, the survival rate is similar at the first (85% vs 86.9%,[19] 87%,[20] 85%,[21] and 79%[22]) and the second year (69% vs 72.4%,[19] 76.3%,[20] 70%,[21] and 70%[22]) and slightly lower at 3 years (55% vs 63.3%,[19] 62.8%,[20] 63%,[21] and 59%[22]).

A similar picture arises when we compare our data with 2 studies that reported the long-term survival of patients treated with SC treprostinil. In the Barst et al[23] series, the

Figure 2 Kaplan-Meier survival curves for patients according to the modality access to prostanoid therapy: Rome group, Referred group, and First-line prostanoid.

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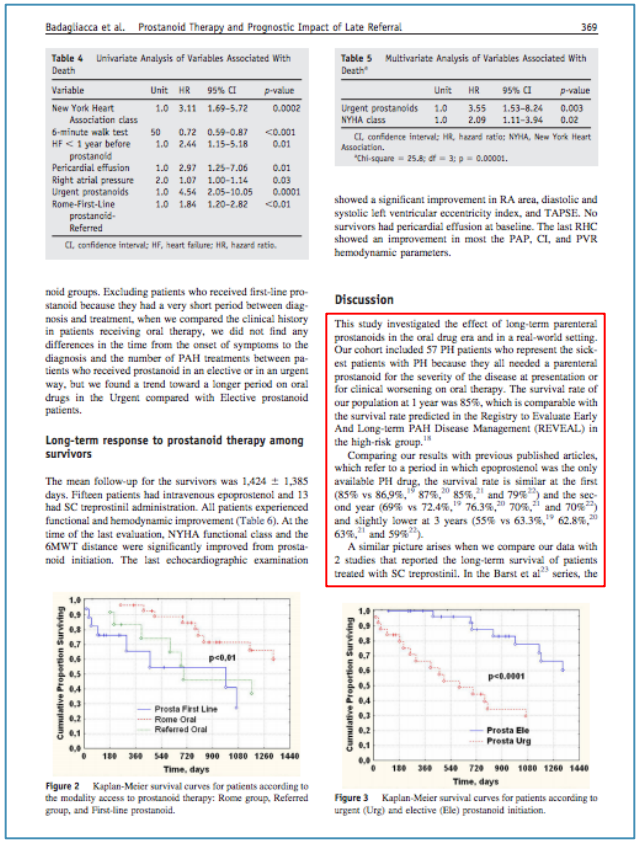

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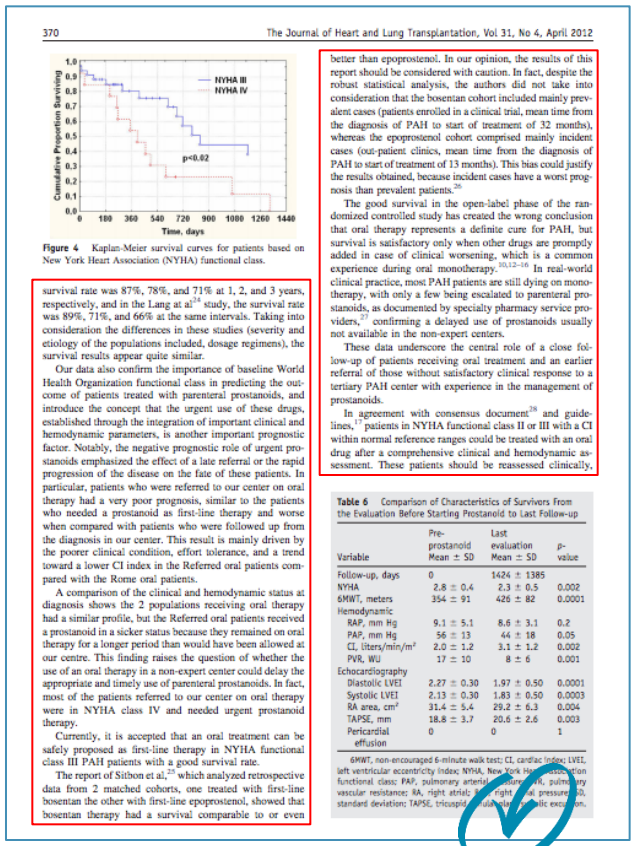

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Figure 4 Kaplan-Meier survival curves for patients based on New York Heart Association (NYHA) functional class.

survival rate was 87%, 78%, and 71% at 1, 2, and 3 years, respectively, and in the Lang at al[24] study, the survival rate was 89%, 71%, and 66% at the same intervals. Taking into consideration the differences in these studies (severity and etiology of the populations included, dosage regimens), the survival results appear quite similar.

Our data also confirm the importance of baseline World Health Organization functional class in predicting the outcome of patients treated with parenteral prostanoids, and introduce the concept that the urgent use of these drugs, established through the integration of important clinical and hemodynamic parameters, is another important prognostic factor. Notably, the negative prognostic role of urgent prostanoids emphasized the effect of a late referral or the rapid progression of the disease on the fate of these patients. In particular, patients who were referred to our center on oral therapy had a very poor prognosis, similar to the patients who needed a prostanoid as first-line therapy and worse when compared with patients who were followed up from the diagnosis in our center. This result is mainly driven by the poorer clinical condition, effort tolerance, and a trend toward a lower CI index in the Referred oral patients compared with the Rome oral patients.

A comparison of the clinical and hemodynamic status at diagnosis shows the 2 populations receiving oral therapy had a similar profile, but the Referred oral patients received a prostanoid in a sicker status because they remained on oral therapy for a longer period than would have been allowed at our centre. This finding raises the question of whether the use of an oral therapy in a non-expert center could delay the appropriate and timely use of parenteral prostanoids. In fact, most of the patients referred to our center on oral therapy were in NYHA class IV and needed urgent prostanoid therapy.

Currently, it is accepted that an oral treatment can be safely proposed as first-line therapy in NYHA functional class III PAH patients with a good survival rate.

The report of Sitbon et al,[25] which analyzed retrospective data from 2 matched cohorts, one treated with first-line bosentan the other with first-line epoprostenol, showed that bosentan therapy had a survival comparable to or even better than epoprostenol. In our opinion, the results of this report should be considered with caution. In fact, despite the robust statistical analysis, the authors did not take into consideration that the bosentan cohort included mainly prevalent cases (patients enrolled in a clinical trial, mean time from the diagnosis of PAH to start of treatment of 32 months), whereas the epoprostenol cohort comprised mainly incident cases (out-patient clinics, mean time from the diagnosis of PAH to start of treatment of 13 months). This bias could justify the results obtained, because incident cases have a worst prognosis than prevalent patients.[26]

The good survival in the open-label phase of the randomized controlled study has created the wrong conclusion that oral therapy represents a definite cure for PAH, but survival is satisfactory only when other drugs are promptly added in case of clinical worsening, which is a common experience during oral monotherapy.[10,12–16] In real-world clinical practice, most PAH patients are still dying on monotherapy, with only a few being escalated to parenteral prostanoids, as documented by specialty pharmacy service providers,[27] confirming a delayed use of prostanoids usually not available in the non-expert centers.

These data underscore the central role of a close follow-up of patients receiving oral treatment and an earlier referral of those without satisfactory clinical response to a tertiary PAH center with experience in the management of prostanoids.

In agreement with consensus document[28] and guidelines,[17] patients in NYHA functional class II or III with a CI within normal reference ranges could be treated with an oral drug after a comprehensive clinical and hemodynamic assessment. These patients should be reassessed clinically,

Table 6 Comparison of Characteristics of Survivors From the Evaluation Before Starting Prostanoid to Last Follow-up

Variable	Pre-prostanoid Mean ± SD	Last evaluation Mean ± SD	p-value
Follow-up, days	0	1424 ± 1385	
NYHA	2.8 ± 0.4	2.3 ± 0.5	0.002
6MWT, meters	394 ± 91	426 ± 82	0.0001
Hemodynamic			
RAP, mm Hg	9.1 ± 5.1	8.6 ± 3.1	0.2
PAP, mm Hg	56 ± 13	44 ± 18	0.05
CI, liters/min/m²	2.0 ± 1.2	3.1 ± 1.2	0.002
PVR, WU	17 ± 10	8 ± 6	0.001
Echocardiography			
Diastolic LVEI	2.27 ± 0.30	1.97 ± 0.50	0.0001
Systolic LVEI	2.13 ± 0.30	1.83 ± 0.50	0.0003
RA area, cm²	31.4 ± 5.4	29.2 ± 6.3	0.004
TAPSE, mm	18.8 ± 3.7	20.6 ± 2.6	0.003
Pericardial effusion	0	0	1

6MWT, non-encouraged 6-minute walk test; CI, cardiac index; LVEI, left ventricular eccentricity index; NYHA, New York Heart Association functional class; PAP, pulmonary arterial pressure; PH, pulmonary vascular resistances; RA, right atrial; RAP, right atrial pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

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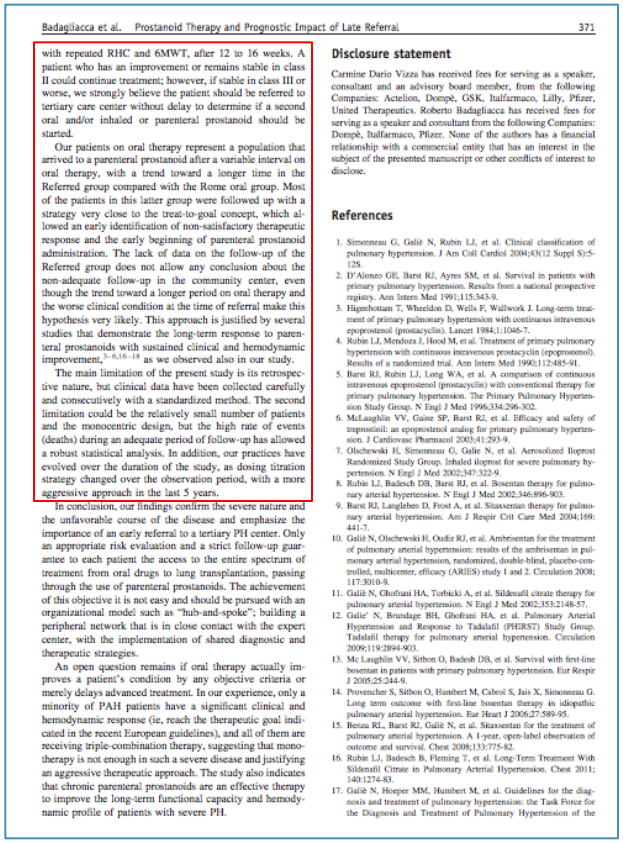

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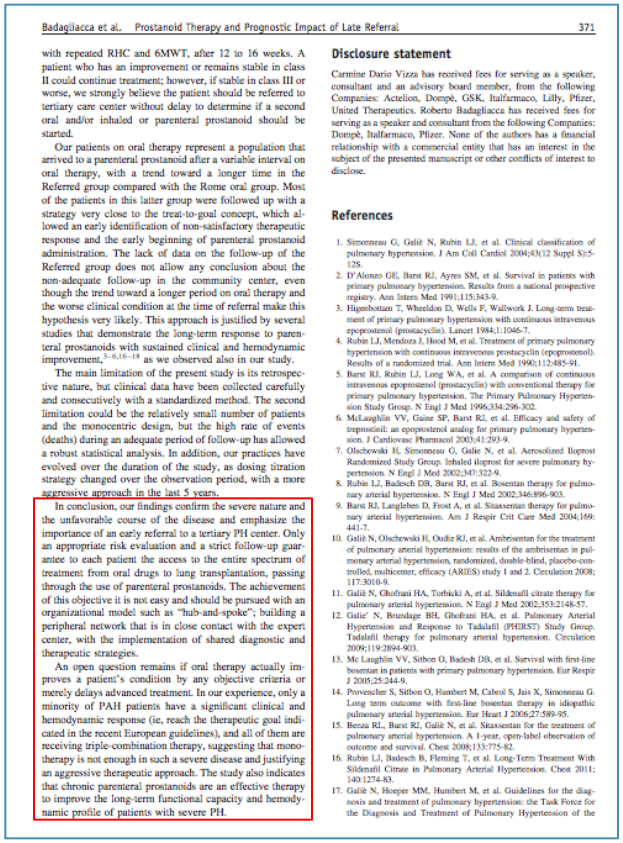

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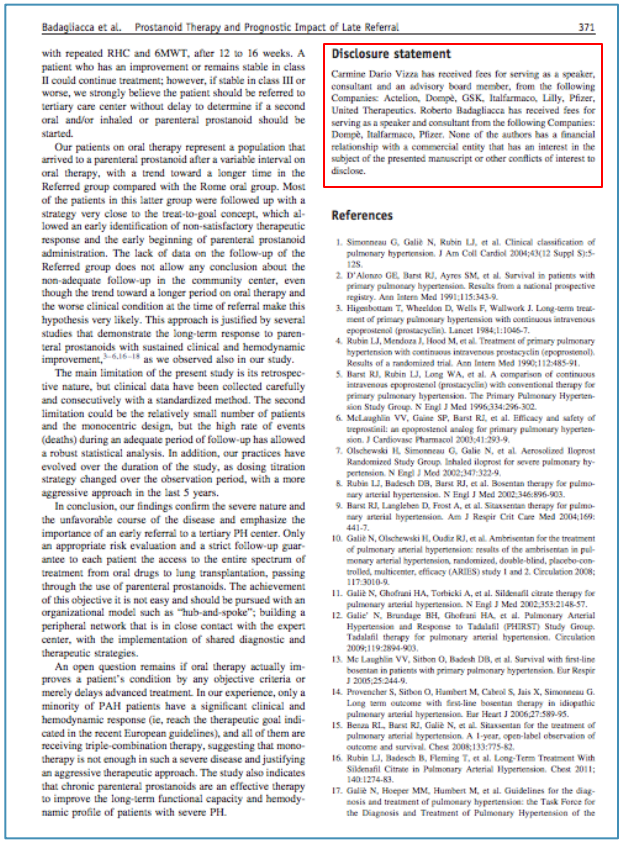

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4. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med 1990;112:485-91.
5. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296-302.
6. McLaughlin VV, Gaine SP, Barst RJ, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. J Cardiovasc Pharmacol 2003;41:293-9.
7. Olschewski H, Simonneau G, Galie N, et al. Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322-9.
8. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.
9. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004;169:441-7.
10. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-9.
11. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2002;353:2148-57.
12. Galie' N, Brundage BH, Ghofrani HA, et al. Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119:2894-903.
13. Mc Laughlin VV, Sitbon O, Badesh DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005;25:244-9.
14. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J 2006;27:589-95.
15. Benza RL, Barst RJ, Galiè N, et al. Sitaxsentan for the treatment of pulmonary arterial hypertension. A 1-year, open-label observation of outcome and survival. Chest 2008;133:775-82.
16. Rubin LJ, Badesch B, Fleming T, et al. Long-Term Treatment With Sildenafil Citrate in Pulmonary Arterial Hypertension. Chest 2011;140:1274-83.
17. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the

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European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.
18. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.
19. Barst RJ, Rubin LJ, McGoon MD et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 1994;121:409-15.
20. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477-82.
21. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-8.
22. Kuhn KP, Byrne DW, Arbogast PG, Doyle TP, Loyd JE, Robbins IM. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med 2003;167:580-6.
23. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J 2006;28:1195-203.
24. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest 2006;129:1636-43.
25. Sitbon O, McLaughlin VV, Badesch DB, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005;60:1025-30.
26. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 2010;36:549-55.
27. Tankersley MA, D'Albini LD, Granich AN, Whitman AJ. A 36 month survival analysis of patients beginning oral PAH monotherapy: an indication for escalation of therapy? Poster 1062. Presented at Pulmonary Hypertension Association Meeting, Houston, Texas, June 20–22, 2008.
28. Barst RJ, Gibbs JS, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009;54(1 Suppl):S78-84.

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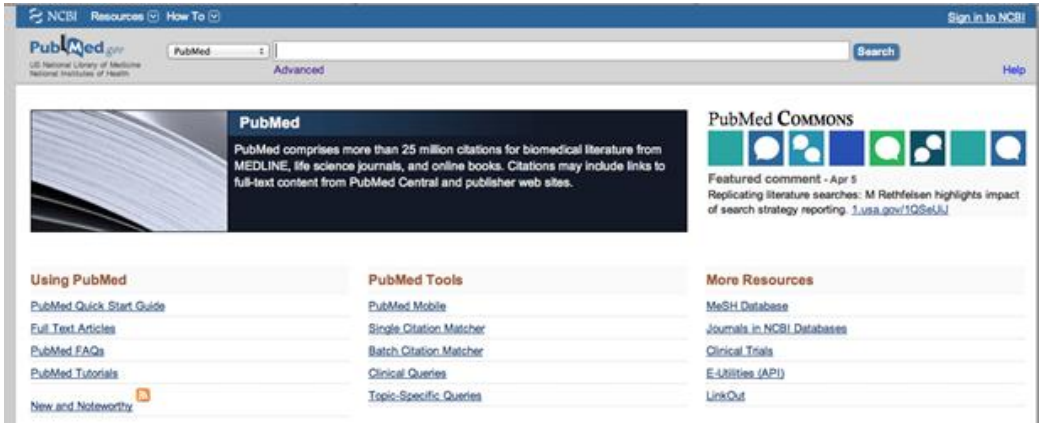
La pubblicazione scientifica e la *peer review*

Peer review = revisione tra pari

Procedura di selezione degli articoli o dei progetti di ricerca proposti da membri della comunità scientifica, effettuata attraverso una valutazione esperta da parte di specialisti del settore, al fine di valutarne l'idoneità alla pubblicazione scientifica su riviste specializzate o, nel caso di progetti, al finanziamento degli stessi



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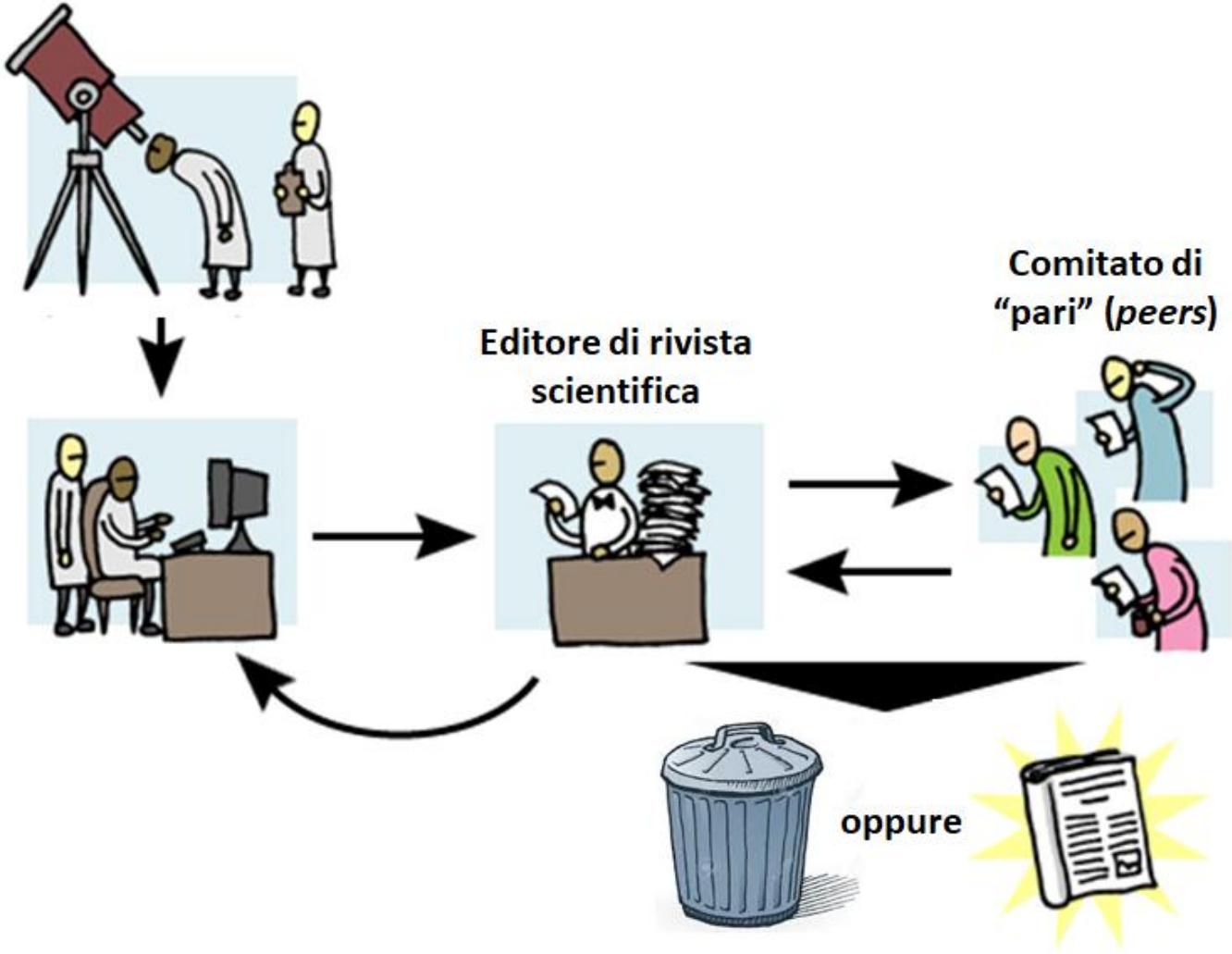
La pubblicazione scientifica e la *peer review*



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La pubblicazione scientifica e la *peer review*

Anche la *peer review* ha i suoi limiti...

EARLY REPORT

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3-10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associ... by the parents, with measles, mumps, and rub... vaccination in eight of the 12 children, with measl... infection in one child, and otitis media in a... All 1... children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to ...phoid ulceration. Histology showed patchy chronic infl... in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Be...oural disorders included autism (nine), disintegrative ...sis (one), a possible postviral or vaccinal encephalitis ...). There were no focal neurological abnormalities and ... and EEG tests were normal. Abno...al laboratory results were significantly raised urinary ...thylmalonic acid compared with age-matched contro... 0·03), low haemoglobin in four children, ...low ... in IgA in ... children.

Inter...ation ...e identi... associated gastrointestinal d...se and ...elopmental regression in a group of pre...y normal ch...n, which was generally associated in time ... possible environmental triggers.

Lancet 199...; **351**: 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell FRCP, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**
Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a p...d of apparent normality, lost acquired skills, includ... comm...ication. They all had gastrointestinal ...mptoms, ...luding abdominal pain, diarrhoea, and ...ting and, in ...some cases, food intolerance. We d...cribe ... clinical f...ings, and gastrointestinal featur... these chi...en.

Patients and meth...

12 children, consec...ively ...ed to ... department of paediatric gastr...terology ... a h...y of a pervasive developmental ...der with los... ...d skills and intestinal symptoms ... abdominal ...n, bloating and food intolerance, were in...gated. All children were admitted to the ward ...week, accomp...ed by their parents.

Clinical investigations

...k histor... including details of immunisations and exposure to infec...s diseases, and assessed the children. In 11 cas...e histor... was obtained by the senior clinician (JW-S). Neur...d psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[3] Developmental ... included a review of prospective developmental records from ...rents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[3] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomysial antibodies and boys were screened for fragile-X if this had not been done

RETRACTED

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Il mio campo di azione: nutrigenomica e prevenzione

Alimentazione

l'UNESCO nel 2010 ha dichiarato la **Dieta Mediterranea** patrimonio mondiale immateriale dell'umanità.

Attività fisica

È determinante per influenzare il nostro stato di salute; soprattutto quando l'età avanza.

Col termine «Sarcopenia» si intende la perdita di massa e di forza muscolare nell'anziano.

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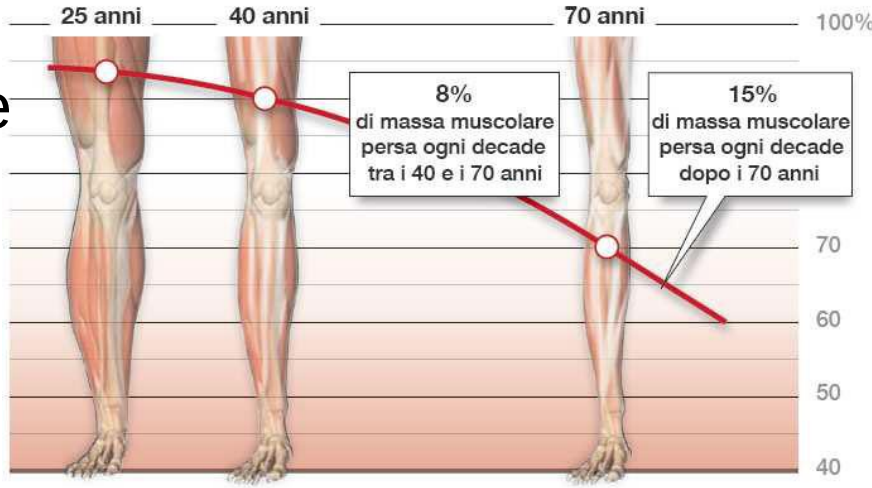
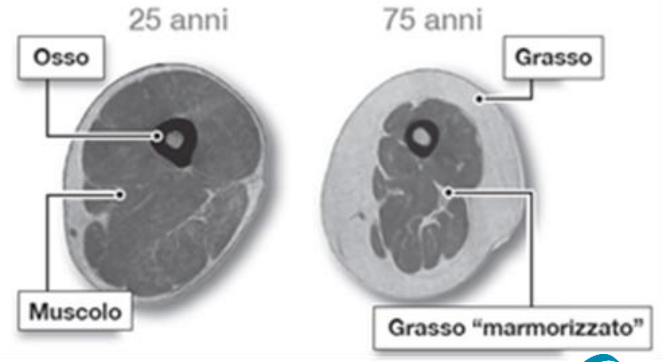
I tratti distintivi della Sarcopenia

- Perdita di massa e forza muscolare
- Aumento di massa grassa
- Alterazione del bilancio tra sintesi e degradazione proteica
- Aumento dello stress ossidativo (ROS)
- Riduzione del *pool* di cellule staminali muscolari



Fonte: Grimby and Saltin, Clinical Physiology, 1983; Janssen, et al., Journal of Applied Physiology, 2000



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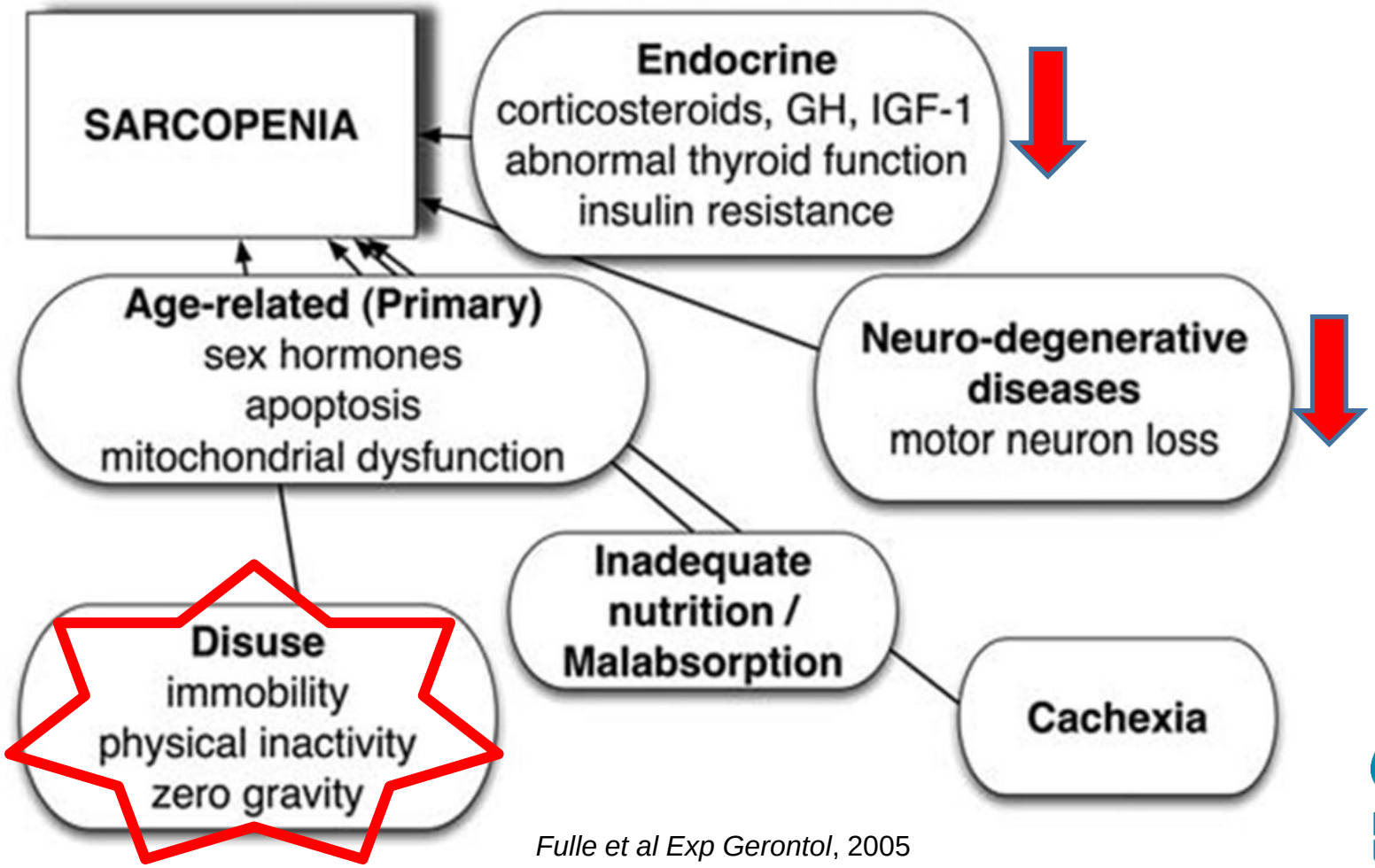
SARCOPENIA

Progressivo declino di massa e forza muscolare



Fulle et al Exp Gerontol, 2005
Pietrangelo et al Exp Gerontol, 2009
Beccafico et al Age, 2011

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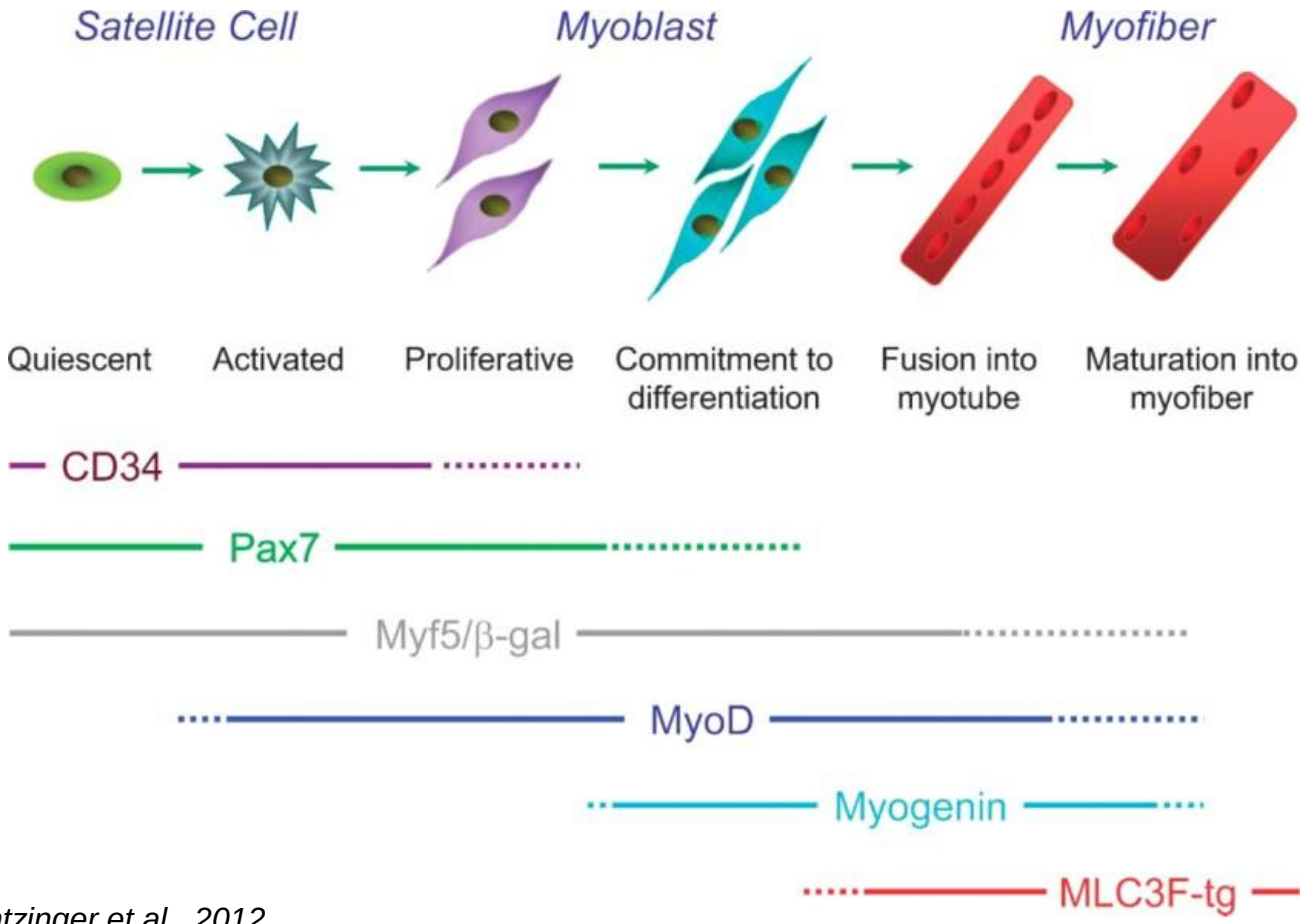
Capacità rigenerativa

CELLULE STAMINALI MUSCOLARI ADULTE: **CELLULE SATELLITI**



Modifiicato da Bentzinger et al., 2012

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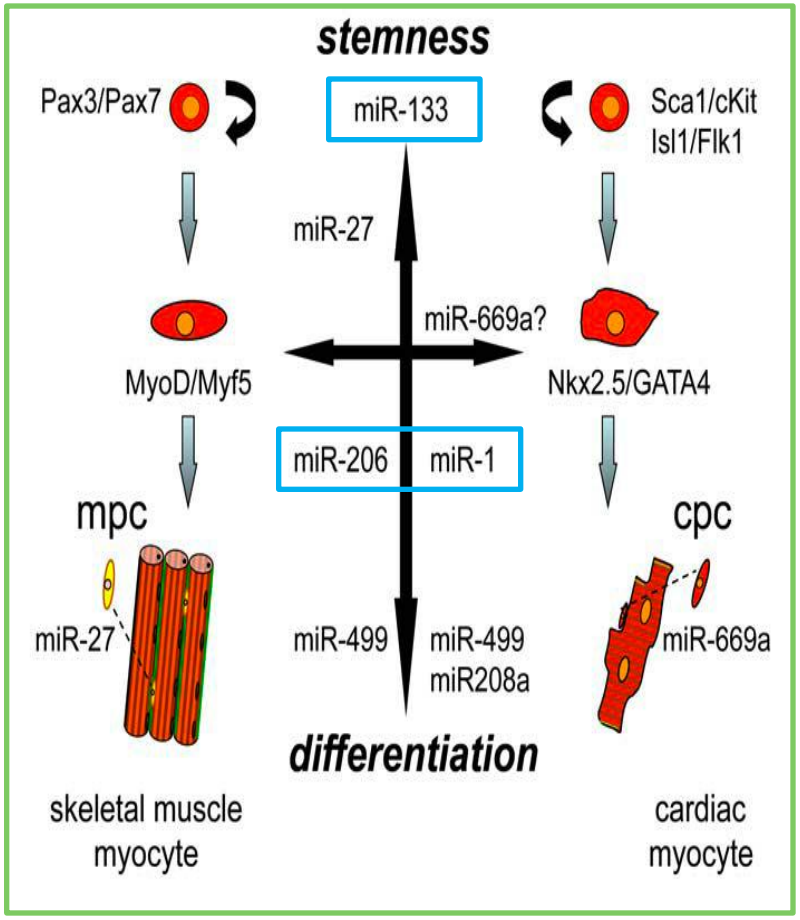
Capacità rigenerativa

CELLULE STAMINALI MUSCOLARI ADULTE: **cellule satelliti**

microRNAs

- Classe di piccoli RNA non codificanti (21-25 nucleotidi)
- Regolano negativamente l'espressione genica a livello post-trascrizionale
- Inducendo la degradazione di specifici RNA messaggeri o impedendone la traduzione in proteina.
- Regolano processi di proliferazione, differenziamento, apoptosi



Crippa et al., 2012 Current Pharmaceutical Design 1718-29

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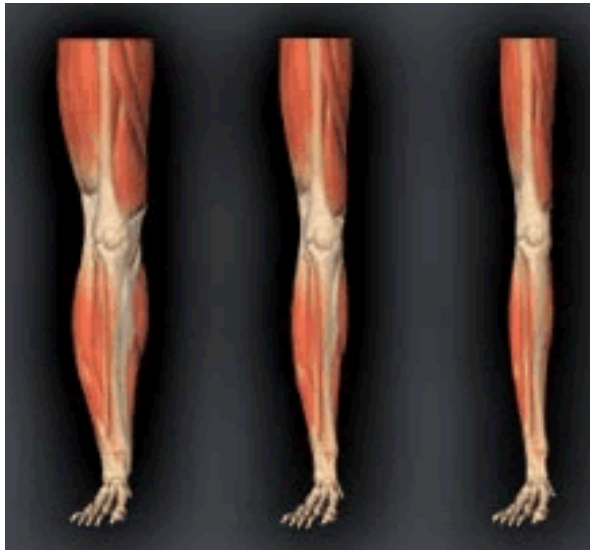
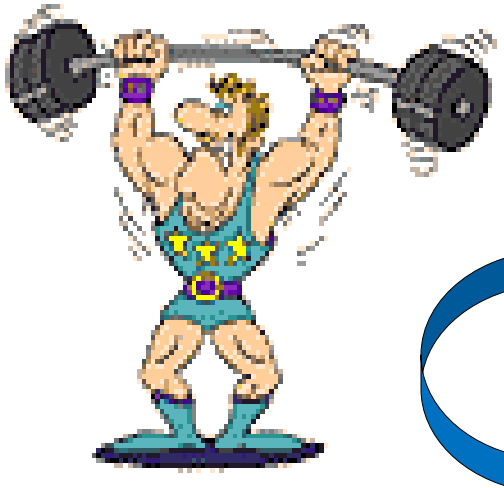
Il mio progetto di ricerca: Nuovi approcci per contrastare la *Sarcopenia*: esosomi e microRNA





SCOPO del PROGETTO: INDIVIDUARE MISURE DI INTERVENTO PREVENTIVO AL DECLINO MUSCOLARE

- Reclutamento degli anziani per allenarli
- saranno monitorati i livelli di antiossidanti che gli anziani assumono con la dieta
- Isolamento delle cellule staminali prima e dopo l'allenamento
- Isolamento degli esosomi rilasciati dalle cellule al fine di individuare *microRNA* coinvolti nel mancato processo di rigenerazione muscolare
- Individuare un allenamento in grado di ridurre i livelli di stress ossidativo sia nelle cellule che nel siero

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- **RALLENTARE IL PROCESSO SARCOPENICO**

Prospettive a lungo termine e possibili applicazioni

- **Lo scopo di questa ricerca finanziata dalla Fondazione Veronesi è quindi quello di studiare la relazione tra ALLENAMENTO FISICO E APPORTO NUTRIZIONALE, per contrastare il declino dannoso che si verifica nel muscolo sarcopenico.**
- **Individuare nuovi signalling molecolari su cui poter intervenire.**
- **Prevenzione per ridurre spese sanitarie dovute alla disabilità-inattività fisica nell'anziano.**
- **Individuare un protocollo di esercizio fisico efficace al fine di programmare una attività fisica individualizzata**

INVECCHIARE si ma IN SALUTE!!!

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Perché è importante sostenere la ricerca scientifica?

- Prevenzione
- Diagnosi precoce
- Farmaci e Terapie

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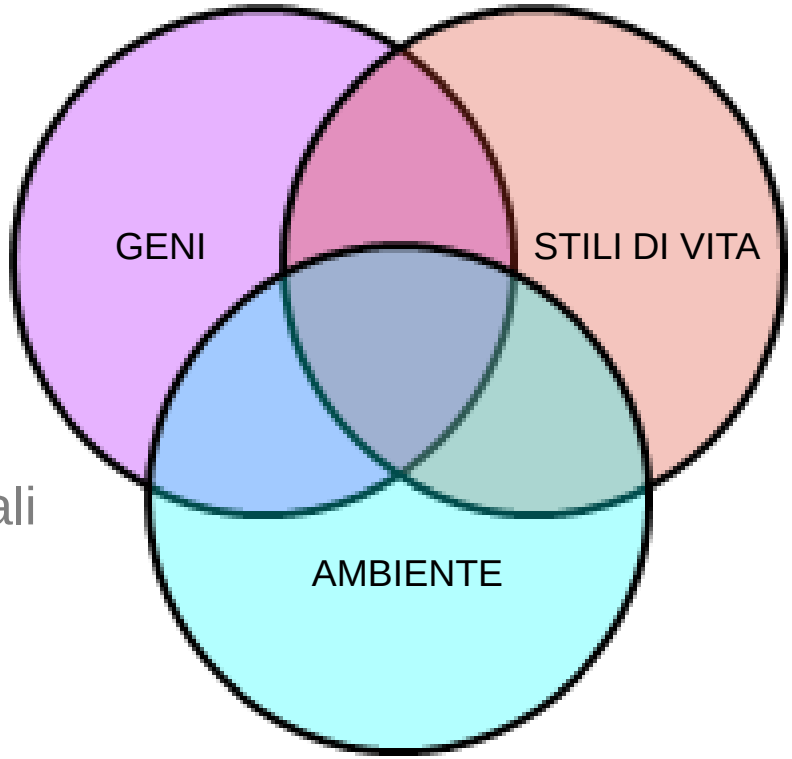
Da cosa dipende la nostra salute?

I fattori di rischio determinano la nostra probabilità di sviluppare una certa malattia

Rischio = fattori genetici x fattori ambientali



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La prevenzione

- Evitare i comportamenti che aumentano il rischio
- Attuare i comportamenti che riducono il rischio

Un'oncia di prevenzione vale quanto una libbra di cure

Benjamin Franklin

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La prevenzione

- **Evitare i comportamenti che aumentano la Sarcopenia**
  Fattori estrinseci o ambientali

Malnutrizione

Scarsa attività fisica

Abuso di farmaci

Un'oncia di prevenzione vale quanto una libbra di cure

Benjamin Franklin

- **Attuare i comportanti che rallentano la Sarcopenia**

Stile di vita sano

Attività fisica

Corretta alimentazione

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Il vostro futuro comincia ora!

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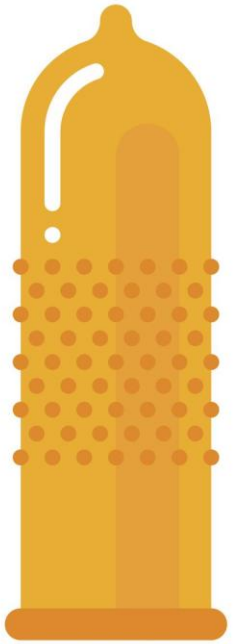
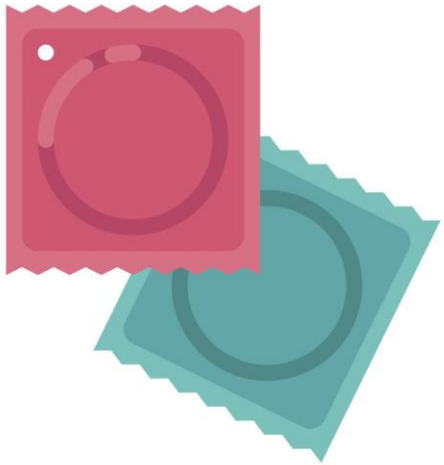
Le malattie sessualmente trasmissibili

Circa 500 milioni di persone al mondo ne sono colpite.
I più esposti sono gli adolescenti e giovani tra i 25 e 35 anni.

Candida, Clamidia, Sifilide, Tricomoniasi, Gonorrea → infezioni e infertilità

Gravi infezioni virali: Epatite B, papilloma virus (HPV), AIDS





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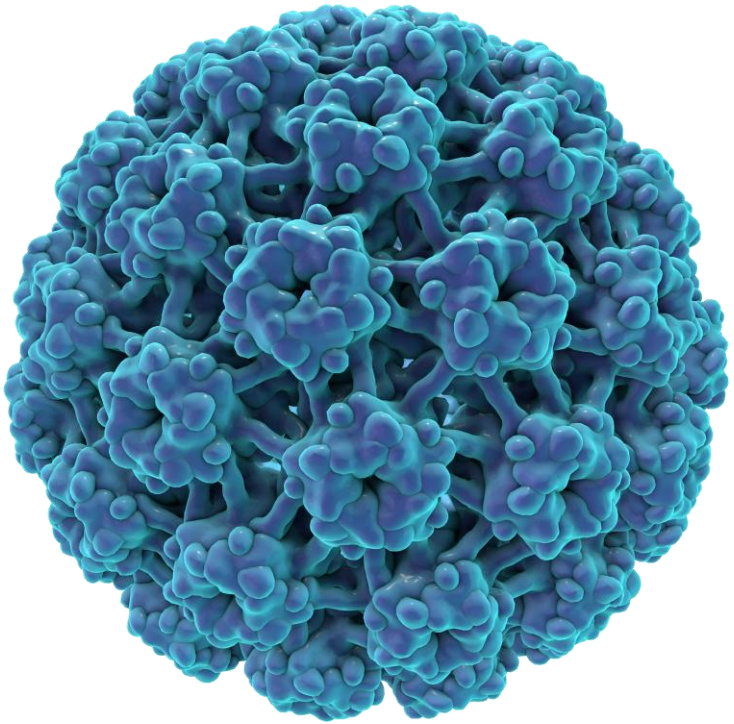
La vaccinazione contro il papillomavirus (HPV)



Ottimo strumento di prevenzione, da associare sempre all'uso del preservativo.

La vaccinazione è fornita gratuitamente dal SSN (Servizio Sanitario Nazionale) alle ragazze di 11 anni.
A partire dal 2017: anche per i ragazzi di 11 anni.

Oggi disponibile un vaccino nonavalente!

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Per concludere…

NON FATE MAI MANCARE NELLA VOSTRA VITA QUESTE 3 SEMPLICI PAROLE

Mettete Passione in tutto quello che fate e la Soddisfazione che proverete sarà così grande da farvi sentire invincibili. Avrete così la forza di affrontare tutte le difficoltà che la vita vi presenterà.

Credete in voi stessi

Impegnatevi per realizzare i vostri sogni

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Ricordate che la RICERCA è il nostro FUTURO, ma VOI SIETE IL FUTURO

Grazie!

Alla Fondazione Umberto Veronesi

Università degli Studi
"G. d'Annunzio" Chieti-Pescara

Laboratorio di
Fisiologia Cellulare

Tutor: Prof.ssa Fulle Stefania

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