JOURNAL OF BONE AND MINERAL RESEARCH
Volume 21, Number 10, 2006
Published online on July 17, 2006; doi: 10.1359/JBMR.060715

Fracture Incidence and Characterization in Patients on Osteoporosis Treatment: The ICARO Study

Silvano Adami,[1] Giancarlo Isaia,[2] Giovanni Luisetto,[3] Salvatore Minisola,[4] Luigi Sinigaglia,[5] Raffaella Gentilella,[6] Donato Agnusdei,[7] Nicoletta Iori,[6] and Ranuccio Nuti,[8] on behalf of ICARO Study Group

ABSTRACT: None of the available osteoporosis therapies have been shown to completely abolish the risk of fractures. In clinical practice, the outcome may be even poorer. In 880 patients prescribed with antiresorptives (alendronate, risedronate, and raloxifene) for >1 year, a fragility fracture was recorded in 8.9%/year of them. This incidence is considerably higher than that observed in randomized clinical trials, and it was significantly related to poor compliance and lack of supplementation with calcium and vitamin D.

Introduction: Osteoporotic fracture is one of the most important public health concerns among the elderly. Currently available therapies have been shown to significantly decrease the risk of fracture, although none of them completely abolishes this risk. In clinical practice, poor treatment response may also result from a number of other factors.
Materials and Methods: The Incidence and ChAracterization of inadequate clinical Responders in Osteoporosis (ICARO) is a multicenter, observational study carried out in Italy. It aimed to analyze, in postmenopausal women with established osteoporosis, the risk factors for an "inadequate clinical response" to drug therapy, defined as the occurrence of new vertebral or nonvertebral fragility fractures in patients prescribed, for at least 1 year, alendronate, risedronate, or raloxifene, with a compliance >50%.
Results: In 880 patients treated with antiresorptive agents for a median of 2.0 years (95% CI: 1.0–4.5) years, the "inadequate clinical responder (ICR)" subjects over the observation period were 220 (25%), with an annual incidence of 8.9%. ICRs, compared with "adequate clinical responders (ACRs)," had more pretreatment fractures and were treated longer (2.8 versus 1.8 years; $p < 0.001$). After multiple adjustment for these confounding factors, significant determinants of inadequate clinical response were a poorer treatment compliance and a less frequent co-administration of calcium and vitamin D supplements.
Conclusions: The incidence of fractures during treatment with antiresorptive agents in a clinical setting is considerably higher than that observed in randomized clinical trials. Inadequate compliance to treatment and lack of supplementation of calcium and vitamin D are major determinants of this poor response.
J Bone Miner Res 2006;21:1565–1570. Published online on July 17, 2006; doi: 10.1359/JBMR.060715

Key words: osteoporosis, treatment resistance, fracture risk, treatment compliance, calcium and vitamin D intake

INTRODUCTION

OSTEOPOROTIC FRACTURES REMAIN a major public health problem, causing substantial morbidity and mortality.[1,2] The primary aims of therapeutic intervention in osteoporosis are to prevent the first fragility fracture and to avoid subsequent fractures in those patients who already sustained a fracture. There is strong evidence from randomized controlled trials (RCTs) for the efficacy of currently available therapies in reducing the risk of fracture in patients with osteoporosis.[3] However, none of the currently available medications completely abolish the risk of fracture, and clinical trials have shown that a significant proportion of patients with existing fractures will sustain new fractures in a relatively short period while on treatment.[4–10]

To date, there is no consensus on what constitutes nonresponse or an inadequate clinical response to therapy in the individual patient. Changes in BMD have been used in clinical practice as a surrogate marker of response to osteoporosis drug therapy, and definitions of inadequate response based on BMD have been proposed.[11] However, changes in BMD vary considerably between individuals, and there is only a weak correlation between changes in BMD and fracture rate.[12,13]

Drs Agnusdei and Gentilella are employees and own stock in Eli Lilly & Co. Dr Lori is an employee of Astra Tech, Italy. All other authors state that they have no conflicts of interest.

[1]Rheumathology Department, University of Verona, Valeggio Sul Mincio Hospital (VR, Verona, Italy); [2]Internal Medicine Department, University of Turin, Turin, Italy; [3]Endocrinology Department, University Hospital of Padova, Padua, Italy; [4]Clinical Sciences Department, "La Sapienza" University, Rome, Italy; [5]Orthopedic Institute "G.Pini," Milan, Italy; [6]Eli-Lilly Italia S.p.A., Florence, Italy; [7]Eli-Lilly & Company, Siena, Italy; [8]Internal Medicine Department, University of Siena, "Le Scotte" Hospital, Siena, Italy.

The occurrence of a fragility fracture while on therapy is a key indicator of poor response to treatment, although its predictive power remains questionable because pharmacological treatment never abolishes the fracture risk in individual patients. The relative risk (RR) reduction of sustaining new fractures while on therapy is ~50% for most RCTs. However, fracture incidence in the active treatment arms of the pivotal osteoporosis drug trials may fluctuate from 2.1% to 18.1% over 3–5 years according to the severity of the disease.[4–9,14] Poor treatment response may result from a number of other factors,[11] usually controlled in RCTs but frequently encountered in daily clinical practice.

Observational studies examine outcomes of treatment in clinical practice and are useful for determining how outcomes vary with patient characteristics and environment. The Incidence and Characterization of inadequate clinical Responders in Osteoporosis (ICARO) is the first study designed to analyze, in postmenopausal women with established osteoporosis and in a naturalistic setting, the risk factors for an inadequate clinical response to osteoporosis drug therapy, defined as the occurrence of a new fragility fracture while on treatment.

MATERIALS AND METHODS

Study design

ICARO is a multicenter, observational study carried out in 55 centers for the management of osteoporosis, evenly distributed over the Italian territory. The main aim of the study is the evaluation of incidence and risk factors for inadequate clinical response in osteoporotic patients prescribed with antiresorptive drugs (alendronate, risedronate, raloxifene) for at least 1 year. The "inadequate clinical response" (ICR) as opposed to "adequate clinical response" (ACR) is defined as the occurrence of X-rays evident of new vertebral or nonvertebral fragility fractures at least 6 months after initiation of the antiresorptive therapy.

Recruitment started in November 2002 and was completed in November 2003. The study was submitted to local ethics committees according with the Italian legislation as an "observational study" (i.e., the patients were not asked to undergo any type of examinations exceeding those routinely performed in each center). All patients gave informed consent for the provision and collection of data regarding care and outcomes for a period of at least 1 year. Investigators were asked to screen for study entry consecutive postmenopausal women referred to the center for a scheduled visit. Here we report the results of the retrospective phase of the study. A prospective phase of the same cohort of patients is currently ongoing.

The inclusion criteria were as follows:

1. Patients who had being prescribed for at least 1 year, but <5 years, with one of the antiresorptive therapies available for the treatment of postmenopausal osteoporosis at the time of recruitment (i.e., alendronate, risedronate, and raloxifene).
2. Patients with a history of one or more vertebral deformities (radiologically documented) and/or hip fracture at the time of prescription. This identifies eligibility to full reimbursement for osteoporosis treatment according to Italian rules (Nota 79).[15]
3. Patients who did not discontinue treatment or with a treatment compliance > 50% (i.e., the patients took >50% of the prescribed doses; patients switching from one to another of the three reference treatments were also included.
4. Patients currently not treated with an investigational drug or procedure.

The exclusion criteria were as follows:

1. Age < 21 years.
2. Patients on corticosteroid therapy for >6 months at the time of recruitment.

Data were collected on data collection forms (DCFs) reporting patient demographics, medical and osteoporosis history, risk factors for osteoporosis, medication use, disease status, and health-related quality of life (data not shown). In 64% of the cases, the recruitment visit coincided with the second visit at the osteoporosis out-patient clinics, and in the remaining cases, this was the third visit. The time lag considered for treatment duration at enrollment was that elapsed since the first visit at the osteoporosis center.

Although not required, in 91% of the patients, a new spine X-ray was taken at the time of recruitment. Previous fractures after age 40 were distinguished between those occurred before treatment, making the patients eligible to "Nota 79," and those occurred during treatment. For all fractures, the following information was recorded: site, type of trauma (if any), radiographic ascertainment, severity of associated symptoms, and hospitalization. The history of the fractures that led to the application for the "Nota 79" was accurate for the legal requirement. Most vertebral fractures in ICRs were diagnosed by the presence of severe and long-lasting back pain, confirmed by X-rays. In ICRs, X-rays coincided with the recruitment time (i.e., the patients came into the center for the occurrence or worsening of back pain and were recruited in the study). Spine X-rays were also obtained in patients complaining of moderate back pain, but none of them were totally asymptomatic.

The occurrence of incident vertebral fracture was not adjudicated by any central reviewer of X-ray data. New vertebral fractures were identified per protocol according to the guidelines included in the "Nota 79"[15] (i.e., a decrease in vertebral height at any level >4 mm or >15%). It should be pointed out that, because the time that elapsed from the initial spine X-ray that made the patients eligible for "Nota 79" and initiation of antiresorptive therapy ranged from 1 to 29 months (Table 1, disease duration minus treatment duration), we cannot rule out that some patients may have been classified ICR as a consequence of a worsening of a previous vertebral deformity rather than for new fractures.

At enrollment, details of previous osteoporosis medications were type of treatment, switching among therapies, level of compliance (categorized as 50–75% and >75%), and addition of calcium and vitamin D (500–1000 mg cal-

TABLE 1. BASELINE CHARACTERISTICS OF STUDY POPULATION

	All patients (N = 880)	*ICRs (N = 220)*	*ACRs (N = 660)*	*ACRs vs. ICRs p*
Age (years)	68 (53–79)	69 (52–79)	67 (53–79)	NS
Body mass index (kg/m^2)	25.2 (19.5–33.3)	25.3 (19.2–35.2)	25.1 (19.5–32.8)	NS
Disease duration (years)*	2.8 (1.1–1.2)	3.8 (1.1–12.8)	2.6 (1.1–10.3)	<0.001
Treatment duration (years)†	2.0 (1.0–4.5)	2.8 (1.1–4.7)	1.8 (1.0–4.4)	<0.001
Prevalent fractures:				
1 vertebral	366 (41.6%)	66 (30.0%)	300 (45.4%)	<0.001
>1 vertebral	415 (47.1%)	121 (55.0%)	294 (44.5%)	<0.001
Hip	40 (4.5%)	9 (4.1%)	31 (4.7%)	<0.001
Vertebral + nonvertebral	59 (6.7%)	24 (10.9%)	35 (5.3%)	<0.001
Prevalent traumatic fractures	95 (10.8%)	26 (11.8%)	69 (10.4%)	NS
Treatment distribution:				NS
Alendronate	468 (53.2%)	128 (58.2%)	340 (51.5%)	
Risedronate	139 (15.8%)	19 (8.6%)	120 (18.2%)	
Raloxifene	99 (11.2%)	17 (7.7%)	82 (12.4%)	
Mixture	174 (19.8%)	56 (25.4%)	118 (17.9%)	
Co-administration of calcium and vitamin D				
No	332 (37.7%)	100 (45.5%)	232 (35.2%)	0.02
Yes, compliance < 50%	109 (12.4%)	22 (10.0%)	87 (13.2%)	
Yes, compliance > 50%	439 (49.9%)	98 (44.5%)	341 (51.7%)	
Compliance to treatment:				
50–75%	55 (6.2%)	21 (9.5%)	34 (5.1%)	0.004
>75%	748 (85.0%)	174 (79.1%)	574 (87.0%)	
Not determined	77 (8.7%)	25 (11.4%)	52 (7.9%)	

Values are expressed as median (95% CI) or absolute numbers (%).
* Time elapsed since the first diagnosis of established osteoporosis.
† Time on treatment with antiresorptive drugs of "Nota 79."

cium and 400–800 IU of vitamin D). This latter information was carefully collected by a specific questionnaire. The patients who had been taking supplements of calcium and vitamin D were further categorized for a compliance lower or higher than 50%.

Analysis

Patients were excluded from the analysis if they did not meet the inclusion criteria or if the DCFs did not include data on demographics, osteoporosis treatment, and previous fractures.

All data management and analysis was centralized and conducted according to a prespecified plan by an independent clinical research organization (MediData, Modena, Italy). Descriptive summary statistics such as frequencies, percentages, means, and SDs were used to describe the study population at baseline and for ICRs and ACRs, respectively. Comparisons between the two cohorts were made using *t*-tests for continuous data. Logistic regression analysis was used to calculate the RR for ICRs. χ^2 tests were used for categorical data. p values <0.003 were considered statistically significant, giving an overall significance level of 0.10 across all tests . Analyses were carried out using SAS software version 8.2.

RESULTS

Characteristics of the study population are reported in Table 1. Of the original cohort of 1421 patients, 302 did not meet the eligible criteria, and 239 patients were excluded because important predefined data were missing. The population analyzed in this study is made up of 880 postmenopausal women. Twenty-five percent ($n = 220$) were defined as ICRs according to the definition previously reported. In this subset, there were 35% of patients with a single vertebral fracture, and 60% with more than one vertebral fracture recorded as new or worsening of previous fractures. All incident vertebral fractures should be defined as "clinical" fractures, even though in 12 cases, the detection of a new vertebral deformity was associated with only moderate and chronic back pain. Only 5% of ICRs presented other osteoporotic fractures (data not shown). Both cohorts of ACRs and ICRs were comparable for age, body mass index (BMI), and type of osteoporosis treatment.

Alendronate was the most frequently prescribed drug (53.2%), followed by a mixture of the three (19.8%), risedronate (15.8%), and raloxifene (11.2%). ICRs and ACRs were significantly different for (1) a more severe disease at the time of prescription of the osteoporosis treatment, with a greater proportion of patients with more than one vertebral deformity; (2) osteoporosis treatment duration (2.79 versus 2.14 years; $p < 0.001$); (3) worse treatment compliance; and (4) less frequent intake of calcium and vitamin D supplements.

Logistic regression analysis results are reported in Table 2. When data were adjusted for the duration of treatment, significant predictors of inadequate clinical response to treatment included poor compliance (RR = 1.68 for compliance 50–75% versus >75%) and number of pretreatment vertebral fractures (RR = 6.21 for more than two prevalent

Table 2. Logistic Regression Analysis for Relative Risk of Inadequate Clinical Response to Treatment

	RR	*95% CI*
Treatment duration (1 year)	1.68	1.46–1.93
Compliance (50–75% vs. >75%)	1.66	1.08–2.54
Supplements of calcium + vitamin D		
(NO vs. YES compliance > 50%)	1.98	1.38–2.83
(NO vs. YES compliance < 50%)	1.14	0.68–1.91
Prevalent vertebral fracture (>2 vs. 1)	6.21	3.09–12.5
Prevalent vertebral fractures (>1 vs. 1)	2.00	1.69–2.77

The model include only the variable that remained significant after adjustment for the duration of treatment.

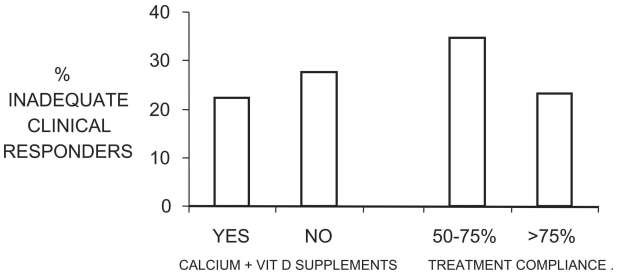

FIG. 1. Proportion of ICRs in relationship with the co-administration of calcium and vitamin D supplements to antiresorptive therapy (compliance level > 50%) and to a compliance to antiresorbers of 50–75% and >75%.

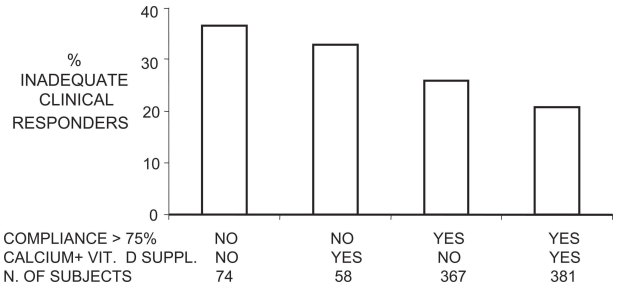

FIG. 2. Incidence of inadequate clinical response in patients with all possible combinations of treatment compliance and intake of calcium and vitamin D supplements > 50% compared with no or inadequate supplementation.

vertebral fractures; RR = 2.00 for more than one prevalent vertebral fracture). In patients taking no calcium and vitamin D supplements, the risk of ICR was increased by 98% versus patients taking the supplements with good (>50%) compliance ($p < 0.001$) and by a nonsignificant 14% versus patients taking supplements with low (<50%) compliance (Table 2).

More patients in the ICR group switched treatment (Table1). Actually, the occurrence of a fracture while on treatment was the cause for changing treatment in one fourth of the cases, but it never led to discontinuation of any antiresorptive therapy. Treatment type was not associated with differences in the risk o5f inadequate response when the data were adjusted for the duration of treatment and the baseline severity of the disease.

The distribution of ICRs according to the compliance level to antiresorptives and the intake of calcium + vitamin D supplements (compliance > 50%) is shown in Fig. 1. The proportion of patients taking calcium and vitamin D supplements with adequate compliance were significantly higher ($p < 0.05$) among compliants (>75%) to antiresorptive (50.9%) than among poor compliants to antiresorbers (34.5%; data not shown). Poor compliance and no intake of calcium and vitamin D supplements were the major determinants of inadequate clinical response to treatment. Figure 2 shows the proportion of ICRs when both parameters were considered in their different combinations. From this analysis, the proportion of ICRs was 36.5% among patients with poor compliance and not taking supplements and 20.7% in patients both compliant and taking supplements regularly (>50%).

DISCUSSION

Osteoporotic fracture is one of the most important public health concerns among the elderly. Available therapies have shown to significantly decrease the risk of fracture and its related morbidity, particularly in women with postmenopausal osteoporosis,[3] but at present, no osteoporosis drug therapy completely abolishes this risk. Both incidence and underlying causes of this inadequate clinical response have not been properly studied.

Here we report the prevalence of fragility fractures in patients prescribed for at least 1 year with alendronate, risedronate, and raloxifene. The proportion of inadequate clinical responders was 25% over an average period of treatment of 2.3 ± 1.15 years. This proportion is considerably greater than that observed in the active arm of any previous RCT for antiresorptives agents, where patients not responding to treatment ranged from 2.1% to 18.1% over 3 years.[4–10,14] There are several explanations for the significant number of ICRs reported in our study. First of all, in this study, only patients with a compliance >50% and those who did not discontinue therapy were enrolled; therefore, our setting is closer to a "per-protocol" than to an "intention to treat" analysis, as reported in RCTs. Because immediate pretreatment X-rays were not available for all patients, an unidentified number of ICRs had possibly worsened from previous deformities rather than being new vertebral fractures. Furthermore, our study population was made up of patients registered for osteoporosis treatment reimbursement according to "Nota 79," which requires the presence of at least one atraumatic severe vertebral or hip fracture. Our cohort was somewhat age matched with patients enrolled in the major RCTs performed using antiresorptives; however, osteoporosis was significantly more severe in our patients compared with the RCT population.[4–7,14] This could be responsible for the switching through different antiresorptives in a large proportion of the ICRs. Unlike RCTS, the average compliance in routine setting is considerably poorer, when different compliance levels are considered. In RCTs, the investigators tend to exclude patients with co-morbidity or with numerous associated therapies to limit the number of trial withdrawals. In our study,

65% of the patients were taking one or more other pharmacological therapies and had several other diseases such as respiratory, heart, liver, and renal conditions (data not shown), all potentially related to an increased risk of fracture. An obvious limitation of the retrospective design of the study is the inclusion only of patients who did return for a follow-up visit. The direction of the bias (if any) associated with this patient selection remains uncertain.

For the first time in our study, we were able to investigate the conditions associated with an inadequate clinical response. The ICRs had a more severe form of osteoporosis, as documented by the number of fractures that led to osteoporosis treatment. The risk of inadequate response was 6.2-fold higher in patients with three or more prevalent vertebral fractures than in patients with one vertebral deformity. This finding was expected, and it has been consistently reported also during pivotal RCTs. In the FIT trial with alendronate, the proportion of patients who sustained a vertebral fracture in the active arm was 5.2% in patients with one prevalent vertebral fracture and 12.8% and 16.3% in women with two or three to four prevalent vertebral deformities, respectively.[16] In the MORE study, patients with prevalent severe vertebral deformities sustained more frequently new vertebral fractures in both placebo and active arms than patients with prevalent mild deformities.[17]

Furthermore, we were able to measure the impact of compliance and calcium and vitamin D supplements to inadequate clinical response to treatment.

The importance of treatment compliance has been addressed by other studies. Rates of noncompliance with osteoporosis therapy were found as high as 50% among women with osteoporosis, limiting the effectiveness of treatment.[18,19] In a study of 11,248 women with osteoporosis in clinical practice, 51% were poorly compliant with osteoporosis medication, and these patients had a 16% greater risk of fracture than patients who were compliant with therapy.[20] In all these studies, the range of compliance was wider, including also patients who discontinued treatment. In our study, we observed that even lowering compliance from 75% to 50–75% increased the risk of inadequate clinical response by 66%.

In all pivotal RCTs, randomized patients were vitamin D repleted, and calcium and vitamin D supplements were given to both placebo and active arms. The antifracture efficacy of the tested drugs cannot be guaranteed in different settings. From a survey done in most of the centers participating in our study, 25-hydroxyvitamin D levels were seldom measured (data not shown), despite that vitamin D deficiency is extremely frequent in all Italian regions.[21,22] It is likely that a large proportion of the patients included in this study were somewhat vitamin D deficient at the time of treatment initiation. Calcium and vitamin D supplements were taken by only one half of the patients. We observed that, in those who took the supplements correctly, the rate of inadequate clinical response to treatment decreased by 98% versus those who did not take any supplement. This seems to explain a large proportion of ICRs observed in this study compared with those reported in the active arms of RCTs with alendronate, risedronate, and raloxifene.

In conclusion, in our study, we, for the first time, assessed the incidence of new fractures in patients prescribed antiresorptive agents for at least 1 year. The incidence of ICR was ~8.9% per year, considerably higher than that observed in the active arm of all previous pivotal RCTs. This was likely explained by the higher disease severity and the more frequent co-morbidity reported in this cohort of patients. Our results emphasize the importance of full compliance to treatment and of adequate supplementation of calcium and vitamin D that, together, may double the risk of inadequate clinical response to osteoporosis treatment.

ACKNOWLEDGMENTS

This study was supported by an unlimited grant from Eli-Lilly Italia. Data collection and statistical analysis was carried out by Medidata (Modena, Italy) under the supervision of SA.

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Address reprint requests to:
Raffaella Gentilella, MD
Eli-Lilly Italia
Via A.Gramsci 731
50019 Sesto Fiorentino, Florence, Italy
E-mail: gentilella_raffaella@lilly.com

Received in original form January 9, 2006; revised form June 7, 2006; accepted July 12, 2006.

APPENDIX: CENTERS WHO PARTICIPATED IN THE STUDY (IN ALPHABETICAL ORDER)

Carlina Albanese, MD, Policlinico Universitario Umberto I, Roma; Marco Antonelli, MD, Ospedale San Camillo Forlanini, Roma; Annamaria Aversa, MD, Ospedale S.Carlo Borromeo, Milano; Cataldo Bancheri, MD, Ospedale Sandro Pertini, Roma; Mario Barbagallo, MD, Policlinico Universitario, Palermo; Alfredo Bardoscia, Fondazione Maugeri, Cassano Murge (BA); Pietro Bertoni, MD, Policlinico San Marco, Mestre (VE); Gerolamo Bianchi, MD, Ospedale La Colletta, Arenzano (GE); Mario Biondi, MD, Ospedale Morgagni Pierantoni, Forlì; Maria Luisa Brandi, MD, Policlinico Universitario Careggi, Firenze; Michele Calitro, MD, Ospedale Civile Caduti in Guerra, Canosa (BA); Rosario Cangelosi, MD, Ospedale San Biagio, Marsala (TP); Francesco Paolo Cantatore, MD, Ospedale Riuniti, Foggia; Giuliano Cenci, MD, Ospedale Santa Croce, Fano (Pesaro Urbino); Antonio Cianci, MD, Ospedale Ferrarotto S. Bambino, Catania; Giovanni Coppi, MD, Ospedale San Camillo Forlanini, Roma; Luca Dalle Carbonare, MD, Policlinico Universitario, Padova; Massimo D'Amore, MD, DIMIMP Università degli studi di Bari, Bari; Giovanni D'Avola, MD, Servizio Reumatologia ed Osteoporosi AUSL 3, Catania; Roberto De Candia, MD, Ospedale Civile San Bortolo, Vicenza; Antonio Del Puente, MD, Policlinico Universitario "Federico II", Napoli; Pier Giorgio Delvino, MD, Ospedale Sant'Andrea, Vercelli; Alessandro Di Felice, MD, Ospedale Civile Renzetti, Lanciano (CH); Paolo Filipponi, MD, Ospedale Civile, Umbertide (PG); Carmelo Erio Fiore, MD, Ospedale Garibaldi, Catania; Cristiano Maria Francucci, MD, Ospedale Umberto I, Ancona; Bruno Frediani, MD, Policlinico Universitario "Le Scotte", Siena; Nicola Frisina, MD, Policlinico Universitario, Messina; Beatrice Fruttero, MD, Ospedale SS Annunziata, Savigliano (CN); Raffaele Ghirardi, MD, Ospedale C. Poma, Pieve di Coriano (MN); Diego Giuntini, MD, Ospedale Riuniti, Trieste; Andrea Giustina, MD, Spedali Civili, Brescia; Giovanni Lentini, MD, Ospedale Buccheri La Ferla, Palermo; Vincenzo Lo Cascio, MD, Policlinico Universitario "G.B. Rossi", Verona; Vittorio Lucchese, MD, Ospedale Estense, Modena; Augusto Manzara, MD, Ospedale Villa Scassi, Genova; Antonia Matina, MD, Policlinico Universitario, Palermo; Domenico Maugeri, MD, Ospedale Cannizzaro, Catania; Quirico Mela, MD, Policlinico Universitario, Monserrato (CA); Alfredo Nardi, MD, Ospedale S. Maria della Misericordia, Rovigo; Rita Occhipinti, MD, Ospedale Civile, Belluno; Giangiacomo Osella, MD, Ospedale S.Luigi Gonzaga, Orbassano (TO); Giuseppe Perpignano, MD, Policlinico Universitario, Monserrato (CA); Eustacchio Pisciotta, MD, Ospedale Civile Tinchi, Pisticci (MT); Giuseppe Quattrocchi, MD, Centro Riabilitazione Mandalari, Messina; Giovambattista Rini, MD, Policlinico Universitario, Palermo; Maurizio Rossini, MD, Policlinico Universitario, Verona; Stefano Savoca, MD, Ospedale Ascoli Tomaselli, Catania; Ferdinando Silveri, MD, Università Politecnica delle Marche, Jesi (AN); Giuseppe Termini, MD, Policlinico Universitario, Palermo.