



Sex Differences in Characteristics and Management of Patients with Acute Heart Failure

Paolo Biagi^{1,*}, Valerio Verdiani², Grazia Panigada³, Vieri Vannucchi⁴, Luca Masotti⁴, Alberto Fortini⁵

¹Department of Internal Medicine, Montepulciano Hospital, Siena, Italy

²Department of Internal Medicine, Misericordia Hospital, Grosseto, Italy

³Department of Internal Medicine, SS Damiano and Cosma Hospital, Pescia, Italy

⁴Department of Internal Medicine, Santa Maria Nuova Hospital, Florence, Italy

⁵Department of Internal Medicine, San Giovanni di Dio Hospital, Florence, Italy

Email address:

chipama@libero.it (P. Biagi)

*Corresponding author

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Abstract: Burden of heart failure (HF) among females is growing. However, whether characteristics and management of acute HF differ according to sex is unknown. Therefore, the aim of the present study was to provide information about this concern from a real life perspective. Data from the Scompenso Cardiaco in Medicina Interna in Toscana (SMIT) Study, an observational, retrospective, multicenter 30-day cross-sectional study performed in thirty-two Internal Medicine wards of Tuscany, Italy, were analyzed. The present sub-analysis focused on the difference between female and male patients. Overall, seven hundred and seventy patients were enrolled in the SMIT Study. Of these, four hundred and twenty-nine (55.7%) were females. Females were significantly older than males. Seventy-two women (16.7%) and forty-eight men (14%) presented a new onset HF, whereas the majority of patients presented at least one previous hospital admission for HF in their history. No difference in length of hospital stay and mortality was found between sexes. Hypertensive (26.8% vs 19.8%, $p = 0.02$) and valvular (13.6% vs 8.6%, $p = 0.03$) were the more prevalent etiologies of HF in females, while ischemic heart disease was in males (25.8% vs 18.2%, $p = 0.01$). HF with a preserved left ventricle ejection fraction (LVEF) was significantly more prevalent in females compared to males (51.3% vs 32.6%, $p = 0.0001$). Chronic obstructive pulmonary disease (COPD), peripheral artery diseases (PAD) and severe anemia were more frequent in males, while cognitive impairment was in females. Mean creatinine clearance at hospital admission was lower in females than in males (44.4 ± 22.2 vs 49.4 ± 26.3 ml/min, $p < 0.05$). Females received more frequently non invasive ventilation compared to males (15.1% vs 9.1%, $p = 0.011$). No difference between sexes was registered in the use of diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta blockers and digoxin, whereas the use of anti-aldosterone agents, ivabradine and statins were more frequently used in males. No difference between sexes was found in the median number of drugs prescribed at hospital discharge [8 (interquartile range, IQR, 6-11) vs 9 (IQR 7-11)]. Eighty-two percent of females and seventy-nine percent of males were discharged at home ($p = ns$). Fifty-six percent of females compared with forty percent of males were dependent in activities of daily living at hospital discharge ($p = 0.0001$). The present study demonstrates that demographic characteristics, etiology, co-morbidity and echocardiographic pattern of HF differ according to sex. Further prospective study are warranted.

Keywords: Heart Failure, Gender, Management, Prognosis, Drugs

1. Background

The prevalence of heart failure (HF) increases steadily with age, reaching 10% among people 65 years old and older [1, 2]. This burden is consequence of the increased life expectancy of patients with cardiovascular diseases, particularly those suffering for coronary artery disease and blood arterial hypertension [2].

HF represents the leading cause of hospital admissions burdening for approximately 20% of all in-hospital admissions, prolonged length of hospital stay (LOS) and hospital re-admissions among the elderly [3]. Therefore, it's not surprising that HF results is one of the most expensive chronic diseases among adult populations in developed countries. In the United States, Canada and Europe, its economic burden amounts for approximately 2% of healthcare resources and hospitalizations encompass for about 60% of these [4, 5].

People suffering for HF represent a heterogeneous population with several differences in terms of etiology, clinical features and outcome. Nearly one half of patients with HF are females and emerging epidemiologic data show a growing burden of this disease among females [6]. Enrollment of women in main HF trials was less than 30%, but in the largest registry of patients hospitalized for decompensated HF women were 52% [7, 8]. Nevertheless, HF remains an overlooked syndrome in females with some important differences from males. Several epidemiological studies showed that females with HF present a better outcome, with a mortality risk 15-20% lower than males [9]. However, data on different management of HF patients in real life according to sex lack. Therefore, the aim of our study was to provide information about this concern.

2. Materials and Methods

We retrospectively analyzed data from the Scopenso Cardiaco in Medicina Interna in Toscana (SMIT) study, an observational, retrospective, multicenter 30-day cross-sectional study performed in thirty-two Internal Medicine wards of Tuscany, Italy, over one month, from 2014 January 30 to February 28. The aim of the SMIT Study was to analyze the epidemiological and clinical data of patients discharged with diagnosis of HF in Tuscany. Details of design and main results of the SMIT Study were previously reported [10]. The study was approved by the local ethic committees of the participating centers. An informed consent was achieved for each patient.

The present sub-analysis focused on the difference between female and male patients. Diagnosis of HF was performed by clinical, instrumental and laboratory data according to the 2013 American College of Cardiology / American Heart Association guidelines for the management of HF [11]. HF was defined as worsening chronic HF associated with a reduced ($\leq 50\%$) or preserved ($> 50\%$) left ventricle ejection fraction (LVEF) or "new onset HF" when a

previous diagnosis of HF was absent.

For statistical analysis, normally distributed quantitative variables were expressed as means \pm standard deviations (SD). Categorical variables were presented as frequencies (percentage). Asymmetrically distributed variables were expressed as medians and interquartile ranges (IQR). In the statistical analysis, categorical variables were compared by using the Fisher's exact test, whereas continuous data were compared by using t test of Student. A p value < 0.05 was considered statistically significant. Statistical analyses were carried out using SAS software (version 9.1, SAS Institute, Cary, NC, USA).

3. Results

The general characteristics of patients are summarized in Table 1.

Table 1. General characteristics of patients.

	Males	Females	p
Number	341 (44.3%)	429 (55.7%)	
Mean age \pm SD (years)	80.8 \pm 8.8	83.4 \pm 8.1	0.001
Age over 70 years	89.1%	93.7%	0.05
Age over 80 years	58.3%	71.5%	0.0001
Age over 90 years	10.8%	19.3%	0.001
In-hospital mortality	7.0%	4.8%	0.2
Median LOS (IQR)	7 (5-10)	7 (5-11)	ns
New onset HF	13.2%	17.9%	ns
Exacerbation of chronic HF	86.8%	82.1%	ns
NYHA class III-IV	83.2%	84.2%	ns
Hospitalization in the last month	24.6%	20.0%	ns
Hospitalization in the last year	55%	46%	0.01
Mean heartrate \pm SD (bpm)	76.01 \pm 12.01	78,60 \pm 13,12	ns
Sinus rhythm	44.8%	43.3%	ns
Echocardiography performed	63.6%	63.8%	ns
LVEF $< 50\%$	71.4%	49.2%	0.0001
LVEF $< 40\%$	58.9%	35%	0.0001
Median LVEF (IQR)	40 (30-50)	50 (40-55)	0.0001

Bond highlights significance

Legend = LOS = length of hospital stay; HF = heart failure; NYHA = New York Heart Association; LVEF = left ventricle ejection fraction; Cr Cl = creatinine clearance

Overall, seventy hundreds and seventy patients were enrolled in the SMIT Study. Of these, four hundreds and twenty-nine (55.7%) were females. Females were significantly older than males. More than seventy percent of females were 80-years old and older and around twenty percent were 90-years old and older.

All cause in-hospital mortality was 5.9% without differences according to sex (7% in males vs 4.8% in females, $p = ns$). Median length of hospital stay (LOS) was not different between males and females [7 (interquartile range, IQR: 5-10) vs 7 (5-11) days, $p = ns$]. No difference was found in hospital admission within the previous latestmonth, whereas males were admitted to hospital more frequently than females in the previous latest year (55% vs 46%, $p =$

0.0166). Seventy-two females (17.9%) and forty-eight males (13.2%) presented a new onset HF, whereas the majority of patients presented at least one previous hospital admission for HF in their history.

Echocardiography was carried out in 63.6% of males and 63.8% of females. Estimated mean of LVEF was $44 \pm 12\%$. Median LVEF was significantly lower in males compared to females [40 (IQR: 30-50) vs 50 (40-55)%, $p = 0.0001$]. Fifty-eight percent of males compared to thirty-five percent of females had LVEF $< 40\%$ ($p = 0.0001$). HF with a preserved

LVEF ($> 50\%$) was significantly more prevalent in females compared to males (51.3% vs 32.6%, $p = 0.0001$). No difference was found in the percentage of HF NYHA class III-IV according to sex. A significant higher percentage of females receive non invasive ventilation in the acute phase of management (15.1% vs 9.1%, $p = 0.011$).

Hypertensive (26.8% vs 19.8%, $p = 0.02$) and valvular (13.6% vs 8.6%, $p = 0.03$) were the more prevalent etiologies of HF in females, while ischemic heart disease was in males (25.8% vs 18.2%, $p = 0.01$) (Figure 1).

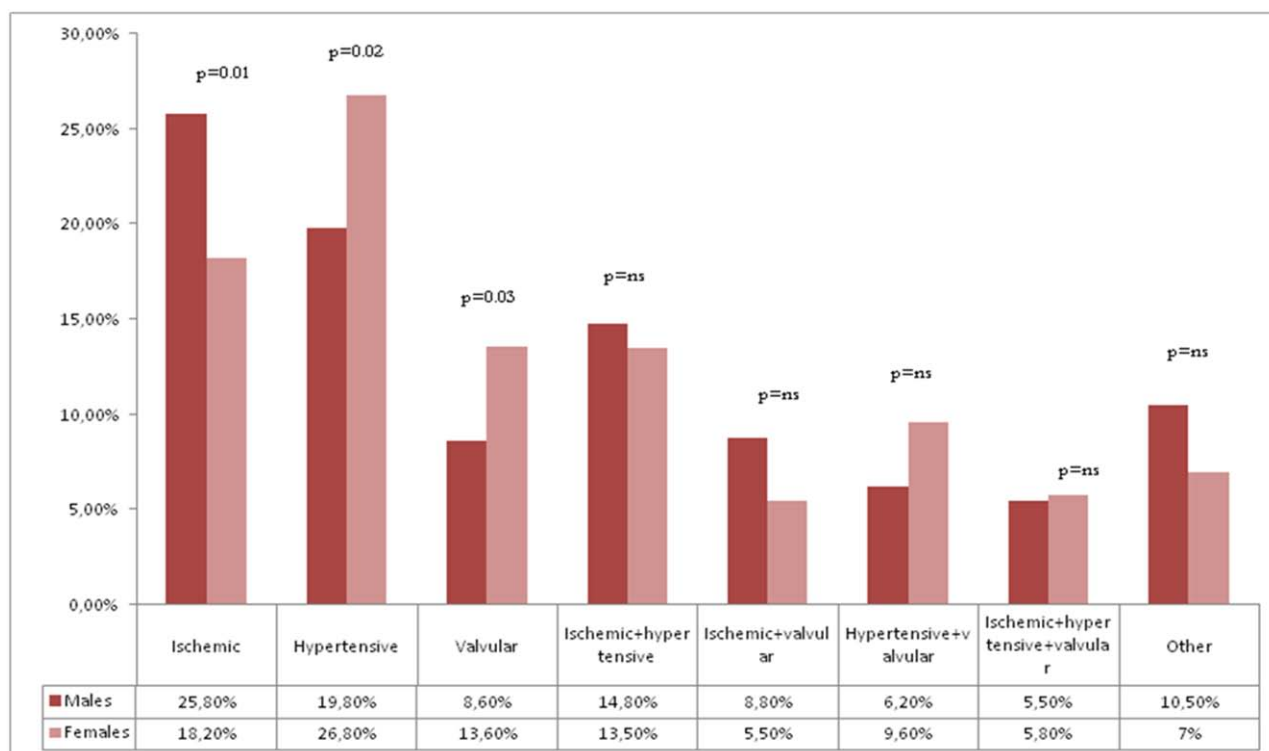


Figure 1. HF etiologies according to sex.

Near ninety percent of patients had at least two or more co-morbidities and more than seventy percent of patients had at least three or more co-morbidities. No difference was found in number of co-morbidities according to sex (Figure 2).

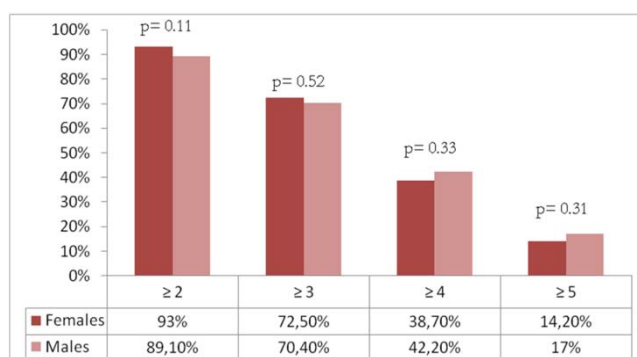


Figure 2. Prevalence of co-morbidity according to sex.

No difference was found in the prevalence of blood hypertension, diabetes, previous TIA / stroke, venous thromboembolism and dyslipidemia according to sex.

Chronic obstructive pulmonary disease (COPD) and peripheral artery diseases (PAD) were more frequent in males, whereas cognitive impairment was in females. A higher percentage of males had haemoglobin levels lower than 10 g/dL compared to females. Despite the prevalence of renal failure was similar in both sexes, the mean creatinine clearance detected at hospital admission by using the Cockcroft – Gault formula was lower in females than in males (44.4 ± 22.2 vs 49.4 ± 26.3 ml/min, $p < 0.05$). A higher percentage of females had severe renal failure.

Table 2 summarizes the difference in co-morbidity between sexes.

No difference between sexes was found in the median number of drugs prescribed at hospital discharge [9 (IQR: 7-11) vs 8 (6-11) drugs, $p = ns$]. No difference between sexes was registered in the domiciliary prescription of oxygen, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs, sartans), beta blockers and digoxin, whereas anti-aldosterone agents, ivabradine and statins were significantly more frequently prescribed in males (Table 3).

Table 2. Main co-morbidities according to sex.

	Males	Females	p
Blood hypertension	69.7%	74.8%	ns
Moderate/severe renal failure	58.6%	64.3%	ns
Mean CrCl \pm SD (mL/min)	49.4 \pm 26.3	44.4 \pm 22.2	0.02
CrCl < 50 mL/min	38.4%	36.1%	ns
CrCl < 30 mL/min	20.2%	28.2%	0.01
Atrial fibrillation	52.4%	56.8%	ns
COPD	42.3%	30.1%	0.0001
Diabetes	39.3%	31.4%	ns
Dyslipidemia	27.3%	23.1%	ns
Cognitive impairment	23.1%	37.1%	0.0001
Previous TIA/stroke	17.4%	18%	ns
Severe anemia (haemoglobin level \leq 10 g/dL)	17.0%	11.4%	0.02
Mean haemoglobin level \pm SD (g/dL)	12.8 \pm 1.9	11.8 \pm 1.8	0.04
Peripheral artery disease	16.2%	6.3%	0.0001
Active cancer	7.9%	5.6%	ns
Previous venous thromboembolism	5.9%	6.6%	ns

Bond highlights significance

Legend: COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack

Table 3. Treatment at hospital discharge according to sex.

	Males	Females	p
Oxygen	17%	21%	ns
Diuretics	80.3%	73.2%	ns
Beta blockers	53.6%	50.1%	ns
ACE inhibitors	43.1%	44.1%	ns
Anti aldosterone agents	25.2%	18.4%	0.02
Sartans (ARBs)	18.7%	20.7%	ns
Calcium channel blockers	15%	17.7%	ns
Digoxin	11.8%	14%	ns
Ivabradine	0.4%	0.1%	0.01
VKAs	27.8%	25.6%	ns
DOACs	0.3%	0.2%	ns
Antiplatelet	48.3%	43.3%	ns
Statins	33.8%	23.8%	0.002
Number of drugs (median, IQR)	9 (7-11)	8 (6-11)	ns

Bond highlights significance

Legend: VKAs = vitamin K antagonists; DOACs = direct oral anticoagulants; IQR = interquartile range; ARBS = angiotensin II receptor blockers

Eighty-two percent of surviving females and seventy-nine percent of surviving males were discharged at home ($p = ns$). Fifty-six percent of surviving females compared with forty percent of surviving males were dependent in activities of daily living at hospital discharge ($p = 0.0001$).

4. Discussion

Gender medicine is an upcoming branch of healthcare aimed to analyze differences in pathogenesis, presentation, management and outcomes of diseases according to sex. In fact, understanding the difference between females and males is of utmost importance for diseases management in clinical practice.

HF is a worldwide healthcare problem, especially in elderly people. Impressive, HF is one of the leading cause of hospital admissions, costs, mortality, disability and hospital

re-admissions. Females enrolled in main HF trials were less than 30% of overall population [7]. In many cases, the smaller percentage of females enclosed compared to males has led to a lack of statistical significance when subgroup analyses were restricted to females; thus, it is unclear whether the true effect of the interventions differ by gender or the results are merely a statistical power issue [12]. In the present study, we focused on difference between sexes on characteristics and management of HF from a real life perspective.

Impressive, in our study we found that one half of patients with HF had been already admitted in hospital for the same problem in the latest year and only one of six patients had a de novo diagnosis of HF whereas five of six patients were admitted for decompensation of known HF. This result arises a relevant problem of healthcare policy, especially in older population. In fact, prevent HF decompensation and hospital re-admissions remains one of the main challenge for healthcare systems.

Our study confirm as among patients admitted to Internal Medicine wards for HF, more than 55% are females with some peculiar distinction from males in terms of demographic, etiology and clinical characteristics. Females hospitalized for HF in Tuscany are on average 3-year older than males and present an age over 80 years in about 70% of cases. It's not surprising because data on annual incidence of HF in females report that about 8.2 cases per 1000 females with 65-74 years, and 45.6 cases per 1000 females older than 85 years, develop HF [13]. Aging leads to a progressive remodeling of myocardium with a decrease of left ventricular mass. However, role of aging in female sex with HF is still unclear. In fact, whether a decreasing of ventricular mass is well described in elderly males, myocardial mass seems to be preserved in older females [14]. The causes of this difference are not well known but a potential explanation may be due to different cardiac loads between females and males [14].

Arterial blood hypertension seems to be the most important risk factor for HF in females and it has been confirmed in our study, where 55% of females were hypertensive [15, 16, 17]. The importance of arterial hypertension as risk factor for HF is well known. However, it is important to remark as hypertensive females present a higher risk to develop HF than hypertensive males [18]. Moreover, arterial hypertension represents a main determinant of cardiovascular risk for females, influencing outcome especially when it is associated with diabetes [19]. Unlike males, ischemic heart disease represents the second cause of HF in females. Nevertheless, females affected by ischemic heart disease and HF even present a worse outcome than males [20]. The lower incidence of myocardial infarction in females is explained by a possible key-role of sex hormones that exert potential benefit on vascular and cardiac remodeling. However, cardiac artery disease is present in a large proportion of females but risk factors for progression to HF in this gender have not been well investigated. A study of Bibbins-Domingo et al. enrolling females patients with coronary artery disease showed as

diabetes, obesity, chronic renal failure and a poor control of arterial hypertension are the most important conditions to develop HF [21].

Differences on genetic, risk factors, etiologies between sexes cause a different clinical presentation of HF. Our study confirms that females present a higher incidence of HF with preserved LVEF than males [15, 16, 17]. In the PRESERVE study conducted on 23,435 patients with HF, equally distributed between preserved LVEF and reduced LVEF, 61.2% of patients with preserved LVEF were females [22, 23]. Several studies on risk factors and clinical features associated with preserved LVEF or reduced LVEF HF have shown as female sex is an independent predictive risk factor for preserved LVEF [15, 16, 17]. The reasons of a higher incidence of preserved LVEF in females may be related to sex-specific hormone differences. Indeed, the decrease of estrogen levels after menopause cause several changes related to the activation of renin-angiotensin system and inhibition of nitric oxide and natriuretic peptides [24].

The present study shows that co-morbidity differs between females and males. COPD and PAD were found to be more prevalent in males whereas cognitive impairment and renal failure were in females. Moreover, our study shows that at hospital discharge females are more dependent in activities of daily living compared to males. There is limited literature evidence about difference of co-morbidity in females with HF compared to males, if not a higher prevalence of blood hypertension and depression in females [8, 25]. Our study reflects the different distribution of co-morbidity between males and females in the overall population. The wider tobacco use in males, especially many years ago, could explain the different burden of COPD and PAD in males compared to females in our study. Cognitive impairment, renal failure and dependency in activities of daily living are age-related. Therefore it's not surprising that in our study where we found females significantly older than males, these co-morbidities were more prevalent in females compared to males.

Discrepancies in HF management for females are evident not only in randomized clinical trials, but also in clinical

practice. The National Heart Failure Project and the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) trial found that older females with HF were less likely to receive guideline-recommended treatments compared with males [26]. In a European population-based study, females with HF and reduced EF were 25% less likely to receive beta-blockers and ACE inhibitors than males [27]. In our study no difference between sexes was registered in the use of beta-blockers, ACE inhibitors, angiotensin II receptor blockers. Which is the reason of this result is unclear. We postulate that our study was conducted in most recent years. Therefore, physicians could be more confident in the use of these pharmacological classes, irrespective of sexes. Moreover, despite females are less represented in randomized clinical trials, from the public health viewpoint the implementation of the evidence in all patients, irrespective of gender, is the key factor in improving the outcome for patients with HF [28].

Despite the strength of our study is the real life perspective, we recognize that the present study presents some limitations mainly due to the retrospective analysis and the lack of a follow-up after discharge.

5. Conclusion

Understanding the difference between females and males is of utmost importance for physicians who manage HF in clinical practice. Findings of the present study demonstrate that demographic characteristics, etiology, co-morbidity, echocardiographic pattern and management of HF differ according to sex. There is growing awareness about gender differences in HF but in randomized studies females are poorly represented. In this real life study, females were the majority of HF patients discharged from Internal Medicine units and were older than males. Gender differences about HF etiology, echocardiographic pattern and co-morbidity were found, whereas treatments were similar in males and females. Further prospective studies are warranted aimed to understand if gender differences in HF need different approaches in standard care.

Appendix

Appendix. The SMIT Study Investigators.

Internal Medicine Wards	Investigators
Firenze AOU Careggi (FI):	Brunetto Alterini, Regina Maria Lammel AOU Alessandro Morettini, Francesco Di Mare AOU Carlo Nozzoli, Francesca Bacci
Arezzo 1 (AR):	Mario Felici, Salvatore Lenti, Angela Tufi
Arezzo 2 (AR):	Stefano Arrigucci
Firenze Santa Maria Annunziata (FI):	Raffaele Laureano, Simone Meini, Cinzia Lusini, Maria Teresa Passaleva
Barga (LU):	Guidantonio Rinaldi, Francesca Dini
Borgo San Lorenzo (FI):	Stefano Spolveri, Fuad Amir Tarmum
Carrara (MS):	Monica Uliana, Antonella Venturi
Casentino (AR):	Emilio Santoro, Silvia Manetti
Cecina (LI):	Alessandro Pampana, Gianni Lorenzini
Empoli (FI):	Giuseppe Lombardo, Alessandro Dei

Internal Medicine Wards	Investigators
Firenze Santa Maria Nuova (FI):	Giancarlo Landini, Cristiana Seravalle, Luca Masotti
Grosseto (GR):	Valerio Verdiani, Mario Camarda, Andrea Montagnani
Livorno 1 (LI):	Marco Cei, Paolo Pasquinelli
Livorno 2 (LI):	Alberto Camaiti
Lucca (LU):	Giovanni Brunelleschi
Massa (MS):	Lucia Tonarelli
Massa Marittima (GR):	Massimo Alessandri, Graziella Cati
Montepulciano (SI):	Luigi Abate
Pescia (PT):	Grazia Panigada, Irene Chiti, Laila Teghini
Piombino (LI):	Michele Piacentini
Pistoia 1 (PT):	Massimo Giusti, Linda Morosi
Pistoia 2 (PT):	Michela Cameron Smith, Florinda Intilla
Poggibonsi (SI):	Carlo Palermo
Pontedera (PI):	Roberto Andreini, Claudio Belcari, Giuseppa Levantino
Portoferraio (LI):	Plinio Fabiani, Giulia Montorzi
Prato 1 (PO):	Giancarlo Bini, Donatella Bruni
Prato 2 (PO):	Massimo Di Natale, Emanuele Calabrese, Michele Bertoni, Alessandra Giani
S. Marcello Pistoiese (PT):	Marco Frati
Firenze San Giovanni di Dio (FI):	Alberto Fortini, Chiara Angotti, Luca Scarti
Valdichiana (AR):	Rino Migliacci, Giovanni Porciello

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