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OPINION ARTICLE

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*Details of Italian Study Group on Cardiometabolic Andrology are given in Appendix.

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The great opportunity of the andrological patient: cardiovascular and metabolic risk assessment and prevention

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SUMMARY

Andrologists, cardiologists and diabetologists (and general practitioners) have the great opportunity to collaborate and find shared clinical workup for the benefit of a large number of men. Several evidence established a link between erectile dysfunction (ED), cardiovascular disease (CVD), diabetes, and metabolic syndrome. Not only these conditions share many risk factors and pathophysiological mechanisms but also an emerging paradigm indicates that ED is, in fact, an independent marker of cardiovascular disease risk, CV events and CV mortality. However, there is no consensus on the best cardiologic investigation in men with ED with no known CVD and, on the contrary, on what is the clinical and prognostic role of detecting ED during cardiovascular investigation and CVD risk assessment. Only vasculogenic ED, which represents the most common type of organic ED, indeed represents a harbinger of CVD, especially for younger patients, and might be diagnosed by dynamic penile color doppler ultrasonography, which represents a real cardiovascular imaging technique that give evidence on the presence of systemic endothelial dysfunction and atherosclerosis. Furthermore, assessment of glucose and lipid metabolism is warranted as first step workup in all ED patients, and diabetologists should ask their patients for erectile function, address ED patients to andrologists, and consider vasculogenic ED in the context of the cardiovascular and metabolic workup and in the context of diabetic complications. Sexual symptoms (and testosterone levels) should sound as harbinger for cardiovascular and metabolic investigation and cardiologists and diabetologists have the opportunity to have a symptom (erectile dysfunction) and a vascular test (penile color doppler) that help them in better management of patients, their comorbidities and complications.

ERECTILE DYSFUNCTION AS A HARBINGER FOR CARDIOVASCULAR DISEASES

Erectile dysfunction (ED), defined as the consistent inability to reach and maintain an erection satisfactory for sexual activity, is common, affecting almost 40% of men >40 years of age. Several evidence established a link between ED and cardiovascular disease (CVD) and offers now the great opportunity for the patients and the clinicians to use this symptom as a guide in cardiovascular and metabolic risk assessment and prevention, as well as in CVD risk mitigation in men with otherwise unrecognized cardiovascular disease.

Not only ED and CVD share many risk factors (hypercholesterolemia, hypertension, insulin resistance and diabetes mellitus, obesity and metabolic syndrome) and pathophysiological mechanisms, but also an emerging paradigm indicates that ED is, in fact, an independent marker of cardiovascular disease risk, CV events and CV mortality (Nehra *et al.*, 2012; Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014; Piepoli *et al.*, 2016). ED is more frequent in patients with CVD, it is associated with asymptomatic coronary artery disease (CAD), and ED patients have higher risk of hypertension, myocardial ischemia, peripheral arterial disease and ischemic stroke (Montorsi *et al.*, 2006; Nehra *et al.*, 2012; Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014; Piepoli *et al.*, 2016). More importantly, ED in a sentinel marker of subclinical CVD and it has been estimated that ED precedes cardiovascular events by 2–5 years (Montorsi *et al.*,

2006; Nehra *et al.*, 2012; Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014; Piepoli *et al.*, 2016). Compared with traditional cardiovascular disease risk factors, incident ED has demonstrated similar or greater predictive value for cardiovascular events (Montorsi *et al.*, 2006; Nehra *et al.*, 2012; Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014; Piepoli *et al.*, 2016).

Guidelines recognize ED as a marker and risk predictor of CVD, consider patients with ED at increased CVD risk, and recommend assessment of cardiovascular risk factors and CVD signs or symptoms in men with ED (Nehra *et al.*, 2012; Piepoli *et al.*, 2016). However, there is no consensus on the best cardiologic investigation in men with ED with no known CVD and, on the contrary, on what is the clinical and prognostic role of detecting ED during cardiovascular investigation and CVD risk assessment.

Although it is now generally accepted that ED is an early marker of generalized CVD and therefore patients with ED should have a CVD risk assessment and cardiovascular workup, the fundamental question is: do all men with ED need a cardiovascular workup?

DO ALL MEN WITH ERECTILE DYSFUNCTION NEED A CARDIOVASCULAR WORKUP?

Two fundamental aspects should be considered to identify ED patients at higher risk of CVD: the cause of ED and the age of the patients. ED can be categorized as predominantly organic, psychogenic or mixed. It is generally accepted that only vasculogenic ED, which represents the most common type of organic ED, indeed represents a harbinger of CVD (Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014). In fact, the pathophysiologic link between ED and CVD is represented mainly by endothelial dysfunction. The artery size hypothesis (Montorsi *et al.*, 2005) well established this link and easily explains why ED usually precedes CVD manifestation. Given the systemic nature of atherosclerosis, all major vascular beds should be affected to the same extent. However, symptoms become evident firstly where arteries are smaller (cavernous district) and later where arteries are bigger (coronaries, femorals, carotids). Therefore, patients with CAD and ED should be considered at later atherosclerotic stages than patients with ED with no known CVD. Actually, these latter patients have the best opportunity for CVD prevention.

However, although vasculogenic ED is the real risk factor for CVD, this is true specifically for younger patients. In fact, ED has an age-dependent impact of CVD development, with major role in men between 40 and 60 years (Nehra *et al.*, 2012; Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014; Piepoli *et al.*, 2016).

The second most important question is therefore: how diagnosis of ED, and vasculogenic ED in particular, is made?

HOW DIAGNOSIS OF ED, AND VASCULOGENIC ED IN PARTICULAR, IS MADE?

The diagnosis of ED is easily made by medical and sexual history, which can also reveal important aspects on the origin of ED itself (psychogenic, organic) (Hatzimouratidis *et al.*, 2010). Questionnaires are an integral part of ED history and diagnosis, the most used of which is the International Index of Erectile Function (IIEF) (Hatzimouratidis *et al.*, 2010). This 15-item, self-evaluation questionnaire is a validated instrument for assessing erectile function, orgasmic function, desire and satisfaction after sexual relations. Validated questionnaires correlate with the extend of CAD and improve the predictive value of ED for total CV events compared with a single question for ED diagnosis (Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014). Importantly, questionnaires can be effectively used not only by andrologists, but also by primary care physicians and a wide array of medical specialists, such as cardiologists or diabetologists.

The vasculogenic nature of ED and the need for a cardiovascular workup is confirmed by dynamic penile color doppler ultrasonography (P-CDU) after pharmacologically induced erection (Ioakeimidis *et al.*, 2016; Rastrelli *et al.*, 2016). This technique is not mandatory for establishment of a diagnosis of ED in all patients (Hatzimouratidis *et al.*, 2010), especially in the era of highly effective orally active agents for the treatment of ED. However, in the context of the link between ED and cardiovascular health, it represents an essential procedure (Foresta *et al.*, 2008; Caretta *et al.*, 2009; Ioakeimidis *et al.*, 2016; Rastrelli *et al.*, 2016). P-CDU allows quantification of different parameters commonly used in vascular diagnostics, of which cavernous peak systolic velocity (PSV) represents the most important to diagnose the patient's penile vascular status (Ioakeimidis *et al.*, 2016; Rastrelli *et al.*, 2016). Importantly, reduced cavernous PSV is associated with increased risk of CVD (Ioakeimidis *et al.*, 2016; Rastrelli *et al.*, 2016). Indeed, P-CDU data include also information on acceleration time, end-diastolic velocity, resistive index, measurement of intima-media thickness (IMT) and stenosis, and therefore represents a real cardiovascular imaging technique that give evidence on the presence of systemic endothelial dysfunction and atherosclerosis (Foresta *et al.*, 2008; Caretta *et al.*, 2009).

THE ANDROLOGIST-CARDIOLOGIST LINK

From the evidence above, it is clear that andrologist and cardiologist should be in strict link during different clinical steps of patients with sexual symptoms and both have a central role in evaluation, prevention and treatment of risk factors and CVD. The first have the role of making the diagnosis of vasculogenic ED, score cardiovascular risk and address the patient (in particular young, with no known CVD) to the cardiologic workup (Fig. 1). The second should investigate the presence of ED (with or without known CVD), address the patient to the andrologic workup, and consider vasculogenic ED in risk stratification and as a sentinel marker for full cardiovascular workup (Fig. 2).

What we need to stress is that assessment of cardiovascular risk is not an exclusive practice of cardiologists, and assessment of ED is not an exclusive practice of andrologists. Several office-based, validated, cardiovascular risk score (i.e. Framingham Risk Score, SCORE system) may be used and initial risk stratification has been considered the cornerstone of cardiovascular risk assessment in clinical practice for decades and it is recommended by cardiologic guidelines (Piepoli *et al.*, 2016). Importantly, this strategy is endorsed also by ED expert groups as first step in patients with vascular ED (Hatzimouratidis *et al.*, 2010; Nehra *et al.*, 2012). On the other hand, all men referred to cardiologists should be questioned about their sexual history and functioning as part of the initial assessment of CVD risk. This is particularly recommended in asymptomatic adults without known CVD.

The central link between andrologist and cardiologist is represented by P-CDU. In general, abnormal P-CDU suggestive of vasculogenic ED should direct to first line cardiovascular

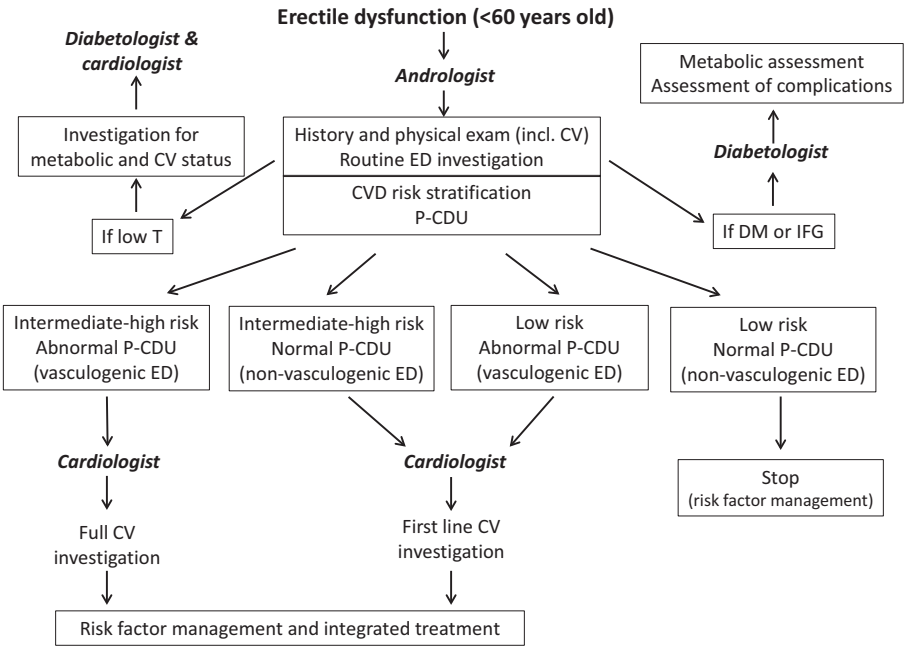

Figure 1 Proposed flowchart integrating andrologist, cardiologist and diabetologist involved in management of young (<60 years old) patients with erectile dysfunction who consult at first andrologist for the symptom. CV: cardiovascular; CVD: cardiovascular disease; DM: diabetes mellitus; IFG: impaired fasting glucose; P-CDU: penile color doppler ultrasonography; T: testosterone.

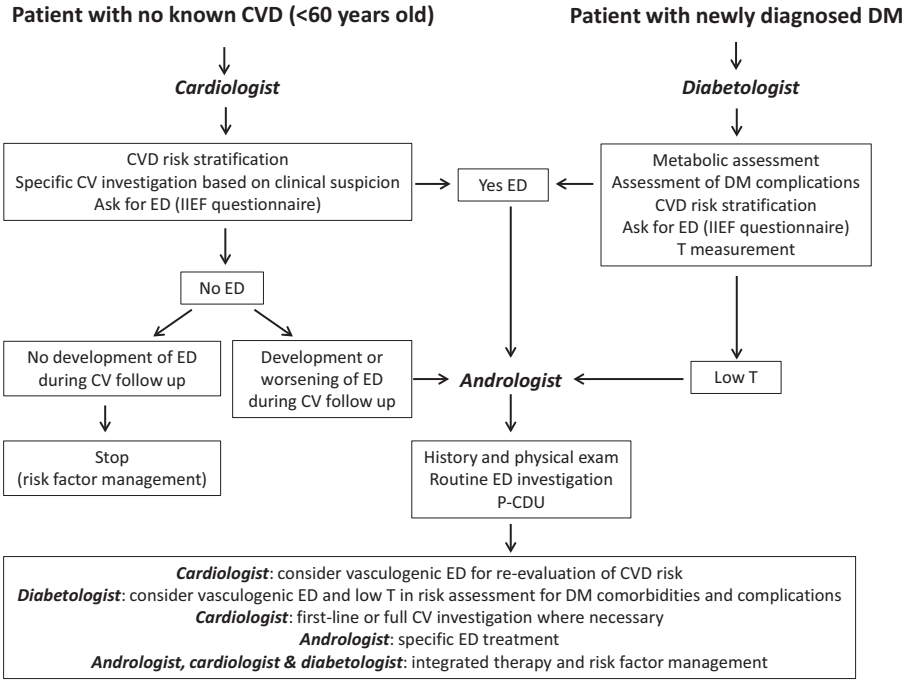

Figure 2 Proposed flowchart integrating andrologist, cardiologist and diabetologist involved in management of patients with no known cardiovascular disease consulting cardiologist and patients with newly diagnosed diabetes mellitus consulting diabetologist. CV: cardiovascular; CVD: cardiovascular disease; ED: erectile dysfunction; DM: diabetes mellitus; IIEF: international index of erectile function; P-CDU: penile color doppler ultrasonography; T: testosterone.

investigation in patients at low CVD risk and to full cardiovascular investigation in patients at intermediate-high risk, and andrologist and cardiologist are both involved in risk factor management and integrated treatment (Fig. 1).

The question that cardiologists should answer to is: which is the best first line and full cardiovascular investigation for patients with vasculogenic ED and no known CVD? A number of tests are available and for most of them there is evidence of association with ED and/or they might be useful to predict CVD risk in ED patients. These include, exercise stress test, femoral and carotid intima-media thickness, coronary artery calcium scoring/CT-angiography, ankle-brachial index, pulse wave velocity, brachial artery flow-mediated dilation. Neither the most appropriate order of testing nor the prognostic superiority of one test over another has been established and defined in cardiologic guidelines (Piepoli *et al.*, 2016). The decision on the best cardiovascular workup should be personalized and should take into consideration clinical judgment and factors as costs, availability and risk for the patient.

COMPLETION OF THE TRIAD: METABOLISM AND THE DIABETOLOGIST

The ED patient has another great opportunity: identify risk of diabetes and prevention of metabolic abnormalities. The general concepts are very similar to the link between ED and CVD, and it is well-known that diabetes is risk factor for both

ED and CVD. ED is more frequent in diabetics, with a risk 2–3 times higher with respect to non-diabetic men (Nehra *et al.*, 2012; Kamenov, 2015). Not only about half of the men with diabetes has ED, but also erectile function correlates with glycemic control. Most importantly, the prevalence of diabetes in men with ED is about 20%, and 15% of ED patients is not aware to be diabetic (Kamenov, 2015). Furthermore, as for CVD, ED is a sentinel marker for diabetes: estimates suggest that ED precedes the onset of diabetes by 10–15 years (Kamenov, 2015). Again, the presence of ED in men with diabetes could be predictor of silent cardiopathy and also the prevalence of other diabetic complications is higher in men with ED (Nehra *et al.*, 2012; Kamenov, 2015). Generally, in diabetes men ED precedes the development of other complications and in 5–10% of cases ED is the first symptom (Kamenov, 2015). Finally, ED in men with diabetes is usually more severe and less responsive to phosphodiesterase 5-inhibitors (Hatzimouratidis *et al.*, 2010; Kamenov, 2015).

From these considerations, it is clear why guidelines on ED clinical management suggest, in patients with no known diabetes, to include assessment of fasting glucose plasma levels (and/or glycated hemoglobin) and lipid profile as first step workup in all ED patients (Hatzimouratidis *et al.*, 2010; Nehra *et al.*, 2012). On the other hand, diabetologists should ask their patients for erectile function, address ED patients to andrologists for further evaluation, and consider vasculogenic ED in the context of the cardiovascular and metabolic workup and in the context of diabetic complications (Fig. 2).

The integration of the three actors (andrologist, cardiologist and diabetologists) is pivotal for CVD risk assessment, assessment of comorbidities and complications, cardiovascular and metabolic health, risk factor management and integrated treatments and follow-up management (Fig. 2).

THE FOURTH WHEEL: LOW TESTOSTERONE

Hypogonadism is defined as low testosterone (T) levels associated with sexual symptoms, as ED, diminished libido and poor morning erections (Wu *et al.*, 2010). Total T determination is recommended in all ED patients both in guidelines for ED management (Hatzimouratidis *et al.*, 2010; Nehra *et al.*, 2012) and guidelines for hypogonadism (Bhasin *et al.*, 2010). In the context of the focus of the present article, determination of T levels is fundamental not only to establish a correct diagnosis of the cause of ED, but also because low T is closely related to CVD, diabetes and metabolic syndrome (Corona *et al.*, 2011a,b).

It is well-known that the prevalence of hypogonadism is very high is diabetics (30–50%), especially if obese and/or affected by ED (Corona *et al.*, 2011a). Indeed, visceral obesity represents one of the most important cause of both diabetes and hypogonadism, and the pathophysiologic links between testicular function, obesity and glucose and lipid metabolism are well documented (Wu *et al.*, 2010; Corona *et al.*, 2011a). On the other hand, testosterone replacement therapy in hypogonadal men ameliorates the metabolic (glycemic and lipid) profile (Corona *et al.*, 2011a). Most importantly, hypogonadism precedes and predicts insulin resistance, diabetes and metabolic syndrome (Corona *et al.*, 2011a).

From a clinical point of view, andrologists have the opportunity to unveil diabetic and prediabetic conditions and hypogonadism in patients with ED (Fig. 1), and diabetologists should measure T levels in their diabetic and obese patients, especially if affected by ED (Fig. 2).

On the contrary, the relationship between T levels and CVD is much more complicated and debated. Nevertheless, hypogonadism could represent a component of the increased risk conferred by ED (Corona *et al.*, 2011b) and low testosterone leads to increased levels of total and LDL cholesterol, as well as to increased production of pro-inflammatory markers and mediators. Indeed, androgen deficiency has emerged as a predictor of CV events, as well as of all-cause and CV mortality, both in the general population and in patients with CV risk factors, hypertension, established CVD, and with ED (Corona *et al.*, 2011b). Anyway, the association found by some studies and metaanalysis (but not by others) between T levels and CVD risk cannot

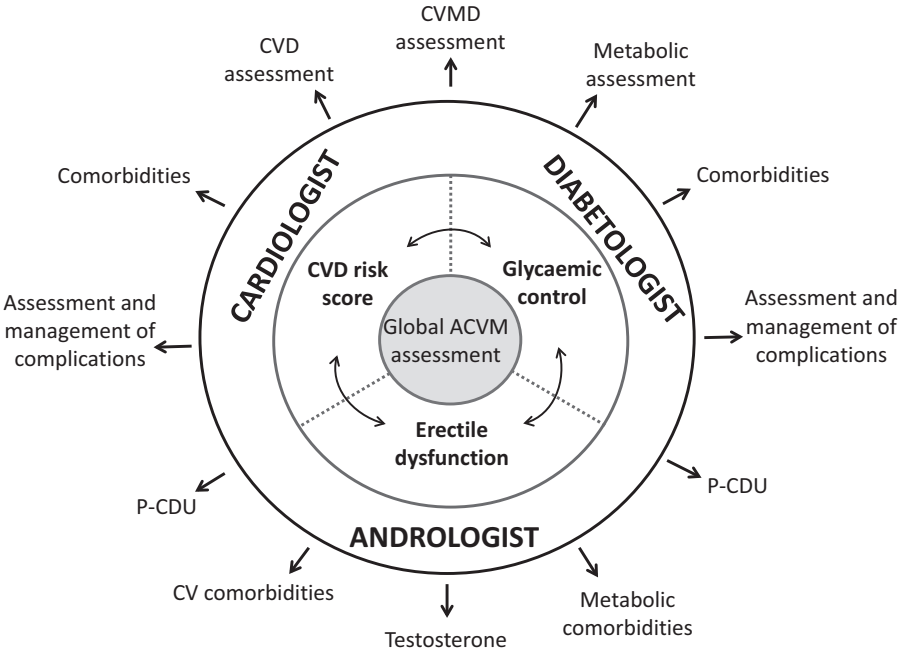

Figure 3 Schematic representation of cardiometabolic andrology: three dimensions (sexual, cardiovascular, metabolic), three specialists (andrologist, cardiologist, diabetologist), three clinical manifestations (erectile dysfunction, cardiovascular diseases, diabetes mellitus) and a fourth wheel (low testosterone) clinically cooperating and integrating for the benefit of the patient. CV: cardiovascular; CVD: cardiovascular disease; CVDM: cardiovascular-metabolic; ACVM: andro-cardiovascular-metabolic; P-CDU: penile color doppler ultrasonography.

prove causality. The possibility that low testosterone may be an epiphenomenon, marking poor general health rather than modulating CVD risk *per se* has to be explored. Nonetheless, a diagnosis of hypogonadism in men with ED and/or men with diabetes should be considered as an alarm bell for further CVD investigation.

Some controversial reports have been published in last years suggesting possible negative effects of testosterone replacement therapy (TRT) on CV safety (Basaria *et al.*, 2010; Vigen *et al.*, 2013; Finkle *et al.*, 2014). However, recently, well-conducted, prospective large studies support accumulating evidence of the benefit of restoring T levels in hypogonadal men (Muraleedharan *et al.*, 2013; Albert & Morley, 2016; Hackett *et al.*, 2014; Maggi *et al.*, 2016) and the European Medicines Agency (EMA) found no consistent evidence of an increased risk of heart problems with TRT administration (European Medicines Agency 2014). Many scientific societies (European Association of Urology, American Association of Clinical Endocrinologists and American College of Endocrinology, Italian Society of Endocrinology, European Menopause Andropause Society) (Dohle *et al.*, 2015; Goodman *et al.*, 2015; Isidori *et al.*, 2015; Dimopoulou *et al.*, 2016) indeed support the ability of T therapy to improve cardiometabolic risk factors and mortality in hypogonadal men. Of note, low T levels predict an increase in all-cause mortality and TRT is independently associated with reduced mortality in hypogonadal men with type 2 diabetes (Muraleedharan *et al.*, 2013; Hacket *et al.*, 2016). A recent multi-national, prospective hypogonadism registry showed that TRT is not associated with increased risk of adverse CV events (Maggi *et al.*, 2016).

CONCLUSIONS: THE CLINICAL VALUE OF CARDIO-METABOLIC ANDROLOGY

Andrologists, cardiologists and diabetologists have the great opportunity to collaborate and find shared clinical workup for the benefit of a large number of men. Men with ED, hypogonadism, diabetes and CVD should undergo a uniform workup whatever the first specialist they consult. More importantly, sexual symptoms (and T levels) should sound as harbinger for cardiovascular and metabolic investigation (Fig. 3). The identification of the right patient to address to cardiovascular and metabolic assessment is crucial, as not all ED patients will benefit from full investigation, and costs will be unsustainable. From their side, cardiologists and diabetologists have the opportunity to have a symptom (ED) and a vascular test (P-CDU) that help them in better management of patients, their comorbidities and complications.

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CONFLICT OF INTEREST

None declared.

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APPENDIX

Italian Study Group on Cardiometabolic Andrology (in alphabetic order): G. Corona (*Bologna*), K. Esposito (*Naples*), G.P. Fadini (*Padova*), A. Ferlin (*Padova*), C. Foresta (*Padova*), A.M. Isidori (*Rome*), S. La Vignera (*Catania*), A. Lenzi (*Rome*), E. Mannucci (*Florence*), P. Montorsi (*Milan*), F. Tona (*Padova*), A. Zaninelli (*Florence*).

