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Impella versus VA-ECMO for the treatment of patients with cardiogenic shock: the Impella Network Project – observational study protocol for cost-effectiveness and budget impact analyses

Vittoria Ardito ,[1] Carla Rognoni ,[1] Marina Pieri,[2,3] Alessandro Barbone,[4] Carlo Briguori,[5] Emanuele Cigala,[6] Gino Gerosa,[7] Mario Iannaccone,[8] Antonio Loforte,[9] Marco Marini,[10] Andrea Montalto,[11] Jacopo Oreglia,[12] Davide Pacini,[13] Mauro Pennacchi,[14] Vincenzo Pestrichella,[15] Italo Porto ,[16,17] Pierluigi Stefano,[18] Giuseppe Tarantini,[19] Serafina Valente,[20] Pietro Vandoni,[21] Rosanna Tarricone,[1,22] Anna Mara Scandroglio[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Carla Rognoni;
carla.rognoni@unibocconi.it

ABSTRACT

Introduction The treatment of patients with cardiogenic shock (CS) encompasses several health technologies including Impella pumps and venoarterial extracorporeal membrane oxygenation (VA-ECMO). However, while they are widely used in clinical practice, information on resource use and quality of life (QoL) associated with these devices is scarce. The aim of this study is, therefore, to collect and comparatively assess clinical and socioeconomic data of Impella versus VA-ECMO for the treatment of patients with severe CS, to ultimately conduct both a cost-effectiveness (CEA) and budget impact (BIA) analyses.

Methods and analysis This is a prospective plus retrospective, multicentre study conducted under the scientific coordination of the Center for Research on Health and Social Care Management of SDA Bocconi School of Management and clinical coordination of Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute in Milan. The Impella Network stemmed for the purposes of this study and comprises 17 Italian clinical centres from Northern to Southern Regions in Italy. The Italian network qualifies as a subgroup of the international Impella Cardiac Surgery Registry. Patients with CS treated with Impella pumps (CP, 5.0 or 5.5) will be prospectively recruited, and information on clinical outcomes, resource use and QoL collected. Economic data will be retrospectively matched with data from comparable patients treated with VA-ECMO. Both CEA and BIA will be conducted adopting the societal perspective in Italy. This study will contribute to generate new socioeconomic evidence to inform future coverage decisions.

Ethics and dissemination As of May 2024, most of the clinical centres submitted the documentation to their ethical committee (N=13; 76%), six centres received ethical approval and two centres started to enrol patients. Study results will be published in peer-reviewed publications and disseminated through conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is an observational multicentre study that will evaluate the cost-effectiveness and budget impact associated with the use of Impella against venoarterial extracorporeal membrane oxygenation in the treatment of patients with cardiogenic shock.
⇒ The analyses will be performed with the twofold perspective of the national health system and the larger society in Italy.
⇒ Data collection will leverage the existing infrastructure of the Impella Cardiac Surgery Registry.
⇒ The outcomes of interests that will be collected are both clinical parameters and socioeconomic data, including healthcare resource use and costs and quality of life.
⇒ This study does not consider alternative therapeutic courses for the treatment of patients with cardiogenic shock (eg, intra-aortic balloon pump, pharmacological therapy alone), nor the combination of devices (eg, ECPELLA (the combined configuration of VA-ECMO and Impella)), as primary therapeutic strategy.

INTRODUCTION

Background

Mechanical circulatory support (MCS) has gained wide application for the treatment of cardiogenic shock (CS) and received a class IIA recommendation by the most recent European Society of Cardiology guidelines

on heart failure.[1] In recent years, transcatheter systems have brought great innovation in this field since they enable mechanical left ventricle (LV) unloading, through a lower invasive approach compared with previous generation extracorporeal support devices, equally providing high anterograde flow to reverse the shock status and end-organ damage. They have also the potential to overcome some typical limitations of MCS providing full support for up to a prolonged period of time and promote patients' recovery at the same time.[2–6]

Although both devices are widely used in daily practice, evidence on their uptake and clinical efficacy is constantly evolving. Several meta-analyses evaluated MCS devices for the management of patients with CS,[7–9] yet only a few were comparative studies on Impella versus venoarterial extracorporeal membrane oxygenation (VA-ECMO).[10–13] In this context, conducting comparative studies like randomised controlled trials (RCTs) has proven to be complex, with five out of seven RCTs on Impella being discontinued due to inadequate patients' enrolment.[14] Comparative effectiveness studies have become increasingly pivotal since the new Health Technology Assessment Regulation (HTAR 2021/2282) was approved in December 2021 by the EU Parliament.[15] With this regulation, high-risk, life-saving technologies would need to be comparatively assessed at the European level, in line also with the national guidelines of several countries in Europe. However, a prior review by Ardito *et al* highlighted that to date virtually no study investigates comparatively socioeconomic variables in association with the use of Impella versus VA-ECMO.[10] In light of the new regulatory provisions, the lack of comparative robust clinical and socioeconomic evidence might be paralysing for Member State who are called to take informed coverage and reimbursement decisions.[16–18] As a matter of fact, the limited healthcare resources need to be allocated considering not only the health impact on patient outcomes but also the financial burden for government budgets. In this context, performing not only economic evaluations (eg, cost-effectiveness analysis (CEA) or cost–utility analysis) but also health technology assessments at large, accounting for social, organisational, legal, ethical or environmental aspects of health technologies, will thus become increasingly pivotal for the uptake of new health technologies and their coverage under national health services. To date, there are only a few studies investigating the cost-effectiveness of MCS devices in the literature. For instance, in a study from 2013 by Roos *et al*, the cost-effectiveness of Impella was compared with the intra-aortic balloon pump (IABP) in the European perspective, by considering only direct costs.[19] In 2015, the clinical and economic impact of percutaneous ventricular assist devices (pVAD) were compared with IABP for high-risk patients undergoing percutaneous coronary intervention (PCI) by means of conducting a retrospective analysis of published evidence.[20] More recently, another study examined the benefits, harms, cost-effectiveness and budget impact of the Impella pVAD in high-risk PCI and CS.[21]

This work builds on the need to conduct more comparative studies in the field of MCS health technologies for the treatment of CS, and to expand the knowledge from existing studies in the Italian framework, which report clinical but not economic data.[22–25]

Study objectives

The aim of this study is to generate comparative evidence on the use of Impella versus VA-ECMO for the treatment of patients with severe CS, with the goal to ultimately perform a CEA and budget impact (BIA) analyses from the national health system (NHS) and societal perspectives in Italy. Both prospective and retrospective data on clinical endpoints and healthcare resource consumption will be collected in Italian heart failure referral centres reunited in what has been named the Impella Network.

The Impella Network

The Impella Network has been created with the purpose of conducting this study. It is a national scientific and medical entity which connects all the Italian institutions within MCS programmes and referral for heart failure treatment in which Impella is already used in the clinical practice. All the centres involved in the Impella Network currently run MCS programmes and treat patients with CS.

The creation of the Impella Network is promoted under the joint scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute in Milan. To answer its specific research question (ie, assessing the cost-effectiveness and budget impact of Impella vs VA-ECMO for patients with CS), the Impella Network will leverage the infrastructure of the existing Impella Cardiac Surgery (ImCarS) Registry, therefore, qualifying as an ImCarS subgroup analysis of the Italian scenario.

Italian centres were eligible to join the Impella Network if all the following requirements were fulfilled: (1) level 2 or 3 centre status (with onsite heart failure and MCS programme); (2) implantation of Impella 5.0 or Impella CP as standard of care per site; (3) at least one Impella 5.0 or 20 Impella CP implants in the last 3 years (from 2020 to present). The centres meeting the inclusion criteria have been asked to join the Impella Network through a formal invitation from CERGAS SDA Bocconi and IRCCS San Raffaele Scientific Institute as principal clinical centre. Table 1 presents the list of clinical centres that agreed to be part of this study.

Interestingly, as the field of MCS evolves at high speed and scientific evidence is pivotal to improve clinical practice, the Impella Network might also become a facilitator for prospective analyses of future technologies and be considered eligible for inclusion in international projects on MCS.

Table 1 List of clinical centres involved in the data collection

ID	Clinical centre	Location
1	IRCCS Ospedale San Raffaele (PI)	Milano
2	ASST Grande Ospedale Metropolitano Niguarda	Milano
3	San Giovanni Bosco Hospital	Torino
4	Azienda Ospedaliera Universitaria di Padova	Padova
5	Policlinico di Sant'Orsola	Bologna
6	Ospedale Careggi	Firenze
7	Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino	Torino
8	Mater Dei Hospital	Bari
9	Azienda Ospedaliera Sant'Anna e San Sebastiano	Caserta
10	Fondazione IRCCS San Gerardo dei Tintori	Monza
11	Mediterranea Cardiocentro	Napoli
12	IRCCS Ospedale Policlinico San Martino	Genova
13	Azienda Ospedaliera S.Camillo Forlanini	Roma
14	Azienda Ospedaliero-Universitaria delle Marche	Ancona
15	IRCCS Humanitas Research Hospital	Rozzano
16	Azienda Ospedaliera-Universitaria Siena	Siena
17	Ospedale Monaldi, Azienda dei Colli	Napoli

ASST, Azienda Socio Sanitaria Territoriale; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico.

METHODS AND ANALYSIS

Study design

This will be an observational multicentre study. Patients with severe CS treated either with Impella (CP, 5.0 or 5.5) or with VA-ECMO will represent the study population in the prospective arm. This study population will be compared with a similar population of retrospective patients treated with VA-ECMO for severe CS, which will represent the control group. There is no randomisation procedure and all patients will be treated according to the standard of care per site. This protocol has been written following the Standardised Protocol Items: Recommendations for Observational Studies guidelines.[26]

The prospective study foresees a period of 6 months of follow-up for each patient. Investigators are requested to enrol all patients with CS in their units, according to the inclusion criteria. Data will be collected on a strictly observational basis. The investigators will carry out their usual activity, without any constraints due to the study, both in terms of diagnosis but also regarding patients' management, and the choice of possible treatments. Medical and MCS treatment will be initiated at the discretion of each investigator, according to routine practice. Overall study duration might be variable depending on the time needed for patient enrolment and follow-up in each site but is estimated to be approximately around 18 months.

Information on comparable patients will be retrieved by retrospectively reviewing the clinical records of patients treated for CS in the Impella Network (retrospective study arm). This information will be retrieved by the clinicians in each participating centre and will be inputted within the Impella Cardiac Surgery (ImCarS) Registry and will ultimately populate the study database together with the information from the prospective study arm. All patients who meet inclusion and exclusion criteria in the appropriate time periods (see 'Study population' paragraph) will be included, both for the patients treated with Impella (study arm) and for the patients treated with VA-ECMO (control arm).

It is anticipated that the study protocol might be subject to minor amendments depending on how the data collection unfolds (eg, fewer patients treated with the technologies in scope to be enrolled in the study or fewer centres participating in the study).

Study population

Patients treated with Impella

The study population will include all patients suffering from CS, according to clinically relevant classifications (Interagency Registry for mechanically assisted circulatory support (INTERMACS) and International Society for Cardiovascular Angiography and Interventions (SCAI)) treated with Impella 5.5, Impella 5.0 or Impella CP at the Impella Network institutions. To be included in the study group (ie, Impella Intention To Treat group), patients must meet all the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E).
- Support as single device strategy.
- Impella support duration of at least 24 hours.
- Patients treated in the last 3 years (2020–2022) (for retrospective data collection).
- Onset of CS from less than 12 hours.

Different primary diseases and aetiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- Impella implantation for elective-protected PCI.
- Impella implantation for postcardiotomy CS.
- Impella support duration for less than 24 hours.

Patients treated with VA-ECMO

The control group will include all patients treated at the Impella Network institutions for severe left ventricular failure with VA-ECMO. To be included in the control group (ie, VA-ECMO intention to treat group), patients must fulfil ALL the following inclusion criteria:

- CS at presentation (as defined by INTERMACS class 1-2-3 or SCAI Class C-D-E).
- VA-ECMO support as single device strategy.
- VA-ECMO support duration of at least 24 hours.
- Onset of CS from less than 12 hours.

Different primary diseases and aetiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- VA-ECMO support for postcardiotomy CS.
- VA-ECMO support duration for less than 24 hours.
- VA-ECMO for refractory prolonged cardiac arrest (ECPR).
- Presence of biventricular failure.
- Onset of CS from more than 12 hours.

In the era of Impella 5.0/5.5, patients with CS treated with VA-ECMO may be indicative of a more severe population compared with the study group counterpart. In order to prevent potential bias, only VA-ECMO patients with isolated LV failure will be included in the study and patients with CS severity profile comparable to the Impella counterpart at baseline will be analysed.

Sample size

For the prospective arms, any patient treated with Impella or VA-ECMO technologies that meet the inclusion criteria will be recruited and considered for the analyses. Therefore, the sample size cannot be estimated ex-ante. For the retrospective arm, based on previous data from the Italian clinical experience, it is expected that data from approximately 200 VA-ECMO patients will be retrieved and included in the analyses.

Outcomes of interest

Clinical parameters

Data related to medical history, shock-related hospitalisation, MCS characteristics (for Impella or VA-ECMO), clinical and hospital outcomes will be collected from each centre and included in a prespecified structured data set. Short-term MCS-related adverse events will be defined according to most recent recommendations.[27] In addition to data registered at specific time points (eg, at baseline) and outcome measures, several haemodynamic, laboratory and clinical data will be assessed regularly during the treatment with Impella or VA ECMO to assess the evolution of the condition of shock during support. The detailed list of clinical parameters to be collected through the study is outlined in online supplemental material 1.

Healthcare resource use and costs

Direct healthcare resource use will be identified through the analysis of collected clinical data (eg, the number of visits, device implanted and possible management of adverse events). Monetary quantification will be performed by applying official reimbursement rates (eg, DRGs for hospitalisations or tariffs for outpatient services).

The collection of 'societal costs' will be performed through the administration to patients of a socioeconomic questionnaire, developed ad hoc by CERGAS researchers and it will include information on out-of-pocket (OOP) expenses (eg, transport costs for carrying out visits or exams), productivity losses and cost of informal care (provided by relatives). The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) and during the follow-up visits (eg, at 30 days).

Direct healthcare resource use will be measured both for prospective and retrospective patients while information on 'societal costs' will only be available for the group of prospective patients as it is collected through patient questionnaires (not available retrospectively). The detailed list of healthcare resource use variables and the questionnaire to assess the societal impact are reported in online supplemental materials 2 and 3, respectively.

Quality of life

Only for the patients prospectively enrolled in the study, the patient's quality of life (QoL) will be measured through the EuroQol 5D-5L questionnaires. EuroQol 5D-5L is a questionnaire capable of providing a generic and synthetic measure of the QoL in relation to health. The questionnaire consists of two parts: the first includes five items that refer to different health aspects: mobility, personal care, usual activities, pain or discomfort, anxiety or depression. For each item, there are five levels of response which indicate, for that area, the absence or presence of mild, moderate, severe or extreme problems. The second part of the questionnaire consists of a graduated Visual Analogue Scale from 0 to 100 on which the subject indicates his/her perceived state of health. The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) if possible and during the follow-up visits (eg, at 7 days, 30 days) using a paper-based format. The clinicians will choose an appropriate timing to fill in the questionnaire, namely when patients are awake, conscious and willing to respond. However, should the patients be too weak to respond, or should they fail to recover from the shock, they will be excluded from the QoL analyses.

The questionnaire has been requested for non-commercial use via the EuroQol website (registration ID 48771) and is reported in its integral version in online supplemental material 4.

Data collection and management

Data will be collected through the infrastructure of the existing ImCarS Registry. While this study qualifies as an independent study answering a specific research question (ie, assessing the cost-effectiveness and budget impact of Impella vs VA-ECMO for patients with CS), it will leverage the ImCarS Registry (ie, eCRF, IT platform, capabilities)

as a facilitator for the data collection phase,[28] therefore, qualifying as an ImCarS subgroup analysis of the Italian scenario. More in details, each centre belonging to Impella Network will join the ImCarS registry and the current project will benefit from the employment of an electronic case report form (eCRF), that will support any activities related to data collection. The company that will handle the eCRF and will ensure data protection is KKS Gießen Marburg. A per-patient fee of approximately 300€ for Impella cases and €100 for VA-ECMO cases will be provided by the ImCarS Registry to each participating centre. Possibly a clinical research organisation could be involved on request of the clinical centres for the management of periodic quality controls to ensure completeness and consistency according to a specific plan agreed among the participating centres. Each clinical centre will maintain the ownership of the data points of their own patients.

Patient data recorded in each participating clinical centre (hospital medical records) as well as responses to QoL and socioeconomic questionnaires will be anonymised and entered by the clinicians in the eCRF of ImCarS Registry. At the end of the applicable operations and checks, the anonymised data set will be transferred to CERGAS researchers in order to perform the CEA and BIA.

Data analysis

Statistical analysis

The data obtained will be analysed in a descriptive and inferential way using the most suitable statistical model for each variable. Continuous variables with a symmetrical distribution (eg, age and questionnaire scores) will be expressed as means and SD. As regards, the asymmetrically distributed continuous variables (eg, hospital stay) they will be expressed as median and range. The categorical variables (gender, intraoperative and postoperative complications) will be expressed as frequencies and percentages. Subgroup analyses may be performed depending on the type of data collected, to have consistent results. Possible missing data for the retrospective group of patients will be treated case by case, depending on the quality of the data themselves.

Cost-effectiveness analysis

The implementation of a CEA model[29] will aim to compare the management of patients with CS with Impella versus VA-ECMO from both NHS and societal perspectives in Italy. The analysis will follow the Consolidated Health Economic Evaluation Reporting Standards.[30 31]

The model will project costs, life-years (LYs) and quality-adjusted LYs (QALYs) on a lifetime horizon in order to evaluate the incremental cost-effectiveness ratio and the incremental cost–utility ratio. They will be calculated as the difference in the mean expected costs divided by the difference in the mean expected health outcomes (LYs or QALYs) of the considered management strategies. It has to be specified that QoL will be measured as long as patients stay alive. Interpolation techniques might be used to manage missing data (eg, to carry forward QoL measurements occurred prior to death); however, patients who never completed QoL measurements will be excluded from QALYs analyses.

The CEA model will be developed based on the following phases: (1) identification of clinical pathways and healthcare resources consumption for the considered strategies; (2) inclusion of patients' clinical outcomes and possibly QoL for the considered strategies (available from data collection phase); (3) monetary quantification of the healthcare resource consumption from both NHS and societal perspectives (eg, DRG charges/tariffs, productivity losses and OOP costs reported by the patients); (4) analysis and interpretation of model results and (5) sensitivity analyses. In addition, if collected data will allow it, centres will be clustered based on the number of implanted Impella devices and patients treated, to investigate if there is a relationship between cost-effectiveness and the volumes of device used in each centre. The definition of the clusters and conduct of subgroup analyses will depend on the data that will be actually collected.

Budget impact analysis

A BIA model will be developed starting from the CEA model to evaluate the impact on the hospital healthcare expenditure in Italy of the adoption of Impella, possibly differentiating by the type of Impella pumps, over a period of 3 or 5 years, according to the following steps: (1) identification of patients' pathways and healthcare resources consumption for the considered strategies; (2) monetary quantification of the healthcare resource consumption from the hospital perspective through a microcosting analysis; (3) definition of the current scenario of distribution of patients among the two considered options: Impella 5.0 and VA-ECMO and (4) definition of future scenarios in which appropriate increased uses of Impella according to different annual penetration rates are considered. The forecasted increased use of Impella may be estimated on the basis of the evidence available in the literature and/or by clinical opinions collected by an ad hoc e-survey and by observing market trends in other jurisdictions (eg, Germany, USA); (5) analysis and interpretation of model results and (6) sensitivity analyses (eg, Impella 5.5).

As a final note, it has to be highlighted that the BIA will be conducted from an Italian perspective, based on the cost framework observed within Italian facilities. Therefore, extending the study results to other geographical contexts should be done with caution, and marginal adjustments might be needed to account for country-specific differences in the costs sustained at the local level.

Patient and public involvement

Being an observational study, patients will be enrolled as part of the research activities. Informed consent will be provided to, and signed by, patients to ensure the purposes of the study are well understood, and the

patients' interests protected. We plan on involving relevant patient associations when disseminating the study results.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigour and follow generally accepted research practices described in Good Clinical Practices. No specific risks related to the enrolment in the study are expected for patients, since the study is observational and patients will receive the best available treatment. Informed consent collection will be performed according to the ImCarS registry protocol and eventually further disciplined according to specific guidelines and/or best practices of the Ethical Committees of each clinical centre. Similarly, the collection of data at each participating site will be performed according to the policies of the local institutional review board/ethics committee.

All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications or other disclosures.

SDA Bocconi received approval for this protocol from Bocconi University's Ethical Committee (EC). IRCCS San Raffaele Hospital Institute also received ethical approval of the ImCarS protocol from its EC. In parallel, each clinical centre had to present the documentation to join the ImCarS Registry to their own ECs for approval. As of May 2024, among the participating centres, the majority (N=13, 76%) already presented the relevant documentation, while six of them—Azienda Ospedaliera San Camillo Forlanini (Rome), Clinica Mediterranea (Naples), San Giovanni Bosco (Turin), Città della Salute e della Scienza (Turin) and Humanitas (Rozzano)—already received the EC approval.

The study results will be disseminated through peer-reviewed scientific publications and presentation in international conferences. The economic analyses, namely the results of the CEA and BIA analyses, will be published in one or more scientific publications in top-tier, peer-reviewed journals. The exact publication pipeline depends on the actual start of the data collection. After the end of the data collection, it will take approximately 9 months for the research team to process the evidence and prepare the aforementioned manuscripts.

Author affiliations
[1]Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Milano, Italy
[2]Department of Anesthesia and Intensive Care, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Raffaele, Milano, Italy
[3]Vita-Salute San Raffaele University, Milano, Italy
[4]IRCCS Humanitas Research Hospital, Rozzano, Italy
[5]Mediterranea Cardiocentro, Clinica Mediterranea SpA, Napoli, Italy
[6]UOC Cardiologia Interventistica, Ospedale Monaldi, Napoli, Italy
[7]Cardiac Surgery Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy
[8]Division of Cardiology, San Giovanni Bosco Hospital, ASL Città di Torino, Torino, Italy
[9]Dipartimento di Scienze Chirurgiche, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[10]Dipartimento di Scienze Cardiovascolari, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy
[11]Azienda Ospedaliera di Caserta Sant'Anna e San Sebastiano, Caserta, Italy
[12]Niguarda Hospital, Milano, Italy
[13]University of Bologna, Bologna, Italy
[14]Dipartimento Cardio Toraco Vascolare, U.O. Cardiologia Interventistica, Azienda Ospedaliera San Camillo Forlanini, Roma, Italy
[15]Division of Cardiology, Ospedale Mater Dei, Bari, Italy
[16]DICATOV-CardioThoracic and Vascular, Ospedale Policlinico San Martino Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia, Genova, Italy
[17]University of Genova, Policlinico San Martino IRCCS, Università degli Studi di Genova Scuola di Scienze Mediche e Farmaceutiche, Genova, Italy
[18]Azienda Ospedaliero Universitaria Careggi, Firenze, Italy
[19]Department of Cardiac, Thoracic, Vascular Sciences and Public Health, Università degli Studi di Padova, Padova, Italy
[20]Azienda Ospedaliera Universitaria Senese, Siena, Italy
[21]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[22]Department of Social and Political Sciences, Bocconi University, Milano, Italy

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Contributors RT and AMS developed the initial study concept. VA, CR and MPi devised the study design, including methodology, and wrote the original draft of the protocol. AB, CB, EC, GG, MI, AL, MM, AM, JO, DP, MPe, VP, IP, PS, GT, SV and PV contributed to critical revisions of the manuscript. RT and AMS are the Scientific Coordinators of the study and took overall responsibility for all aspects of study design, the protocol and the study conduct. RT acquired funding for the study. All authors VA, CR, MPi, AB, CB, EC, GG, MI, AL, MM, AM, JO, DP, MPe, VP, IP, PS, GT, SV, PV, RT and AMS contributed to review and editing of the protocol and have read and approved this manuscript.

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ORCID iDs
Vittoria Ardito http://orcid.org/0000-0003-2034-716X
Carla Rognoni http://orcid.org/0000-0002-6330-0591
Italo Porto http://orcid.org/0000-0002-9854-5046

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