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Rationale and design of the "long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease in post myocardial infarction patients" (TIGRIS) study

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Summary

Background

The long-term progression of coronary artery disease (CAD) as defined by the natural course of the disease years after a myocardial infarction (MI) is an important area of clinical research that has been poorly studied. The “long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease in post myocardial infarction patients” (TIGRIS) study was designed to address this knowledge gap by evaluating patient management and clinical outcomes following MI in different regions worldwide.

Methods

TIGRIS (ClinicalTrials.gov Identifier: NCT01866904) is a multi-center, observational, prospective, longitudinal study enrolling patients with history of MI 1 to 3 years previously and high-risk of developing atherothrombotic events in a general practice setting. Overall, 9,225 patients are being followed in 369 different centers worldwide, which will allow for the description of regional differences in patient characteristics, risk profiles, medical treatment patterns, clinical outcomes, and healthcare resource utilization. Patients will be followed for up to 3 years (minimum of 2 years).

Discussion

We report the rationale, design, patient distribution and selected baseline characteristics of the TIGRIS study. This study will describe real-world management, quality of life, and healthcare resource utilization for patients with stable CAD at least 1-year post MI.

1. Introduction

Atherosclerotic plaque ulceration, erosion, or rupture, followed by platelet activation and thrombus formation is thought to constitute the main cause of cardiovascular (CV) events. Medical management of patients after an acute coronary syndrome (ACS) is based on multiple randomized clinical trials defining the acute, typically first year, treatment after the index event. While evidence-based management has reduced mortality significantly in recent years, patients surviving the first year after an ACS remain at high-risk for future CV events.[1-4] This risk is aggravated by distinct comorbidities, including hypertension, diabetes mellitus and chronic renal dysfunction as well as a history of recurrent myocardial infarction (MI) or documented history of angiographic evidence of multi-vessel coronary artery disease (CAD).[5-7] These comorbidities will also impact on medical management.

With better survival of the first year after an ACS, the prevalence of this high-risk population is growing worldwide, and rehospitalization remains frequent and unchanged over decades.[8, 9] Therefore, it is important to establish an understanding of the demographics, treatments, and outcomes of these patients over time. The availability of the “long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease patients in post myocardial infarction patients” (TIGRIS) registry will complement the current armament of generally country-specific registries of variable design, that render extrapolation of observations to other countries and regions difficult.[10, 11] Furthermore, the limited information that is available suggests that management patterns and outcomes may vary for different nations. Direct comparisons of regional differences in post-MI

management and outcomes would be facilitated through the standardized aggregation of this information across different countries.

The TIGRIS study was initiated to achieve this objective. The goal of TIGRIS is to provide a standardized prospective and longitudinal description of patient characteristics, events (per person years at 12 and 24 months), healthcare resource utilization and current treatment patterns as seen in a relatively unselected patient population post ACS. In this prospective observational study, patients from 25 different countries with a previous MI 1 to 3 years before enrollment in the registry and at high-risk of developing future atherothrombotic events, will be followed for up to 3 years (minimum of 2 years).

2. Methods

2.1 Overall study design

TIGRIS (clinicaltrials.gov NCT01866904) is ongoing with a follow-up period of up to 3 years. All patients undergo routine clinical assessments and receive the standard medical care, as determined by the treating physician. Patients will not receive any experimental intervention or treatment because of their participation in the study. The overall study design and patient flow chart is shown in Figure 1.

2.2 Study population

TIGRIS includes patients aged 50 years or older with a documented history of presumed spontaneous MI with their most recent MI having occurred 1 to 3 years prior to enrollment, and with at least 1 of the following risk factors: ≥65 years, diabetes treated with medication, documented history of a second MI >1 year prior to enrollment, multi-vessel CAD, and/or chronic non-end stage renal dysfunction (creatinine clearance calculated by Cockcroft Gault equation 15 mL/min to <60 mL/min). All patients provided written informed consent for participation. The inclusion and exclusion criteria are described in Table 1.

2.3 Aim and objectives

The TIGRIS study will evaluate prospectively over a follow-up period of up to 3 years (minimum of 2 years), the risk for recurrent CV events in this high-risk stable post MI population. The primary objective is to evaluate clinical events and healthcare resource utilization associated with hospitalization for these events (duration of hospitalizations, and procedures) over the follow-up period. Secondary objectives are

to describe the rate of individual ischemic events as described above, including CV-related death and death for unknown reasons and ischemic stroke, and to evaluate the incidence of bleeding events requiring medical attention. Other objectives are to describe associations between patient characteristics with quality of life and with the use (duration, adherence, discontinuation) of evidence-based therapies, association between oral antiplatelet therapy and clinical events (ischemic, death for any cause, and bleeding; including in high-risk subgroups such as the elderly, diabetic, renally impaired, or with recurrent MI), and to describe risk factor control in this high-risk population.

2.4 Site selection and patient enrollment

In total, 334 sites (333 active with at least 1 patient recruited, and 1 site with no patients) have participated in the TIGRIS study in 25 countries worldwide. A National Principal Investigator (NPI) was identified for each participating country. In an attempt to obtain a representative sample at a country level, recruitment of sites and subjects was initially based on predefined selection of physicians (office-based primary care physicians and cardiologists as well as cardiologists based in hospitals with outpatient clinics) by NPIs; this was intended to provide a distribution of physicians across regions and locations (ie, urban, suburban, or rural areas). The aim was for each participating site to enroll at least 10 patients. A complete list of participating sites and principal investigators is provided in Appendix I (supplementary materials). All patients will be followed up to 3 years in accordance with the overall patient flow chart shown in Figure 1.

2.5 Study duration and phases

The planned duration of the study is from June 2013 (first patient in) until September 2017 (last subject last visit). Data collection is performed during the initial visit, and every 6 months such that every patient will have between 2 and 3 years of follow-up. These follow-ups are conducted either by a telephone call or personal visit (Figure 1). This provides information on these high-risk patients for a period from a minimum of 1 year to a maximum of 6 years since the index MI event.

2.6 Study variables

Variables obtained during the baseline visit were patient demographics including gender, age, race, place and type of residence, education level, and professional status. Sociodemographics including living arrangement status, income, and health insurance status were also collected. In addition, the prevalence of CV and bleeding risk factors, history of CAD and other CV disease as well as details of the medical history related to the index MI with a focus on antithrombotic medications has been assessed.

Variables from routine physical examination (heart rate, blood pressure [BP], weight, height, waist circumference) and from existing routine lab test (renal function tests, lipid profile, hemoglobin and glucose/glycated hemoglobin) if they were available and were performed within 3 months prior to the visit and up to 1 month after the visit (assuming no clinical events within this time window) were also captured in the initial visit.

Emphasis was paid to healthcare utilization related to CV or bleeding conditions during 6 months preceding enrollment.

Measures of health status as assessed by the EuroQol 5-Dimensions (EQ-5D) and EuroQol Visual Analog Scale (EQ-VAS) were collected at baseline. This measures self-reported health status in 5 dimensions (EQ-5D™; mobility, self-care, usual activities, pain or discomfort, anxiety or depression) with 3 levels of severity (none, moderate, severe). For each patient, a single health state value, or utility, was calculated (EQ-Index and EQ-VAS scores) and set on a scale ranging from 0 (which corresponds to death) to 1 (EQ-Index) or from 0 to 100 (EQ-VAS; which corresponds to a best imaginable state of health).

Information was also collected at baseline regarding clinics/outpatient center characteristics.

During the follow-up period, clinical outcomes (death, CV events, and bleeding events), antithrombotic medications and other evidence-based medications, patient-reported health status assessed by the EQ-5D are collected. Productivity loss such as sick leave for the patient and the caregiver which is event-related are being captured from a subset of around 10% of the study population from several countries where this information was considered particularly relevant (Nordic Region and The Netherlands). A complete list of variables captured in the study at baseline and during follow-up, are provided in Appendix II (supplementary materials).

2.7 Collection of data

The data are collected using electronic case report forms (eCRFs). Initial data collection was performed by the investigator. During the follow-up period, patients are either contacted via telephone every 6 months or attend for a study visit from the site. Follow-up phone calls are performed by either trained staff from the enrolling hospital

or from a designated call center, in accordance with a standard protocol to assist in recording of treatments, events and medical visits.

At each follow-up time point predefined clinical outcome events in the study as well as the variables related to associated healthcare utilization during hospitalization are collected directly from the treating physician/hospital through a standardized event confirmation eCRF and hospital module in the eCRF respectively in accordance with the following protocol. If, during interview, the patient or relative reports a predefined CV or bleeding-related hospitalization, the treating physician or hospital is contacted for confirmation of this event. Further information allowing determination of final diagnosis, primary cause of hospitalization, duration of hospital stay, procedures and interventions, and related healthcare resource utilization during hospital stay is collected from the treating physician or hospital directly through a standardized hospital module in the eCRF. If a death occurred, efforts are made to identify the cause of death (CV-related or non-CV) through the death certificate where available, or relatives, physicians, hospitals where it is not.

2.8 Statistical methods and sample size determination

This is a descriptive observational study without predefined hypothesis testing. The primary objective is to describe the incidence of CV events (time to first occurrence of any event from the composite CV endpoint of MI, unstable angina with urgent revascularization, stroke or death from any cause). The envisaged statistical methods included the description of the patients in accordance with their inclusion risk factors that define high-risk CAD: ≥65 years; treated diabetes; documented history of a second MI >1 year prior to enrollment; multi-vessel CAD; and/or chronic renal

dysfunction. Medication, and specifically the use of antithrombotic medication, over the study period will be described in terms of use at specific time points during follow-up, as well as the duration of antithrombotic medication and changes in regimen. EQ-5D data collected during the study will be reported descriptively. Healthcare resource utilization associated with events reported during the follow-up period will be assessed.

Events will be calculated both as risk (cumulative incidence) and rate using person-time methods whereby follow-up either terminates at the first occurrence or is censored at the last contact with the patient.

No formal power calculation has been undertaken for this descriptive study. Sample size was primarily driven by the country's needs based on payer requirements from their markets. Initially a sample size of 10,170 patients was estimated; due to delays in ethical approval in some countries, 9,225 patients were ultimately recruited into the study.

2.9 Ethics approval

The final protocol was approved by the relevant ethics committee from each country, and the site ethics committee. The study is being performed in accordance with ethical principles consistent with the Declaration of Helsinki revision, International Conference on Harmonization Good Clinical Practice guideline, and the applicable legislation on non-interventional studies.

2.10 Funding and responsibilities

TIGRIS is sponsored by AstraZeneca and is non-interventional in nature, with no drugs being supplied or funded. The TIGRIS Executive Committee comprises 12 members (7 cardiologists, 1 clinical pharmacologist, 1 health economist and 1 statistician, and 2 representatives from AstraZeneca). The executive committee with support from AstraZeneca is responsible for the design and conduct of this study, and all study analyses.

2.11 Participating regions

The participating regions were: Asia-Pacific, with 5 countries: Australia, China, India, Japan, and South Korea (n = 2,850 patients, 31%); Europe with 13 countries: Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Romania, Spain, Turkey, and the UK (n = 4,240 patients, 46%); North America: Canada and USA (n = 1,024 patients, 11%); and South America, with 5 countries: Argentina, Brazil, Colombia, Mexico, and Venezuela (n = 1,111 patients, 12%) (Table 2 and Figure 2).

2.12 Patient characteristics

Characteristics of patients in TIGRIS are shown in Table 2. Patients in Asia-Pacific and South America were younger, hence the risk factor age over 65 years was less frequently met as an inclusion criterion; there was a higher percentage of patients with treated diabetes mellitus in these 2 regions compared to patients from Europe or North America. On the other hand, the percentage of patients with a second prior MI (before the index MI) was higher in Europe and North America, while multi-vessel

CAD was seen more frequently in patients from North America and Asia-Pacific. The rates of chronic renal dysfunction were similarly distributed worldwide.

3. Discussion

This report describes the rationale and design of the TIGRIS study, which is unique in being a study of unselected patients that reflects the heterogeneity of patients who have stable CAD but are at high-risk. Specifically, TIGRIS will address regional differences in patient characteristics, clinical outcomes, medical treatment patterns, and healthcare resource utilization of patients with high-risk of future CV events 1 to 3 years post MI.

The risk of future CV events in patients with a history of MI is increased by comorbidities like diabetes mellitus, chronic kidney disease as well as the age and the complexity of CAD. While many randomized clinical trials have addressed this risk with emphasis on the first 12 months after an MI, little is known about the risk of subsequent ischemic events beyond this time in a “real-world” population. The improved survival post MI and the aging population are creating an emerging population for whom there is a problematic knowledge gap; specifically, there is a growing number of patients with a remote history of MI for whom there is little evidence to guide appropriate treatment.

Recently, Jernberg and colleagues published outcome data from a large Swedish national registry including 108,315 patients after MI with long-term follow-up.[12] Overall, 10% of the patients died during the hospital stay and within 1 week after hospital discharge, and an additional 12.3% over the following year. The cumulative rate of the CV composite outcome, including recurrent MI and stroke and CV death, was 18.3% in the first year after a MI. The CV risk remained high with 9.0% in the next 12 months and 20.0% in the following 36 months. Similarly,

Rapsomaniki and colleagues investigated patients aged 65 years and older from 1 year following a MI in the 4-nation APOLLO study. The adjusted risk of mortality over the subsequent 3 years ranged from 12.8% to 19.5%; the corresponding risks of hospitalized bleeding events ranged from 2.7% to 4.9%.[13] These data, derived from datasets from France, Sweden, the United States and the United Kingdom, were generated for a variety of purposes using different collection and validation methodologies, hence it is difficult to ascertain whether the variation in event rates between countries reflected real differences, or variations in methodology.

In 2 recently reported acute dual antiplatelet therapy randomized clinical trials, mortality risk (Kaplan-Meier) in the 12 months following randomization were generally low eg, for PLATO (4.5% ticagrelor; 5.9% clopidogrel)[14] and TRITON (3% prasugrel; 3.2%; clopidogrel).[15] PEGASUS investigated the long-term addition of ticagrelor to aspirin initiating treatment 1 to 3 years after a MI.[16] The 3-year Kaplan-Meier mortality risk was 5.2% in the aspirin arm, substantially lower than that observed in the APOLLO program. Therefore, it is clear, compared to more selected and generally younger patients within randomized clinical trials, the unselected population has a substantially higher risk.[17] This emphasizes the need for 'real-world' data collected using standardized rigorous consistent methodology to access outcomes during the years following a MI.

In addition to the provision of representative, general practice evidence, a major strength of TIGRIS is the focus on different countries. Notably, 30% of study patients derive from Asia-Pacific and 12% from South America, areas where the availability of such information is relatively limited. This study has already shown that

post-MI patients from Asia-Pacific and South America are younger and have a higher incidence of diabetes mellitus compared to patients from Europe or North America. Given these baseline differences in populations, TIGRIS will provide unique information on comparative outcomes and healthcare resource utilization in the years after a MI. Interpretation of these outcomes will be greatly aided though the recording of medical management patterns in different international settings and their association with clinical outcomes.

4. Conclusion

In conclusion, TIGRIS is a unique study that documents demographics, comorbidities, treatment patterns and outcome data in unselected stable CAD patients with previous MI in general practice settings. Data are being collected internationally in a rigorous, standardized and consistent fashion providing a relevant picture of both the burden of recurrent events and variability in management and outcomes in this poorly studied patient population.

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Authorship contributions

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Dirk Westermann	Data analysis and interpretation, drafting and revision of the manuscript
Shaun G. Goodman	Study design, data analysis and interpretation, and revision of the manuscript
Jose Carlos Nicolau	Study design, data analysis and interpretation, manuscript revision
Gema Requena	Study design, data analysis and interpretation, manuscript revision
Andrew Maguire	Study design, data analysis and interpretation, manuscript revision
Ji Yan Chen	Study design, data analysis and interpretation, manuscript revision
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Richard Grieve	Study design, data analysis and interpretation, manuscript revision
Stuart J. Pocock	Study design, data analysis and interpretation, manuscript revision
Tabassome Simon	Study design, data analysis and interpretation, manuscript revision
Satoshi Yasuda	Study design, data analysis and interpretation, manuscript revision
Ana Maria Vega	Study design, data analysis and interpretation, manuscript revision
David Brieger	Study design, data analysis and interpretation, manuscript revision

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Figure legends

Figure 1: Study design

MI, myocardial infarction; QoL, quality of life

Figure 2: Patient enrollment in “long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease patients in post myocardial infarction patients” (TIGRIS) by country and region

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 65 years • Diabetes mellitus requiring medication • Documented history of a second prior presumed spontaneous MI (>1 year ago) • Documented history of angiographic evidence of multi-vessel coronary artery disease • Chronic, non-end stage renal dysfunction (15 mL/min ≤ creatinine clearance calculated by Cockcroft Gault equation <60 mL/min)	• Presence of any condition or circumstance which in the opinion of the investigator could significantly limit the complete follow-up of the patient (eg, tourist, non-native speaker or does not understand the local language where interpreter services are not reliably available, psychiatric disturbances, alcohol or drug abuse) • Presence of serious/severe co-morbidities in the opinion of the investigator which may limit life expectancy (<1 year) • Current participation in a blinded randomized clinical trial • Patients receiving treatment with ticagrelor beyond 12 months, or off label use of ticagrelor

MI, myocardial infarction

Table 2: Patient characteristics

Patients, n (%)	All	Asia-Pacific & Australia	Europe	North America	South America	*P*
Patients	9225 (100)	2850 (30.9)	4240 (46.0)	1024 (11.1)	1111 (12.0)	
Inclusion risk factors						
Age ≥ 65 years	5766 (62.5)	1652 (58.0)	2814 (66.4)	666 (65.0)	634 (57.1)	<0.001
Diabetes requiring medication	2805 (30.4)	999 (35.1)	1118 (26.4)	307 (30.0)	381 (34.3)	<0.001
Second prior MI	943 (10.2)	210 (7.4)	491 (11.6)	131 (12.8)	111 (10.0)	<0.001
Multi-vessel CAD	6052 (65.6)	1921 (67.4)	2714 (64.0)	715 (69.8)	702 (63.2)	<0.001
Chronic renal dysfunction (CrCl 15–60 mL/min)	707 (7.7)	212 (7.4)	327 (7.7)	78 (7.6)	90 (8.1)	0.898

CAD, coronary artery disease; CrCl, creatinine clearance; MI, myocardial infarction

P-values estimated using Chi square test

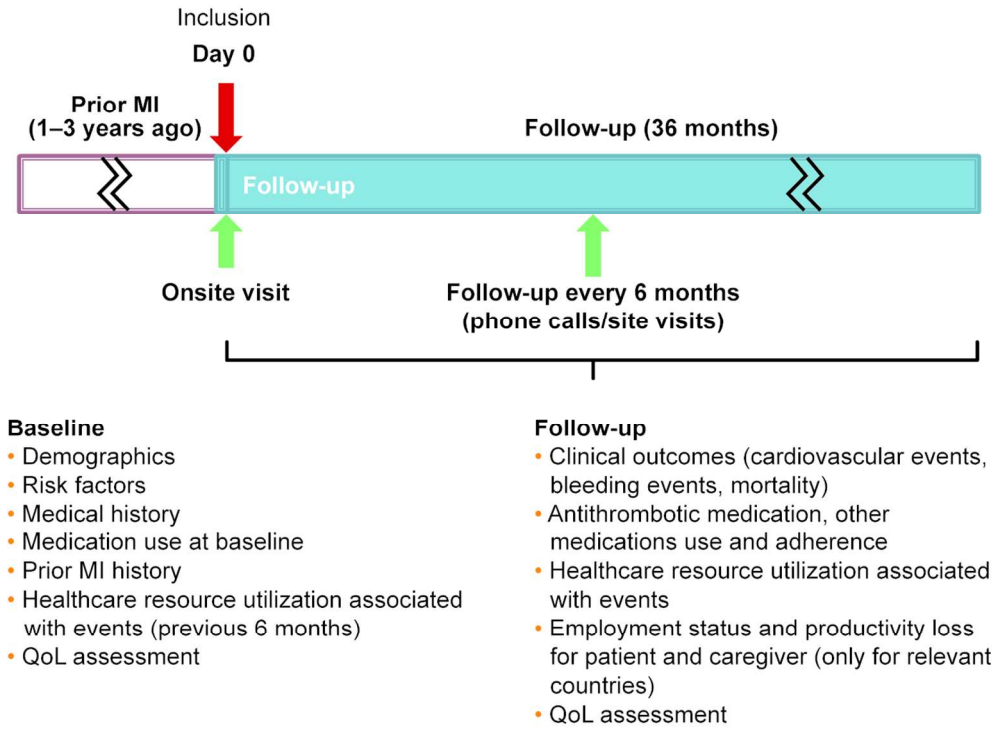

Figure 1: Study design

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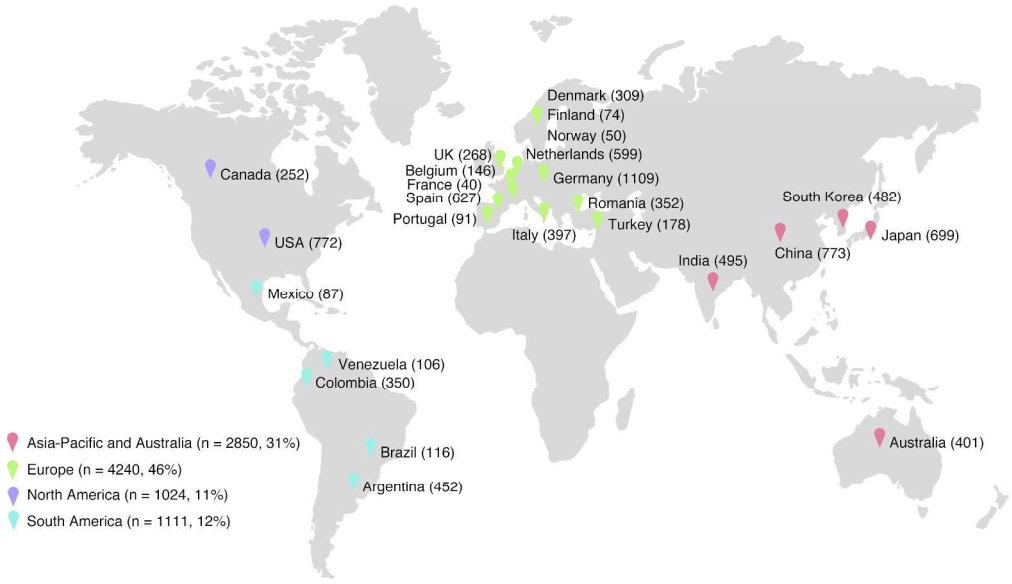

Figure 2: Patient enrollment in "long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease patients in post myocardial infarction patients" (TIGRIS) by country and region

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Supplementary Materials

APPENDIX I: TIGRIS National principal investigators (NPIs) and site study investigators

Site name	Investigator	Sub-investigator(s) and coordinator(s)
Asia		
China		
NPI: G Junbo		
Zhongda Hospital affiliated to Southeast University	M Genshan	Z Hong; Z Kongbo
The 2nd Hospital affiliated to Guangzhou Medical University	X Longgen	C Luo
Jinan Central Hospital affiliated to Shandong University	S Guohai	M Wei; W Fang; L Zhenhua
Guangdong General Hospital	C Jiyan	F Yingqing; C Anping
Zhongshan Hospital affiliated to Fu Dan University	G Junbo	Y Ming; X Lei
Shanxi CDV hospital	L Bao	A Jian; S Jing
Tianjin Union Medicine Center	Y Zhuhua	J Wang
1st Hospital of Liao Ning Medical College	T Guizhou	M Liu
Fuwai CV Hospital	Q Shubin	S Chunli; L Xiaoliang; Liu Rong; Z Jun; L Jia
Beijing University 1st Hospital	H Yong	Z Bo
The 1st Hospital affiliated to Chongqing Medical University	L Han	H Wei; C Jing
Wuxi 2nd People's Hospital	J Yan	
The 1st Hospital of Jilin University	Z Yang	L Quan; W Yonggang
1st Affiliated Hospital of Xi'an Jiaotong Univ, College	W Yanni	R Jie

Med		
The 1st Hospital affiliated to Lanzhou University	Z Zheng	Z Cunrui
Tanjin Thoracic Hospital	C Hongliang	Z Yingyi
Kunming General Hospital of Chengdu Military Region	Y Lixia	F Jun
Wuxi People's Hospital	Y Zhenyu	B Xiaoping; Y Fang; Z Xiaoxi
The Affiliated Hospital of JiangSu University	Y Jinchuan	L Peijing; D Shu; W Jun
India		
NPI: K Upendra		
Meenakshi Mission Hospital & Research Centre, Madurai	R Sivakumar	J Balan
Sir Ganga Ram Hospital	JP Sawhney	R Gehlot; MK Sharma
Escorts Heart Institute, New Delhi	U Kaul	M Kent
G. B. Pant Hospital	V Mehta	S Dalal
Heart First Cardiac & Vascular Centre	A Abhyankar	A Mistry
Fortis, Jaipur	R Gupta	B Mishra; S Chaturvedi; P Saxena; MK Sharma
PRS Hospital, Trivandrum	T Nair	TC Aneesh
West Fort Hitech Hospital	PP Mohanan	D Davies
B. M. Birla Heart Research Center	D Kahali	S Chatterjee
Fortis Hospital, Mohali	HK Bali	H Chauhan
Fortis Hospital, Noida	P Arora	S Singh
Ruby Hospital, Pune	MS Hirematth	R Pawar
Madras Medical Mission	A Mullasari	R Bhavani
Apollo Hospital	PC Rath	Adepu Aruna; Byomkesh Dikshit
Japan		
NPI: S Yasuda		

Iwate Medical University	Y Morino	T Ito; M Ishida; T Mifune; Y Ishikawa; S Nakajima; M Nagai; T Fusazaki; T Kimura; Y Shimoda; R Sakamto; Y Nakajima; K Komuro; Y Okuyama
St Luke's International Hospital	Y Nishi H Niinuma	H Mitsuhashi; K Masuda; A Mizuno; T Asano; I Komatsu; M Kikuchi; S Kimijima
Saiseikai Kumamoto Hospital	K Nakao	M Otaguro; K Nakano
Kimitsu Chuo Hospital	T Himi	M Yamamoto; H Fujimaki; Y Matsudo; T Sekine; K Hou; N Tonoike; S Tanaka; YHB Ge; S Tokimasa; A Fujino; S Hashidume
Kumamoto University Hospital	S Hokimoto	H Ogawa; Kenichi Tsujita; H Soejima; E Yamamoto; S Tayama; T Tanaka; S Kojima; Y Arima; M Yamamuro; K Sakamoto; Y Izumiya; S Takashio; T Akasaka; Y Kimura; H Kurokawa; K Yamanaga; N Komuro; T Miyazaki; K Nishiyama; Y Kawanami
Fujita Health University	Y Ozaki	E Watanbe; M Sarai; Y Kato; S Motoyama; H Naruse; Y Sobue; M Okumura; K Shiino; M Ohta; M Yamamoto; H Ito; Y Takakuwa; T Ichikawa; R Okuyama; M Ishikawa; M Koshikawa; Y Nagahara; M Miyagi; M Iwase; M Otsuki; N Hoshino; Y Hashimoto; T Muramatsu; S Matsui; S Ishikawa
Sapporo Medical University Hospital	T Miura	A Hashimoto; T Miki; H Yoshida; N Kokubu
Hirakata Kohsai Hospital	S Kitaguchi	M Ozaki; R Yamauchi; Y Haruna; H Takenaka; K Takenaka; T Yamamoto; Y Kurozumi; N Takemoto
Fukuoka University Hospital	K Saku	A Kawamura; H Nishikawa; A Iwata; K Fujimi; E Yahiro; M Sugihara; A Ike; K Urabe
Kitasato University Hospital	J Ako	T Tojo; T Shimohama; H Fukaya; T Naruke; H Shinagawa; J Kishihara; T Yanagisawa; Ouchi; K Yamamura
Nippon Medical School Hospital	W Shimizu	K Asai; H Takano; G Takagi; K Kato; M Yoshikawa; K Murai; S Nakamura; Y Tsukada; T Yamamoto; K Akutsu; Y Hosokawa; K Inui; E Nakamura; K Kawakami
Chikamori Hospital	K Kawai	R Imai; S Kubokawa; S Seki; S Yamamoto; Y Nakaoka; H Hosoda; T Matsui
Chiba University Hospital	Y Kobayashi	K Sugimoto; Y Aoki; K Ishikawa; M Takahara; T Nakayama
Fukui CardioVascular Center	S Mizuno	K Osato; I Moriuchi; T Murakami; K Misawa; H Kokado; M Saga; Ma

		Tsuchida; Y Takasawa; J Yamaguchi; M Suzuki; N Maekawa; S Yoneda
Ehime Prefectural Central Hospital	Y Kazatani	H Okayama; T Yamada; G Hiasa; Y Kawada; M Kinoshita; T Shigematsu; H Nakagawa; T Ozaki; S Hosokawa; M Matsubara; K Fukuchi
Ishikawa Prefecrual Central Hospital	H Kanaya K Miwa	T Matsubara: T Yasuda; M Inoue; Y Tamura; M Hashimoto; S Niwa; K Hakko
Tohoku University Hospital	H Shimokawa	J Takahashi; Y Matsumoto; K Ito; K Hao; R Tsuburaya; E Ishida
Yokohama City University Medical Center	N Maejima	K Kimura; T Ebina; K Hibi; K Konishi; N Iwahashi; T Matsuzawa; H Akiyama; Y Kimura; Y Minamimoto; K Matsushita; S Kataoka; S Ichikawa; S Kuji; K Takahashi; C Kawashima; K Hashiba; H Nakahashi; M Kosuge; M Ninomiya
Osaka City University Hospital	Y Minoru	M Yoshiyama; S Ehara; T Hasegawa; K Shimada
Gunma Prefectural Cardiovascular Center	R Kawaguchi	S Ooshima; H Kan;Y Miyaishi; M Maruhashi
Seiyu Memorial Hospital	Y Tomoguchi	S Fujiwara; Y Ueno; M Gohda; K Takei; Y Shimomoto
Shizuoka Hospital	T Onodera	R Nawada; K Murata; R Takeuchi; Y Watanabe; T Yoshizaki; S Kageyama; N Hosoya; T Takagi; S Yamashita; G Matsukura; A Fujinami
Tokushima Red Cross Hospital	S Hosokawa	Y Hiasa; R Ohtani; K Kishi; T Takahashi; K Yuba; H Miyajima; R Ogura; Y Tobbeto; T Yasuoka; Y Ooga; H Kiyobe; Y Shima
National Cerebral and Cardiovascular Center	M Ishihara; T Noguchi	S Yasuda; M Fujino; M Nakanishi; T Arakawa; R Kumasaka; T Kanaya; S Honda; T Nagai; Y Goto; Y Asaumi; K Nakao; M Kawakami; R Yamada; A Matsuyama; Y Kawakami; T Nishimura
Juntendo University Shizuoka Hospital	S Suwa	N Kubota; S Tsuboi; T Shimizu; H Wada; H Endo; Y Kato; M Sesoko; M Kunimoto; S Ouchi; J Shitara; K Shiba
Oji General Hospital	T Matsumoto	J Ohata; D Yoshida; N Kato; H Hotta; T Ito; S Tanaka; H Narikawa
Hyogo Prefectural Amagasaki General Medical Center	T Miyamoto	Y Takatsu; Y Sato; R Taniguchi; K Yoshitani; R Fukuhara; S Saga; T Kobayashi; H Shinomiya; S Imura; H Inazumi; T Kuragaichi; M Shiba; H Nakayama; C Uwajima; A Negimoto
Tenri Yorozu Hospital	S Enomoto;	S Enomoto; K Kaitani; C Izumi; T Tamura; H Kondo; N Onishi; M

	Y Nakagawa	Miyake; Y Tamaki; K Takahashi; N Kuroda
Kusatsu General Hospital	A Wada	M Fujii; T Matsumoto; K Mori; A Taniguchi; S Kimura; Y Fujito
Tokai University Hospital	Y Ikari	F Yoshimachi; N Ogata; N Shinozaki; N Masuda; G Nakazawa; T Murakami; T Nakano; M Sato; S Torii; H Nagamatsu; T Suzuki; H Shimizu; T Suzuki; S Minakawa; H Horinouchi
Kurume University	T Ueno	S Yokoyama; T Nakayoshi; N Itaya; M Sasaki; H Chibana; Y Aoki; K Sasaki; Y Sugi; M Otsuka; E Ogura
Hiroshima City Hospital	K Nishioka	Y Nakama; T Oka; K Dai; K Ooi
South Korea		
NPI: Y-J Kim		
Wonju Christian Hospital	J Yoon	SH Han
Pusan National University Hospital	K Soo Cha	HC Lee; J-H Oh; J-H Choi; HW Lee; J Lee; J Hong; SH Ji; WJ Kim
Kosin University Gospel Hospital	T-J Cha	IK Noh
Chonbuk National University Hospital	J-K Chae	EJ Cho; JY Hong; SM Lee
Keimyung University Dongsan Hospital	C-W Nam	M Y Shin; M H Choi
Chung-Ang University Hospital	S W Kim	KH Kim; M Choi
Inje University Haeundae Paik Hospital	D Kim	KN Park
Chungbuk National University Hospital	M-C Cho; SM Kim	CS Lee; EK Kim
Chonnam National University Hospital	M-H Jeong	KH Park; DS Sim; YJ Hong; A Choi; C Kim
Gyeongsang National University Hospital	Y-H Jeong; JS Koh	CH Kwak; J-Y Hwang; JR Park; ES Kim
Yeungnam University Hospital	Y-J Kim	D Shin; JS Park; SH Lee; U Kim; JW Son; KH Yim; YM Ha; HS Lee; JM Kim
Chungnam National University Hospital	S W Choi	JH Lee; NM Jeon
Australia		
NPI: D Brieger		

Concord Hospital	D Brieger	K Xu
John Hunter Hospital	N Collins	A Gordon; E Hicks
St George Hospital	M Sader	P Shrestha; K Dobinson; J Brimley; D Vrachas; E Watson
Royal Brisbane and Women's Hospital	C Hammett	L Carr; C Booth; S Hayman; A Brazzale; C Cosgrove; A Lin; G Goodman; L Palethorpe; L Hindom; L Lilwall
Wollongong Hospital	A Lee	P Hedge; D Devenney; T Fetahovic; S Mackay; J Gibbs
Royal North Shore Hospital	G Nelson	M Ward; E Reid; A Loxten
Princess Alexandra Hospital	P Garrahy	C Hall; C Sieg
Sir Charles Gairdner Hospital	P Thompson	C-Di Camillo; H Anderson; L Ferguson; S Zafer; K Mohammadi; S Nagel
Gold Coast Hospital	R Jayasinghe	L Howes; S Quinlan; T Brumbly
Royal Melbourne Hospital	D Eccleston	K Phan; J Ward
Northern Hospital	W van Gaal	I Subiatko; N Rudd; M Park
Fremantle Hospital	A Whelan	R Kamne; S Atique; T Nunn; A Rehmani; D Greenwell; G Tulloch; N Forrest
Liverpool Hospital	J French	E Plotz; A Croucher
Coffs Harbour Base Hospital	J Waites	V Joseph; P Keays; L Gill
Epworth Hospital	R Dick	C Savage; B Slait
Nambour General Hospital	A Willson	R Poulter; M Johnson; P Larsen; S Wadham; M Fellner; L Webber; K Greaves
Europe		
Belgium		
NPI: M Vrolix		
ZOL Genk	M Vrolix	W Helsen; N Peters; C Swijsen
OLV Aalst	E Barbato; C Van Mieghem	E Lievens; H Batjoens

AstraZeneca (AZ) St Augustinus Veurne	M Detollenaere	L De Bruyne; M Everaert
AZ Klina	F Cools	N Simons; V Thyssen
Imelda Bonheiden	B Vankelecom	Y Daelemans; C Vissers; R Janssens
Maria Ziekenhuis Overpelt	D Faes	A Van Dorpe
UZ Gent	S Gevaert	P Vervaet
AZ Groeninge - Campus LS	P Dejaegher	M DeConinck
Denmark		
NPI: H Nielsen		
Hjerteklinikken Plan 5 Regionshospitalet Randers	H Rickers	B W Friis; M Morsing
Gentofte Hospital Hellerup	J S Jensen	J Laage-Petersen; LH Simonsen
Rigshospitalet Hjertecentret, København	L Holmvang	A Karlsdottir; L Klovgaard; SB Nielsen; M Tarras-Wahberg
Bispebjerg Hospital	H Nielsen	E Stokholm; B Hauggaard; D Petersen
Ålborg Sygehus	L H Rasmussen	A Gammelmark; BG Sorensen; F Hellum; B Mortensen
Amager Hospital, København S.	J Brønnum-Schou	JB LLægelig; H Hempel; P Hadsund
Haderslev Sygehus Kardiologisk sektion	E V Friis	C Markussen; I Christensen
Finland		
NPI: I Tierala		
Turku University Hospital	J Airaksinen	K Lahtonen; T Vasankari
Tampere University Hospital	S Vikman	V Rasanen; H Nappile; H Schemakka
Keski-Suomen keskussairaala	J Niva	
France		
NPI: T Cuisset		
Hôpital Pasteur	E Ferrari	L Marthoud; M Douillet
Centre Hospitalier Louis Pasteur	G Range	C Laure

Centre Hospitalier de Versailles	J L Georges	J B Azowa
CH St Joseph St Luc - LYON	O Dubreuil	S Rio
Hôpital de bligny	A Ohanessian	
CHU de la Timone, Marseille	T Cuisset	
Centre Hospitalier Sud Francilien, Service de cardiologie	P Goube	P Brito
Germany		
NPI: S Blankenberg		
Klinikum Leverkusen gGmbH	P Schwimmbeck	I Wenzel
Robert-Bosch-Krankenhaus	T Schäufele	I Wenzelburger
Medizinische Klinik II am UKSH Campus Luebeck	A Joost	A Constantz; C Lüttecke; M Werner
St. Josefs Hospital	S Lüders	U Venneklaas; I Medizin
Univ.-Klinikum	E Giannitsis	H Deigentasch; S Stegmaier
Klinikum Coburg gGmbH	J Brachmann	A Hoehn; U Göbel
Klinikum Stadt Ludwigshafen Herzzentrum	U Zeymer	H Tolksdorf; S Baumann; N Veth-Leonhardt; P Riedmaier
Kliniken Maria Hilf GmbH	J vom Dahl	U Gareis; B Krug-Hoeren
Carl-von-Basedow-Klinikum Merseburg	R Prondzinsky	D Brosseit; S Koegel
Elisabeth-Krankenhaus	O Bruder	E Blank; V Reuter; M Steffen
Universitäres Herzzentrum Hamburg	D Westermann	M Redlefsen; E P Tigges; M Hermes; I de Boer; M Redlefsen; M Karakas
Universitätsmedizin der Johannes Gutenberg-Universität Mainz	T Gori	I Walther; K Schulz
Kardiologie am Tibarg	F Stahl	J Schiller
University Heart Center Köln (Cologne)	V Rudolph	I Berg
Sana Kliniken Lübeck	J Weil	M Miodek; T Köllner
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Kardiologischen Gemeinschaftspraxis am Park Sanssouci Potsdam (St. Josefskrankenhaus)	R Gaub	V Gaertner
Krankenhaus Dresden-Friedrichstadt II. Medizinische Klinik, Dresden	S Schellong	R Frommhold; B Voigts; L Pomper; J Gehre; M Hahn; M Langer; R Oelsner; T Wolf
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University of Ulm Medical Center	S Markovic	O Smirnova; A Maass; K Kraus; M Holl; U Schneeu
Katholisches Krankenhaus St. Johann Nepomuk Medizinische Klinik II	H Ebelt	J Anacker
Kardiologische Praxis	J Bott	M Erdas; J Bott
Klinikum Frankfurt Höchst GmbH	C Kadel	G Rahn; N Zulauf
Medizinisches Beratungs- und Therapie-Zentrum Chemnitz GmbH	K Kleinertz	E von der Planitz; F Froehlich-Grimm; S Geserick
Städtisches Klinikum München GmbH	H Mudra	P Setzer; J Fiedler; M Segerer; A Stote
Vivantes Klinikum Neukölln	H Darius	A Maselli; G Biller; S Bodogh; S Gaulke
Universitätsklinikum Erlangen	S Achenbach	C Uecker; S Fechner
Synexus Frankfurt Research Centre, Frankfurt	C Contzen	N Freibott
Synexus Berlin Research Centre, Berlin	J Stößel	F Bauch; T Trachte; AM Peukert
Synexus Leipzig Research Centre	K Kreutzmann; O Maus	H Knopf; I Schiefer; N Zimmer; T Kusly
Synexus Bochum Research Centre	A Rinke	A Rauscher; S Laube; P Doelken
Bundeswehrzentralkrankenhaus Klinik für Innere Medizin	C Bickel	B Jürgens; M Halfter
Italy		

NPI: C Cavallini		
Ospedale Santa Maria della Misericordia	C Cavallini	E Grikstaite
Presidio Ospedaliero Ca' Foncello, Treviso	Z Olivari	P Pantano
Ospedale del Delta, Lagosanto	GF Percoco; R Mazzucco	
Centro Cardiologico Monzino	G Marenzi	M De Metrio
Ospedale Pediatrico Apuano G. Pasquinucci	S Berti	KJ Tyack; E Koni
A.O.U. Federico II	PP Filardi	T Losco; S Conte; L Casaretti
Ospedale Misericordia e Dolce di Prato	F Pestelli	_
Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone di Palermo	S Novo	C Vicari; C Paleologo
Cardiologia del Policlinico S. Orsola di Bologna	A Branzi; C Rapezzi	G Melandri; G Norscini
Azienda Ospedaliera per l'Emergenza "Cannizzaro"	A Fiscella; C Condorelli	M Pardini
Ospedale Unico della Versilia	G Casolo	M Pardini; L Robiglio; F Vivaldi
ASL Sassari Ospedale Civile S.S. Annunziata	P F Terrosu	C Podddighe; C Denurra; G Sanna; A Canu; E Mura
Azienda Ospedaliera di Rilievo Nazionale Antonio Cardarelli	C Mauro	D D'Andrea; A Sasso; F Furbatto
The Netherlands		
NPI: AFM Kuijper		
BovenIJziekenhuis	M van de Wetering	L Klijn; SJ Groeneveld
Rijnstate Ziekenhuis	FF Willems	E Maasen; J Marx; A Dekker; E Verhaah; P Verhoeven
Tergooiziekenhuizen, loc. Blaricum	G Hoedemaker	M van der Zeijst
IJsselland Ziekenhuis	B J Berg van den	I Hendriks

Reinier de Graaf Gasthuis	E Ronner	A Wissenburg; L van Setten van der Meer; L van der Hout; A Dijkshoorn
HagaZiekenhuis, loc. Leyenburg	M JW Götte	M Hugo; E Karijodikoro; C de Jonge; H de Lange-van Bruggen
Slingeland Ziekenhuis	JCM Hal van; DAAM Schellings	
Ziekenhuis Gelderse Vallei	F den Hartog	D van Wijk; M Singerling
Martini Ziekenhuis	GL Bartels	M Hendriks - van Woerden; B van der Roest; Z Aukema-Wouda
Kennemer Gasthuis - locatie EG	JF Küpper	J Vooges; C Kalkman
Röpcke Zweers Ziekenhuis	HP Beijerbacht	M Beijering; B Baarslag
Atrium Medisch Centrum	T Lenderink	I Kremer
Spaarne Ziekenhuis	AFM Kuijper	M Schiks; E Bayraktar
Orbis Medisch Centrum	MERM van Daele	O Douven; M Bouwens
Gelre Ziekenhuizen, loc. Zupthen	NYY Al-Windy	T Tiemes; M van Nistelrooy
Ziekenhuis Bethesda	SHK The	F Geerlings; J Krikken
Norway		
NPI: F Kontny		
Stavanger Universitetssjukehus Helse Stavanger	D Nilsen	S Moen; T Brugger-Andersen; V Ponitz
Diakonhjemmet Sykehus	EH Oie	H Muriq; RU Quazi
Sykehuset Ostfold	RAM deBoer	
Portugal		
NPI: C Gavina		
Unidade Local de Saúde de Matosinhos	C Gavina	C Ponte; M Centeno; H Maia; I Goncalves; R Barrades; J Tavares
Unidade Saúde Familiar Santo André de Canidelo	F Ferreira	L Alves
Unidade Saúde Familiar São João	P Santos	C Franclim

Hospital de Santiago	JF Santos	
Hospital da Cruz Vermelha	F Matias	
Hospital da Luz	D Ferreira	MB Fonseca
Hospital de Faro	J Mimoso	W Santos; J Amando
Unidade Local de Saúde do Alto Minho	R Lima	R Lima; CC Dias; C Mateus; V Enes; G Silva
Hospital de Braga	A Gaspar	J Oliveira; M Goncalves
Romania		
NPI: S Balanescu		
Spital Judetean de Urgenta	G Stanciulescu	
Spital Clinic Judetean Urgenta Arad	D Darabantiu	AM Pop; CD Patrascanu
Spital Clinic de Recuperare	D Zdrenghea	I Gusetu
Spitalul Judetean Drobeta-Turnu Severin	N Trocan	V Toman; J Cristian
Spitalul Clinic de Urgenta Bucuresti	M Dorobantu	O Tautu; I Petre; A Deaconu
Spital Clinic Municipal de Urgenta	M C Tomescu	I M Citu
Spitalul Universitar de Urgenta Elias	S Huidu	L Ionescu
Centru Clinic de Cardiologie	R Musetescu	D Toader
Spitalul Judetean de Urgenta 'Sf. Pantelimon' Focsani	C Bengus	M Miron; M Burca; V Ochean
Spital Judetean de Urgenta Braila	M Bogdan	L Serban
Spitalul Monza Bucuresti	S Balanescu	C L Caldararu; T Cristion-Razvan; A Linte; A Georgescu
Spital Clinic de Urgenta Sf. Pantelimon	L Protopopescu	
Spitalul Clinic Judetean de Urgenta Sibiu	I Manitiu	M Teodoru; C Zagoni
Clinica Polisano	M Vladoianu	O Purcar; R Dobrin
Institutul de Boli Cardiovasculare Timisoara	L Petrescu	D Maximov; R Dan; R Nicola
Spain		

NPI: AF Ortiz		
Complejo Hospitalario Virgen del Rocio	JN Portero	
Hospital de Baza	MM Robles; G Arquero	
Hospital General de Vic	JS Serrasolsas	RR Fernandez
Hospital Vall D´Hebron	JAB Riu	J Baneras
Complejo Hospitalario Universitarion de Santiago	PM Ramos	J Seijas
Hospital General Universitario de Alicante	VIA Esteban	RA Ferrer
Hospital Clinico San Carlos	AF Ortiz	R Guerra; S Mera
Hospital Puerta de Hierro	P Pavia	A Gonzalez; M Cordoba
Hospital del Mar de Barcelona	JB Cortada	P Cabero; C Soleer
Hospital de Bellvitge	AC Filiat	M Nato; O Alegre
Hospital Virgen del Mar de America	JLB Coronado	
Hospital San Pedro de Alcantara	FJF Portales	P Dominguez; S Romani
Hospital Ramón y Cajal	M Sanmartin	LM Rincon; D del Van
Hospital 12 de Octubre	RM Asenjo	
Hospital Virgen de Arrixaca	F Marin Ortuno	E Orenes; M Quintana Giner
Hospital de Lerida	M Pique	M Agusti; L Barta
Hospital Principe de Asturias	A Garcia Lledo	JAS Barrio; FL Bachiller; JG Pérez-Velasco; VP Mir; VB Jimenez; GB Lopez
Hospital Son Llatzer	T Ripoll	Y Gomez
Hospital Univeritario San Cecilio	BG Extremera; JGS Ramos	E Jimenez; E Garcia; ML Abaraca; A Guarnido; I Merida
Turkey		
NPI: E Bozkurt		
T.C. Sağlık Bakanlığı Yıldırım Beyazıt Üniv. Atatürk	E Bozkurt	H Ayhan

Eğt. Arşt. Hastanesi		
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T.C. Sağlık Bakanlığı Yıldırım Beyazıt Üniv. Dışkapı Eğt. Arşt. Hastanesi	E Yeter	A Nallbani
Mersin Üniversitesi Tıp fakültesi	A Camsari	İT Ozcan
Diyarbakır Eğit. Araş. Hast	R Altindag	S Akkaya; İ Erkek
İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yerleşkesi	İ Keles	OO Tok; M Cimci
Hacettepe Üniversitesi Tıp Fakültesi	E Atalar	H Yorgun
Adnan Menderes Üniversitesi Araşt Hastanesi	C Ceyhan	H Gungor
UK		
NPI: K Ray		
Craigavon Area Hospital	A Moriarty	A Mackin; A Mcmullan
Northern General Hospital	R Storey	C Bridge; S Spedding-Dutton; G Sangha; R Ecob
Hairmyres Hospital	B O'Rourke	S Clements; C Malcolson
Monklands Hospital	A Pell	J Anderson
Musgrove Park Hospital, Taunton	D McKenzie; M Dayer	K James; F Venn; P Hill
St George's Hospital NHS Trust Research Centre	R Sharma	D Cole
Papworth Hospital NHS Foundation Trust	S Hoole	R McClean; S Meakins; T McGovern; A Shook; G Charman; S Smith
Barnet General Hospital	A Bakhai	L Lim; S Hoole; S Metherell; Vi Krishnamurthy
Royal Wolverhampton NHS Trust, New Cross Hospital	J Cotton	A Smallwood
North America		
Canada		
NPI: S Goodman		

Clinique Sante Cardio MC	C Constance	M Gauthier; J Piche-Giroux
Vizel Cardiac Research	S Vizel	B Fox
Glanz Medicine Professional Corporation	A Glanz	C Vilag
Hamilton Health Sciences - General Site	A Lamy	P Power; T Rizzo; F Toito
Brampton Research Associates	M Gupta	CD La Cruz; R Kahlon; Y Thevakumaran
St-Jerome Medical Research Inc.	Y Pesant	V Sardin; S Grigorova; M Lambert; YS Laframboise
York PCI Research	W Cantor	K Robbins; N Popel
Lawson Health Research Institute	R Petrella	C Dihel; J Duncan; C Bartol; Z Majeed
Saint John Medical Clinic	R Bessoudo (Marr)	G O'Blenis
Cambridge Cardiac Care Inc.	AS Pandey	M Pandey; S Juranics
Keele Medical Place	A Bell	P Kailey
Yorkview Medical Center	I Teitelbaum	J Teitelbaum; J Dimarino
Viacar Recherche Clinique Inc.	R Chehayeb	P Carmichael
Centre de Sante et de Services Sociaux de Thetford	R Dupuis	F Ouimet; M Couture; B Roberge
USA		
NPI: M Cohen		
Central Bucks Cardiology	JJ Kmetzo	D Taylor; R Riley
Ventura Cardiology Consultants Medical Group	N Mayer	B Mitchell
Atlanta Heart Specialists LLC	N Singh	K Turner
Doylestown Cardiology Specialists-VIAA	R Sangrigoli	L Schwarz; S Martin
Kootenai Heart Clinics LLC	W Bennett	L Passey; A Kavanaugh
Fletcher Allen Health Care	D Schneider	M Rowen; K Begin
Maine Research Associates	R J Weiss	D Murphy; A Gagergan
Minneapolis Heart Institute Foundation	M Newell	M Buescher

Heart Center Research LLC	N K Mann	B Lamb
The Miriam Hospital	P Gordon	L Felix; J A Gomes
Heart and Vascular Center of West TN	E Korban	A Harrington
Jackson Cardiology Associates PC	R Mehta	Kristy Watkins
Baylor Research Institute	M McKenzie	R Buckner; IS Mohiuddin
Cardiovascular Specialists of Central Maryland	K Friedman	T Burley
Harbor - UCLA Medical Center	WJ French	CC Morales
Duke	TY Wang	S Decker; R Mehta
North Ohio Research Ltd	W Sheldon	A Bohn; K Humphrey; M Fazio
Clearwater Cardiovascular and Interventional Consultants	JK Amin	M Cameron; L Selker
Heart Care Center	M Baig	C Yough
Virginia Heart	T Haddad	J Jain; D Overbeck
Eastern Maine Medical Center	A Wiseman	A Coombs
Northwest Heart Clinical Research, LLC	A Soni	S Bellini; D Golen
Virginia Cardiovascular Associates	H Taheri	K Morgan
South FL Research Group, LLC	J Roberts	K Shatsky
UNC Heart and Vascular Center	P Kaul	A Que-Xu
UPMC Heart and Vascular Institute - Shadyside	K Tummalapalli	M Travis; A Malecky
South Miami Hospital	J Ghitelman	J Jean-Mary
Cardiology Associates of New Jersey	A Schwarcz	
Long Island Cardiovascular Consultants	R D'Agostino	L Lavelle
CAPRI LLC	R Davidson	S Davidson
Apex Research Institute	J Duffy (Tonkon)	J Dolen; M Gonzalez
Robert Packer Hospital	E Kaluski	C Lanning (Lorraine Barten)

Swedish Medical Center	J Petersen II	
St. Vincent Medical Group	JS Rossi	J Gall
Southern Medical Group, P.A.	W Batchelor	P Knap
South America		
Argentina		
NPI: JLCN Estrada		
Hospital Italiano de Buenos Aires	JLCN Estrada	E Castillo
Fundación Favaloro para la Investigación y la Docencia Médica	EA Duronto	L Arrechavala
Hospital Central de Mendoza	RBS Zarandon	O Caruso; G Segui
Sanatorio El Carmen	EA Falu	MC Iriarte
ICBA - Instituto Cardiovascular de Buenos Aires	MS Trivi	A Navarro
Instituto de Cardiología Juana Francisca Cabral	SM Macin	MJG Salazán; L C Vargas
Sanatorio Profesor Itoiz	CA Rapallo	V Ferreiro; R Santos
Sanatorio Modelo de Quilmes S.A.	AD Hrabar	CM Funosas; A Cappi
Hospital Universitario Austral	HE Fernandez	G Marinsalta; J-M Bonorino
Sanatorio Los Arcos	SM Rahabani	
Sanatorio Mayo Privado S.A.	DJ Anauch	M Barrionuevo
Hospital Español	DL Paolantonio	A R Quiroga; I Gribaudo; G Matkovich
Hospital Privado Centro Médico de Córdoba S.A.	OA Salomone	N Konicoff
Brazil		
NPI: JC Nicolau		
Hospital Santa Isabel	APM Kormann	A Marchi; J Spricigo
Hospital Universitário UFMS	DG da Silva Jr	RM Uehara; R Nakasone
Instituto do Coração de Marília	JC Ferreira	L Silva; D Funai; D Rodrigues

	Braga	
Hospital de Base - FAMERP	LN Maia	RP de Brito; O da Silva Jr; N Goes
Colombia		
NPI: N Jaramillo		
Centro de Investigaciones Clínicas S.A.S.	C Arana	M Ceballos; M Gonzalez; O Sierra
IPS Unidad Cardiologica de Cartagena.	M Herrera	D Perez; M Jazime
Asociación IPS Medicos Internistas de Caldas	DI Molina	H Urrea; JM Patiño; GC Giraldo; I Rodriguez
Centro de Investigaciones Cardiodiagnostico S.A. / Fundación del Caribe para la Investigación Biomedica (Fundacion BIOS)	M Urina	N Ramirez
Centro de medicina del Ejercicio y Rehabilitacion Cardiaca	N Jaramillo	M Toloza; G Rasterepo; RMT Giraldo; V Jaramillo
Clinica Cardiovascular Santa Maria	R Fernandez	E Gonzalez; A Quintero
Instituto del Corazon de Bucaramanga	B Vesga	PS Delgado; DPS Avciniegas; H Hernandez; L Rodriguez
Cardiología Hugo Duque, Centro de Excelencia S.A.S. CHD Cardiology	H Duque	M Zuluaga
IPS Centro Cientifico Asistencial Jose Luis Accini SAS	JL Accini	T Valencia
Centro de diagnostico Cardiológico	F Manzur	D Rosales; D Boneu; F Manzur
Centro de Investigacion Clinica Avanzada y Multidisciplinaria, CICLAM S.A.S.	C Jaramillo	G PG Lopez; ML Jaramillo; C F. Jaramillo; L Velasquez
Mexico		
NPI: FP Padilla		
Unidad Medica de Alta Especialidad; Hospital de Cardiología. Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social	ED y Díaz	
Sitio Dr. Alberto Esteban Bazzoni Ruiz	AB Ruiz	D Monreal; AC Tovar
Cardiosalud	GR Martínez	V Delgado; C Preciado; PS Guzman

Cardioarritmias e Investigacion SC	IR Briones	M Ramos
Consultorio Privado Dr. Padilla	FP Padilla	S Fernandez; VM Delgado; L Ruiz
Hospital General de Puebla “Dr. Eduardo Vázquez Navarro”	JCP Alva	M Macip; SR Paboios
Unidad de Investigacion en Salud	O Fierro Fierro	I Gonzalez; DAS Carreon
Venezuela		
NPI: ML Fariña		
Hospital Universitario de Caracas	N Antepara	A Ruggiero; S Martinez
Hospital Militar "Dr. Carlos Arvelo"	S Tovar	E Moya; L Ramirez; M Wilman
Hospital Universitario "Dr. Angel Larralde"	ML Fariña	
Centro Policlínico La Viña	C Delgado	R Rey
Unidad Cardiológica Clínica IDET. Caracas	Á Avendaño	A Sanchez; J Marin

APPENDIX II: Study variables and healthcare resource utilization

Variable	Details
Baseline / Enrollment	
Clinic/outpatient center type	University General Hospital (UGH), n = 49; non-UGH, n = 144; Other type of hospital/clinic (CCU/cardiology/cardiovascular/research), n = 137; Private clinic, n = 24; Ambulance, n = 10
Patient characteristics	Gender, age, race (latter if allowed by local regulations)
Place of residence	Rural, metropolitan
Educational level	Measured by years of education due to differences in degree programs across countries
Professional status	Employed, self-employed, unemployed, homemaker, retired, student, sick leave, maternity leave, disability pension
Type of residence	Home, nursing home, etc.
Living arrangement status	Living alone, not living alone
Income	Only in countries where feasible
Health insurance status	Only in countries where feasible
Cardiovascular risk factors	Hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking, family history of CAD
Major bleeding risk factors	History of major bleeding or severe liver disease
History of other CVD	PAD, HF, stroke, TIA, ICD, permanent pacemaker, VTE, valve repair/replacement, AF
Medical history re index MI 1 to 3 y prior	Date of occurrence and management strategy (PCI, CABG or medical)
Antithrombotic medication use	Antiplatelets (incl OTC aspirin), and anticoagulants since last MI; dose, duration, switching, planned/unplanned treatment interruptions and reasons eg, intolerance, hypersensitivity, GI bleeding, other bleeding complications, other GI side effects
Medical conditions that may impact antithrombotic therapy use or study outcomes	History of peptic ulcer, renal-, liver-, disease, and lung-disease, other indices precluding frailty, previous invasive surgical treatment considered relevant by the investigator
Medication use at enrollment	Oral antiplatelets, anticoagulants, antidiabetic drugs, lipid-lowering agents, ACE inhibitors, ARBs, diuretics and β-blockers, and antidepressants
Healthcare resource use related to cardiovascular or bleeding conditions during the 6 months preceding enrollment	Medication use, and resource use related to medical visits/procedures/investigations: GP or specialist visit, ER admission, number of event-related hospitalizations and duration of stay, and procedures and interventions performed
Routine physical examination	Heart rate, seated blood pressure, weight, height, waist circumference (if current normal practice)
Laboratory safety measures	Serum creatinine (renal function), lipid profile (total cholesterol, HDL, LDL, triglyceride), hemoglobin and glucose/HbA1c; if available and performed within 3 months prior to the visit or 1 month after

	enrollment
Quality of life evaluation	EuroQol 5-Dimensions (EQ-5D-3L)
Follow-up	
Clinical events – Primary variable	MI, unstable angina with urgent revascularization, stroke or death (any cause) - Primary
Bleeding events requiring medical attention	*TIMI definition:* needing intervention (practitioner-guided medical/surgical treatment, including temporary or permanent discontinuation/change in medication/study drug dose), or leading to hospitalization, or prompting evaluation (unscheduled visit to a HCP) and diagnostic testing (laboratory or imaging)
Other events of interest	Including pneumonia and associated death outcome, and macular degeneration
Intercurrent medical procedures and hospitalizations unrelated to predefined events	If hospitalization occurred, patients were asked to confirm the duration and primary cause
Prescription status of antithrombotic medication	Antiplatelets (including OTC aspirin) and anticoagulants, dose, duration, adherence, planned/unplanned treatment interruptions, and reasons for interruptions, eg, intolerance, hypersensitivity, GI bleeding, other bleeding complications, other GI side effects
Other medications	Antidiabetic drugs, lipid-lowering agents, ACE inhibitors, ARBs, diuretics, β-blockers, and antidepressants
Quality of life evaluation	EuroQol 5-Dimensions (EQ-5D)
Healthcare resource use related to cardiovascular or bleeding conditions needing medical attention within 6 months since the last call/visit	*Patient:* *Medication use* *Resource use related to medical visits/procedures/investigations:* GP or specialist visit, ER admission *Productivity loss:* employment status for patient and the primary informal caregiver (latter who stays at home from employment to assist the patient); number of event-related days' sick leave for the patient and/or informal caregiver if either employed/self-employed *Intercurrent medical procedures/hospitalizations:* number of hospitalizations, primary cause of and duration of stay, not related to a predefined event *Event treating physician/hospital:* *Hospitalization:* primary cause, number, and duration of stay where event related including level of care per hospitalization (eg, how many days in ICU, general ward, etc.) *Procedures/interventions* *Investigations* Where applicable, in-hospital resource utilization before patient death

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; ER, emergency room; GI, gastrointestinal; GP, general practitioner; HbA1c, glycated hemoglobin; HCP, healthcare professional; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HF, heart failure; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; MI, myocardial infarction; OTC, over the counter; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TIMI, 'Thrombolysis In Myocardial Infarction'; VTE, venous thromboembolism