ORIGINAL ARTICLE

ST-Segment Elevation ACS: Impact of Time to Diagnosis on Door-To-Balloon Time in the Real World. Data from the ARGEN-IAM-ST Registry

SCA con elevación del st: impacto del tiempo al diagnóstico en el tiempo puerta balón en el mundo real. Datos del Registro ARGEN-IAM-ST

YANINA CASTILLO COSTA, FLAVIO DELFINO, VÍCTOR MAURO, HERALDO D´IMPERIO, STELLA MACÍN, JUAN MUNTANER, MARÍA PÍA MARTURANO, HORACIO POMÉS IPARRAGUIRRE, ADRIÁN CHARASK, JUAN GAGLIARDI

ABSTRACT

Background: Time elapsed from the onset of symptoms to diagnosis (TTD) can influence in achieving a door-to-balloon time <90 min (DBT <90 min).
Methods: A retrospective analysis was performed on 1,518 patients prospectively and consecutively included in the ARGEN-AMI-ST registry. In 37.8% of cases. patients were treated with DBT <90 min and a median TTD of 120 min (IQR 60-266). The population was divided according to TTD above or below 120 min. A DBT <90 min was achieved more frequently in those with TTD <120 min: 44% vs. 32.2% (p<0.001) respectively.
Results: In patients with in situ percutaneous coronary intervention (PCI) and TTD <120 min, DBT <90 min was achieved in 56% vs. 37.1% of cases with TTD >120 min (p <0.001). In referred patients, there were no differences in DBT <90 min according to TTD: 27.5% vs. 25.7% (p: 0.3). In patients admitted during working hours, DBT <90 min was achieved with TTD <120 min in 49.8% vs. 36.3% with TTD >120 min (p: 0.003), as well as in patients admitted during non-working hours: 41.9 % vs. 30.4% (p <0.001). The independent predictors of achieving a DBT <90 min in the multivariate analysis were age <75 years: OR 1.57 (1.1-2.25; p: 0.01), PCI during working hours: OR 1.32 (1.04-1.67; p: 0.002), PCI in situ: OR 2.4 (1.9-3.0; p <0.001), having a pre-hospital ECG: OR 2.22 (1.73-2.86; p <0.001) and a TTD <120 min: OR 1.53 (1.23-1.9; p <0.001).
Conclusions: In patients with TTD <120 minutes, a DBT <90 minutes is more frequently achieved, especially in those treated in situ and during working hours. In referred patients, only 1 in 3 achieves a DBT<90 min and there is no relationship with TTD.

Key words: Myocardial Infarction - Angioplasty, Balloon, Coronary - Registries -Time Factors

RESUMEN

Introducción: El tiempo trascurrido desde el inicio de los síntomas hasta el diagnóstico (TAD) puede influir en lograr un tiempo puerta balón<90min (TPB<90min).
Material y métodos: Análisis retrospectivo que incluyó 1518p ingresados en forma prospectiva y consecutiva al registro ARGEN-IAM-ST. El 37,8% de los p fue tratado con un TPB<90min y el TAD (mediana) fue 120min (RIC 60-266). Se dividió a la población de acuerdo al TAD mayor o menor de 120min. Un TPB<90min se logró más frecuentemente en aquellos con un TAD<120 min: 44% vs 32,2% (p<0,001) respectivamente.
Resutados: En aquellos con CTA in situ y TAD<120 min se logró un TPB<90 min en el 56% vs37,1% con TAD >120 min (p<0,001). En p derivados, no hubo diferencias en TPB<90min de acuerdo al TAD: 27,5% vs 25,7 (p: 0,3). En p ingresados en horario laboral el TPB<90min se logró con TAD<120min en un 49,8% vs 36,3% con TAD >120 min (p:0,003)así como en p ingresados en horarios no laborales: 41,9% vs 30,4% (p<0,001).Los predictores independientes de lograr un TPB<90 min en el análisis multivariado fueron la edad <75 años: OR 1,57 (1,1-2,25; p:0,01), ATC en horario laboral: OR 1,32 (1,04-1,67; p:0,002), ATC in situ: OR 2,4 (1,9-3,0; p<0,001), tener un ECG prehospitalario: OR 2,22 (1,73-2,86; p<0,001) y un TAD<120 min: OR 1,53 (1,23-1,9; p<0,001).
Conclusiones: En los pacientes con un TAD<120 minutos se logra más frecuentemente un TPB<90 min, especialmente en los tratados in situ y en horario laboral. En los pacientes derivados, solo 1 de cada 3 logra un TPB<90 min y no hay relación con el TAD.

Palabras clave: Infarto del Miocardio – Angioplastia Coronaria con Balón - Sistema de Registros- Factores de Tiempo

INTRODUCTION

It is well known that the time-window to indicate a reperfusion strategy after infarction is 12 hours, but the sooner this is performed, the greater the clinical benefit obtained. (1) Guidelines recommend performing primary percutaneous coronary intervention (PCI) within 90 minutes of the initial medical contact and many factors influence its achievement (2, 3).

Rev Argent Cardiol 2020;88:508-515. http://dx.doi.org/10.7775/rac.v88.i6.19252

Received: 05-05-2020 – *Accepted:* 07-18-2020

Address for reprints: Yanina Castillo Costa - Argentine Society of Cardiology - Research Area - Azcuénaga 980 - CABA - E-mail: yanu_c@hotmail.com

One of them could be the time elapsed from the onset of symptoms to diagnosis of the infarction (TTD), which can impact on the perception of the clinical benefit of the procedure by the treating team and condition the response of the system. Our hypothesis is that the shorter the TTD, the greater the percentage of patients who meet adequate door-to-balloon times (DBT) of infarction treatment <90 minutes.

Objectives

1) To evaluate the percentage of patients undergoing primary PCI in whom the reperfusion times proposed by the guidelines are met according to TTD.

2) To analyze the effect of TTD on DBT according to whether or not patients have been referred and whether they have been treated during working hours or in the emergency-room.

3) To evaluate if TTD is an independent predictor to achieve a DBT <90 minutes.

METHODS

Patients who received primary PCI were selected from the continuous ARGEN-AMI-ST registry. Registry characteristics and the inclusion criteria have already been published (4). The protocol was registered in ClinicalTrials.gov as NCT2458885. Briefly, this is a prospective, consecutive and nationwide registry including patients with ST-segment elevation myocardial infarction (STEMI). In the continuous phase, 78 centers in 19 provinces of the country plus the Autonomous City of Buenos Aires (42% public and 58% private entities) participated in the registry, 73% of which were exclusive coronary units and 65% were centers with PCI capability.

"Time to diagnosis" (TTD) was defined as the time from the onset of pain to the completion of the first ECG. Median TTD was calculated, and based on this value, patients were divided into two categories (above and below the median). Door-to-balloon time (DBT) was analyzed globally and patients were divided according to DBT into <60, <90 and <120 minutes categories.

Data was analyzed globally and according to whether the primary PCI was performed in situ or in referred patients, as well as whether patients were treated within working hours (Monday to Friday from 8 a.m. to 5 p.m.) or not (Saturday, Sunday, holidays or Monday to Friday from 5:00 p.m. to 8:00 p.m.).

Non-reperfused patients (n: 286), those who received thrombolytic agents (n: 443), underwent PCI beyond the first 24 hours of evolution of the condition (n: 15) or received non-primary PCI (n: 13), patients in cardiogenic shock (n: 114), those in whom DBT did not appear in the database (n: 49), or with DBT between 0 and 15 min (n: 1) and those with unrecorded TTD (n: 25) were excluded from the study.

Statistical analysis

Continuous variables were expressed with their arithmetic mean and standard deviation or as median and interquartile range 25%-75%, depending on whether the distribution was Gaussian or non-Gaussian, while discrete variables were expressed as percentage and analyzed in contingency tables. Continuous data with Gaussian distribution were compared using Student's t test and those with non-Gaussian distribution, with the Wilcoxon Rank-sum test, while discrete data were compared with the chi square test or Fisher's exact test. Univariate analysis and multivariate logistic regression analysis were performed to determine independent predictors of DBT <90 minutes. A p value <0.05 was considered as statistically significant. Analyses were carried out with Epi Info 7 statistical software package.

Ethical considerations

The ARGEN IAM-ST registry protocol was approved by the ethics committees of the Argentine Society of Cardiology and of each participating institution.

RESULTS

The ARGEN-AMI-ST registry (continuous phase) included 2,464 patients from November 2015 to August 2019. After applying the exclusion criteria, 1,518 patients, whose characteristics are detailed in Table 1, remained for the analysis.

In the total population, only 37.8% of patients were treated with a DBT <90 minutes as recommended by the guidelines, 20.4% with a DBT <60 minutes and 50.2% of the population with a DBT <120 minutes.

Median TTD was 120 min (IQR 60-266 minutes). In 46.8% of cases, patients had TTD <120 min (n: 711) and 53.2% had TTD >120 minutes (n: 807). The population characteristics are presented in Table 2.

Patients with TTD <120 minutes were younger, had a similar prevalence of male gender, risk factors and history of infarction but a shorter DBT (median 100 vs. 135 min, p<0.01), lower TIT and significantly higher percentages of compliance with the times proposed by the guidelines (Table 2).

If we analyze the prevalence of different intervals of DBT in relation to TTD, we observe that a higher frequency of optimal DBT is obtained when TTD is <120 min (Figure 1).

Median DBT in PCI performed in situ was 94 (60-163.5) minutes while in referred patients it was 160 (84-274) minutes. If we analyze the frequency of the different DBT intervals in relation to the TTD (< or ≥ 120 min), and considering whether the PCI was performed in situ or in referred patients, we observe in the former a greater probability of being treated with DBT <90 minutes. The same is not the case of referred patients, in whom it is much more common to have a longer DBT, regardless of the TTD (Table 3).

The analysis according to working hours showed that the difference in favor of a lower DBT in patients with TTD <120 minutes was independent of the time in which the PCI was performed (Table 4).

In the univariate analysis, the predictors of achieving a DTB <90 minutes were age under 75 years, history of infarction, having a prehospital ECG, non-anterior location, in situ PCI, during working hours, and having a DTB <120 minutes (Table 5).

The independent predictors of achieving a DBT <90 minutes in the multivariate analysis were age <75 years: OR 1.57 (95 CI 1.1-2.25; p: 0.011), PCI during working hours: OR 1.32 (95 CI 1.04-1.67; p: 0.002), in situ treatment: OR 2.4 (95 CI 1.9-3.0; p <0.001), having a pre-hospital ECG: OR 2.22 (95 CI 1.73-2.86;

Table 1. General characteristics (n: 1,518).

	n: 1,518 (%)
Age, years. Median (IQR 25-75)	61 (53-67)
Male gender	1,220 (80.4)
Smokers	659 (43.5)
Diabetes	337 (22.3)
HTN	862 (57)
History of infarction	154 (10.5)
Previous location	547 (36)
Pre-hospital ECG	356 (23.6)
DBT, minutes. Median (IQR 25-75)	119 (61-21)
DBT in patients treated in situ (min)	94 (60-163.5)
DBT in referred patients (min)	160 (84-274)
TTD, minutes. Median (IQR 25-75)	120 (60-266)
TIT, minutes. Median (IQR 25-75)	287 (181-520)
KK >A	209 (14.1)
Referred patients	652 (43.2)
Admitted on working days/hours	443 (29.2)

HTN: Hypertension; DBT: door-to-balloon time; TTD: time to diagnosis; TIT: Total ischemic time; KK: Killip and Kimball class.

Table 2. Demographic and clinical characteristics according to TTD.

	TTD <120 min 711 (%)	TTD ≥120 min 807 (%)	p
Age, years. Median (IQR 25-75)	0.01	0.01	0.01
Age <75 years	0.012	0.012	0.012
Male gender	0.21	0.21	0.21
Smokers	0.67	0.67	0.67
Diabetes	0.1	0.1	0.1
HTN	0.15	0.15	0.15
History of infarction	0.2	0.2	0.2
Pre-hospital ECG	0.001	0.001	0.001
DBT, minutes. Median (IQR 25-75)	<0.001	<0.001	<0.001
In situ DBT, minutes. Median (IQR 25-75)	<0.001	<0.001	<0.001
Referred DBT, minutes. Median (IQR 25-75)	0.39	0.39	0.39
TIT, minutes. Median (IQR 25-75)	<0.001	<0.001	<0.001
KK>A	0.23	0.23	0.23
Referred patients	0.2	0.2	0.2
PCI working days/hours	0.15	0.15	0.15
DBT <60 min	<0.001	<0.001	<0.001
DBT <90 min	<0.001	<0.001	<0.001
DBT <120 min	<0.001	<0.001	<0.001

TTD: time to diagnosis; HTN: Hypertension; DBT: door-to-balloon time; TIT: Total ischemic time; KK: Killip and Kimball class. PCI: Percutaneous coronary intervention.

p <0.001) and a TTD <120 minutes OR 1.53 (95 CI 1.23-1.9; p <0.001).

Overall in-hospital mortality of patients from the ARGEN-AMI-ST registry was 8.81%, (4), and that of the patients selected in this study (n: 1,518) was 3.75%, with no significant differences according to TTD, probably due to the low number of events.

DISCUSSION

Myocardial infarction is still one of the main causes of cardiovascular mortality despite advances in its treatment (5), with time for treatment onset as a relevant predictor of morbidity and mortality. (6) Current guidelines for STEMI management recommend PCI within 90 minutes of the initial medical contact (5). There is scarce information available to analyze which are the factors that most influence an optimal DBT, including patient characteristics (age, gender, time to consultation, history), clinical presentation (AMI location, Killip and Kimball, time of evolution on admission) and system organization (in situ PCI, working hours, whether there is or not pre-activation

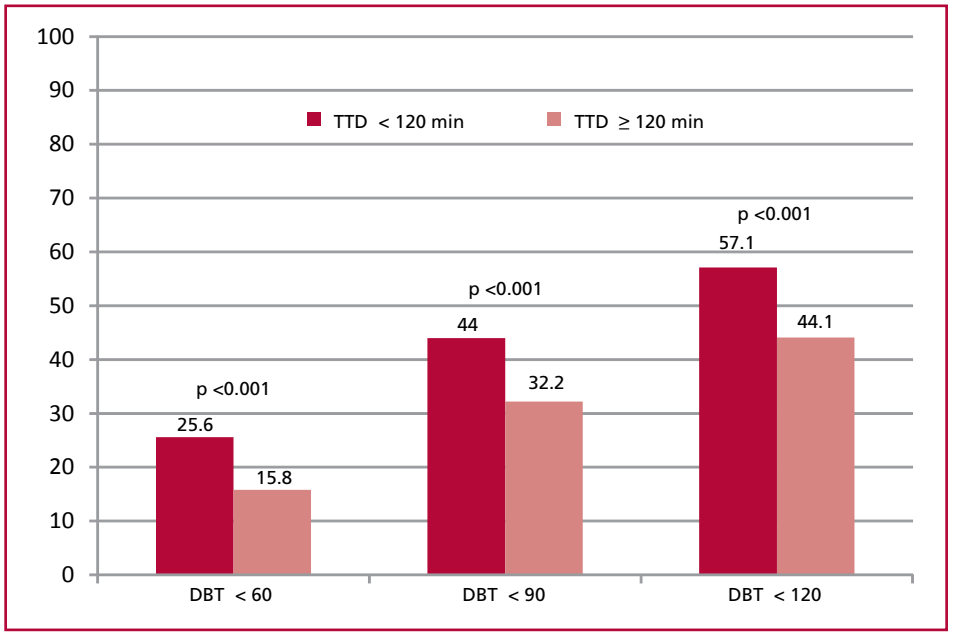

Fig. 1. Prevalence of compliance (%) of different door-balloon times according to whether the time of evolution to diagnosis was above (red) or below (blue) 120 minutes. TTD: time to diagnosis. DBT: door-to-balloon time.

Patients treated in situ: (n: 856)	TTD <120 min 411 (%)	TTD ≥120 445 (%)	p
DBT < 60	136 (33.1)	74 (16.6)	<0.001
DBT <90	230 (56)	165 (37,1)	<0.001
DBT <120	293 (71.3)	219 (49.2)	<0.001
Referred patients: (n: 652)	**TTD <120 min 298 (%)**	**TTD ≥120 354 (%)**	**p**
DBT < 60	46 (15.4)	53 (15)	0.47
DBT <90	82 (27.5)	91 (25.7)	0.3
DBT <120	112 (37.6)	132 (37.3)	0.5

TTD: time to diagnosis; DBT: door-to-balloon time.

Table 3. Door-to-balloon time according to time to diagnosis in patients with in situ percutaneous coronary intervention or referred from other centers.

Working hours	TTD <120 min 198 (%)	TTD ≥120 min 245 (%)	p
DBT < 60	62 (31.3)	48 (19.6)	0.003
DBT <90	98 (49.5)	89 (36.3)	0.003
DBT <120	117 (59.1)	113 (46.1)	0.004
Non-working days/hours	**TTD <120 min 513 (%)**	**TTD ≤120 min 562 (%)**	**p**
DBT < 60	120 (23.4)	80 (14.2)	<0.001
DBT <90	215 (41.9)	171 (30.4)	<0.001
DBT <120	289 (56.3)	243 (43.2)	<0.001

TTD: time to diagnosis; DBT: door-to-balloon time.

Table 4. Door-to-balloon time according to time to diagnosis in patients treated in working hours or in non-working days/hours.

of the hemodynamic service). Understanding the factors that influence achieving adequate DBT will improve quality of care.

In our population, median total ischemic time was 287 minutes. It is known that the total ischemic time, especially if it is greater than 4 hours, presents an inverse linear relationship with epicardial TIMI 3 flow, the myocardial blush achieved post PCI, and mortality at one year. (7, 8) In addition, 40% of patients were referred from other centers and 1 out of every 3 patients was admitted during working days/hours. Median time to diagnosis was 120 minutes, as in previous studies, (9-12) and as in other experiences, a TTD <120 minutes was associated with better attainment of the goals established by the guidelines, especially in patients who were treated in situ

Table 5. Predictors to achieve a DBT <90 minutes. Univariate analysis.

	TTD <120 min 711 (%)	TTD ≥120 min 807 (%)	p
Age, years. Median (IQR 25-75)	61 (53-67)	61 (53-68)	0.056
Age <75 years	516 (90.7)	816 (87)	0.014
Male gender	464 (81)	756 (80)	0.34
Smokers	256 (44.7)	403 (42.6)	0.23
Diabetes	121 (21.1)	216 (22.8)	0.23
HTN	325 (56.7)	537 (56.8)	0.5
History of infarction	48 (8.6)	106 (11.7)	0.033
Anterior AMI	178 (31)	369 (39)	<0.001
Pre-hospital ECG	185 (32.6)	171 (18.2)	<0.001
KK >A	76 (13.5)	133 (14.5)	0.32
Referred patients	173 (30.5)	479 (51)	<0.001
Non-referred patients	395 (69.5)	461 (49)	<0.001
PCI working days/hours	187 (32.6)	256 (27.1)	0.012
TTD <120	313 (54.6)	398 (42.1)	<0.001

DBT: door-to-balloon time; HTN: Hypertension; AMI: Acute myocardial infarction; KK: Killip and Kimball class; PCI: Percutaneous coronary intervention; TTD: time to diagnosis.

in whom the objective of achieving a DBT <90 minutes was significantly higher (69.5% vs. 30%) than in those referred from other centers. The consultation on working days/hours or having a pre-hospital ECG was associated with a faster system performance and more likely treatment within 90 minutes. Having a pre-hospital ECG deserves to be specially mentioned, since although in our work we could not collect the data on whether there was pre-activation of the hemodynamic service; it has already been shown that it is an optimal strategy to reduce the time to reperfusion.

It is now known that the relationship between DBT and short and long-term mortality is not actually linear but exponential, as demonstrated by Foo et al. in a meta-analysis of 32 studies and with more than 300,000 patients, (13) and that the greatest clinical impact of achieving an adequate DBT is obtained in patients who present with less than 2 hours of TTD. (14-16) This forces us to look beyond the DBT as a measure of quality of infarct care and implement coordinated measures to reduce the pre-hospital delay to the first medical contact and to the diagnostic ECG.

Although there is a 12-hour window for reperfusion in infarction, it is well known that as time passes the percentage of potentially viable myocardium decreases. (17) This concept probably plays a role on whether the health team perceives greater or less clinical benefit from reperfusion and tries to improve or not the goal of achieving a DBT <90 minutes. Recently, it has been shown that if we evaluate the percentage of transmurality in AMI by cardiac magnetic resonance imaging, the transmurality index is already between 76% and 100% (18) beyond 121 minutes of coronary occlusion, so achieving a prompt time to reperfusion is of great importance.

Only 3 out of 10 patients who were referred from another center with no hemodynamic availability managed to receive primary PCI within 90 minutes; therefore, we consider that the reperfusion strategy should be reviewed in this group of patients, since in cases in which the system could not be pre-activated and times reduced, an increase in the use of thrombolytics and eventually a pharmaco-invasive strategy would have to be evaluated.

Many factors determine the achievement of an adequate time to reperfusion, one of them being TTD. In this sense, other factors such as the delay in the decision to carry out the procedure, referral from a center with no hemodynamic availability, activation of the interventional team, waiting time in the emergency room, if the first medical contact is by a cardiologist or a general practitioner, the search for medical coverage and even the technique for performing the initial angiography, among others, influence in the achievement of therapeutic objectives. Nonetheless, the importance of reducing factors of prehospital delay (in our work one of them being TTD) is proven, as a measure of greater efficiency in achieving myocardial reperfusion.

Limitations

The ARGEN-IAM-ST continuous registry is not free from biases since it mostly involves large institutions, both public and private and may not adequately represent lower complex centers. There was no audit of the data in the centers since we did not have financial support for its performance. However, the participating institutions have a high degree of commitment with the registry.

CONCLUSIONS

The ARGEN-AMI Registry verified that only 4 out of 10 patients receive primary PCI in less than 90 minutes, 2 out of 10 in less than 60 minutes, and half of

them do so in more than 120 minutes. Analyzing the relationship between the time of condition progression and the percentages of DBT compliance recommended by the guidelines, it is observed that patients with a TTD <120 minutes have significantly better percentages of compliance with the different DBTs, especially those treated in situ and during working hours.

The importance of TTD <120 minutes to achieve better DBT could reflect the effort of the medical system to meet improved treatment times in patients with greater chance of salvaging a larger extent of viable myocardium and focuses on trying to reduce barriers until early diagnosis as a way to improve the quality of care.

Conflicts of interest

None declared.
(See authors' conflicts of interest forms on the website/Supplementary material)

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LIST OF PARTICIPATING CENTERS AND RESPONSIBLE PHYSICIANS

Hospital Gral. de Agudos Dr. Cosme Argerich – Luciana Puente
Instituto Cardiovascular de Rosario – Gerardo Zapata
Hospital San Juan de Dios de La Plata – Oscar Pisana/Diego Echazarreta
Sanatorio Güemes – Ricardo Villareal
Clínica Santa Isabel – Víctor Mauro/Yanina Castillo Costa
Clínica Bazterrica – Carlos Barrero/ Adrián Charask
Sanatorio San Carlos – Matías Calandrelli
Sanatorio Allende Nueva Córdoba – Julio Bono
Centro Privado de Cardiología – Eduardo G. Hasbani
Instituto de Cardiología J. F. Cabral – Stella Macín/Facundo Falcón
Centro Modelo de Cardiología – Juan Muntaner
Hospital El Cruce "Dr. Néstor Kirchner" – Tomás Vassia
Hospital Luis Lagomaggiore – Jorge Piasentin
Sanatorio Privado Gatti – Pablo Moreno
Sanatorio Pasteur – María Pía Marturano
Sanatorio Juan XXIII – Roberto Bernardini/Nicolás Menichini
Hospital para la Comunidad de Arias – Joaquín Sangiorno
Centro de Alta Complejidad – Pablo Agüero
Hospital Dr. Raúl F. Larcade – Gabriel Jans
Hospital Gral. de Agudos "Juan A. Fernández" – Patricia Guitelman
Hospital San José de Pergamino – Luis Bahamonde
Hospital Gral. de Agudos "Dr. T. Álvarez" – Daniel H. Avayu/Marcos P. Tomasella
Hospital Universitario Austral – Horacio Fernández
Clínica de Cuyo – Ariel Baigorria Jayat/María Elisa de la Fuente
Hospital Subzonal "Dr. Andrés R. Isola" – Norman Casado
Hospital Dr. Guillermo Rawson – Adrián H. D'Ovidio
Sanatorio de la Ciudad, Puerto Madryn – Julián Tiranti
Hospital Artémides Zatti – José Luis Rovasio/Silvia Framarini
Instituto de Cardiología Dr. González Sabathié – Antonio Gentile/Mario Ciafardoni
Hospital Español de Buenos Aires – Liliana Nicolisi
Sanatorio Fueguino de Diagnóstico y Tratamiento – Mauro Dotto/Raúl E. Figueroa
Hospital de San Bernardo – Augusto Barbosa
Fundación Médica de Rio Negro y Neuquén – Demetrio Thalasselis
Instituto. Modelo de Cardiología Privado de Córdoba. – Eduardo Conci/Walter Quiroga
Hospital Italiano de Córdoba – Fernando Gragera
Hospital Ramón Carrillo – David Marcelo Krivich
Hospital Córdoba – Marcos De la Vega
Clínica y Maternidad Suizo Argentina – Juan Caros Medrano
Hospital San Felipe San Nicolás – Raúl Alejandro Quijano
Hospital El Carmen, Mendoza – Oscar Fernando Vidal
Clínica Universitaria Reina Fabiola, Córdoba – Raúl Jesús Barcudi
Clínica Pasteur SA, Neuquén – Claudio Ploger/Ana Duret
Hospital Gral. de Agudos Dr. Zubizarreta – José María Soler
Sanatorio San Martín, Venado Tuerto, Santa Fe – Javier Matcovik
Sanatorio de la Trinidad, San Isidro, Bs. As. – Juan Taccari/Walter Nieto
Hospital Italiano de Buenos Aires, CABA – José Luis Navarro Estrada/Francisco José Romeo
Hospital Británico de Buenos Aires, CABA – Horacio Alberto Avaca/Mauro Gastón Gingins
Hospital Mi Pueblo, Florencio Varela, Buenos Aires – Santiago Tur/Federico Bodega
Hospital Pablo Soria – Franz Rivero Paz
Sanatorio Allende Cerro, Córdoba – Roberto Miguel A. Colque
Hospital Privado del Sur – Raúl Cermesoni/Marcelo Guimaraenz
Hospital Privado de la Comunidad de Mar del Plata – Álvaro Facta
Hospital General de Agudos Dr. Ramos Mejía – Justo Cabrales
Hospital Luisa C. de Gandulfo – Juan Pullido
Clínica San Martín – Pablo Maldonado
Hospital Italiano de La Plata – Cecilia Beltrano
Hospital Iriarte – David Parisi
HIGA Gral. San Martín – Luis Medesani
HIGA Rossi – Carlos Martínez
Hospital Pirovano – Ricardo Mejail
Hospital Español de Rosario – Daniel Edgardo Miraglia
Clínica Yunes – Edgar Aguilar
Sanatorio Modelo Quilmes – Adrián Hrabar/Alberto Fernández
Sanatorio Ntra. Sra. del Rosario – Gustavo Bustamante Labarta

Hospital Teodoro J. Schestakow – Leonardo Schiavone
Hospital Dr. J. M. Valdano – Ramiro Alberto Astegiano
IOT – Oscar Ariel Vogel
Hospital Héctor Cura, Olavarría – Ernesto Ylarri
Policlínico Regional Juan D. Perón – Sandra Mugnaini
Policlínico Modelo de Cipolletti –Diego Figoni
RAPIAM (Red de Atención Prov. del IAM La Rioja) – Horacio Pomés Iparaguirre
Sanatorio Los Lapachos de Jujuy – Luis Freijo
Hospital Lamadrid de Monteros – Andrea Piredda
Clínica Del Valle – Miguel Salva
Hospital Zonal Bariloche – Germán Santamaría
Hospital de Alta Complejidad J. D. Perón – Christian Smith/Nicolás Areco
Hospital L. Molas, Santa Rosa, La Pampa – Fabián Kubaruk
Sanatorio Mitre – Hernán Cohen Arazi