

Statins at Discharge in Acute Coronary Syndrome over the past 10 Years. The Epi-Cardio Registry

Estatinas al alta en la coronariopatía aguda en los últimos 10 años. Registro Epi-Cardio

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ABSTRACT

Background: Statins have been incorporated for secondary prevention of cardiovascular disease for over two decades, with a remarkable impact in the reduction of morbidity and mortality. Currently, the evidence available recommends the use of high-intensity statin therapy in all patients presenting an acute coronary syndrome.

Objective: The aim of this study was to evaluate the use of statins at discharge in acute coronary syndrome patients included in the Epi-Cardio registry and its variation over the past 10 years.

Methods: Patients hospitalized between 2005 and 2014 with diagnosis of acute coronary syndrome were included; those deceased or without data of the treatment at discharge were excluded. The frequency of statin indication, agents, doses used over the 10-year period and the indication of high-intensity therapy (rosuvastatin 20-40 mg, atorvastatin 40-80 mg) were analyzed. The use according to the field of care was compared.

Results: 22,905 records were analyzed. The most common agents used were atorvastatin 68%, simvastatin 22.7% and rosuvastatin 9.1%. The temporal trend revealed higher frequency of statin prescription (from 83% in 2005-2007 to 92.5% in 2014), higher doses, lower indication of simvastatin and higher of other agents, and greater use of high-intensity statin therapy from 7.7% in 2005-2007 to 52.6% in 2014. The use of high-intensity therapy was lower in the public health care system.

Conclusions: The frequency of statin indication reaches optimal levels and the use of high-intensity therapy increased during the period evaluated, including over half of the patients. The differences in the public health care system suggest a lower access to treatment. Additional studies are necessary to identify the barriers for implementing high-intensity statin therapy.

Key words: Acute Coronary Syndrome - Statins HMG-CoA - Quality of Health Care

RESUMEN

Introducción: Las estatinas se han incorporado a la prevención secundaria de la enfermedad cardiovascular hace más de dos décadas, con un impacto notable en la reducción de la morbimortalidad. De acuerdo con la evidencia disponible, actualmente se recomienda su indicación en dosis altas en todos los pacientes que presentaron un síndrome coronario agudo.

Objetivo: Evaluar el empleo de estatinas al alta en pacientes con síndrome coronario agudo incluidos en el registro Epi-Cardio y su variación en los últimos 10 años.

Material y métodos: Se incorporaron los pacientes con síndrome coronario agudo ingresados entre 2005 y 2014, excluidos los fallecidos o sin datos del tratamiento al alta. Se analizó la frecuencia de indicación de estatinas, fármacos y dosis utilizadas a lo largo de los 10 años, así como la indicación de terapia de alta intensidad (rosuvastatina 20-40 mg, atorvastatina 40-80 mg). Se comparó el uso de acuerdo con el ámbito de atención de la salud.

Resultados: Se analizaron 22.905 registros. Los fármacos más empleados fueron atorvastatina 68%, simvastatina 22,7% y rosuvastatina 9,1%. Las tendencias temporales fueron significativas hacia el incremento de la indicación de estatinas (de 83% en 2005-2007 a 92,5% en 2014), aumento de las dosis, reducción de la indicación de simvastatina en favor de los otros agentes e incremento de la terapia de alta intensidad de 7,7% en 2005-2007 a 52,6% en 2014. El empleo de terapia de alta intensidad fue menor en el ámbito público.

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Conclusiones: La frecuencia de indicación de estatinas se acerca a niveles óptimos y el empleo de dosis elevadas se incrementó durante el período de estudio alcanzando a más de la mitad de los pacientes. Las diferencias en el sector público sugieren un menor acceso al tratamiento. Son necesarios estudios adicionales que identifiquen las barreras para implementar los regímenes de elevada intensidad.

Palabras clave: Síndrome coronario agudo - Estatinas HMG-CoA - Calidad de la atención de salud

Abbreviations

LDL	Low density lipoprotein	ACS	Acute coronary syndrome
IQR	Interquartile range	CCU	Cardiovascular care unit

INTRODUCTION

Statins have been incorporated for secondary prevention of cardiovascular disease for over two decades, with a remarkable impact in the reduction of morbidity and mortality. Initially, statins were indicated for patients with elevated cholesterol levels, (1) but now the indication has been extended to the universe of patients with coronary artery disease due to the evidence provided by several controlled trials. (2-5) Currently, the evidence available recommends the use of high-intensity statin therapy in all patients presenting an acute coronary syndrome (ACS). (6)

The process through which the conclusions of controlled trials become routine practice is very complex, and may not be attained or may take years. (7) Standardized processes contribute to improve the quality of care, the effectiveness of clinical decisions, and cost reduction. (8) An association has been demonstrated between the use of evidence-based treatments, expressed as adherence to guidelines, and improvement in terms of survival and morbidity in patients with coronary artery disease. (9-11) In addition, the indication of treatments for secondary prevention in general, and of statins in particular, has an inverse relationship with the socioeconomic status. (12-14)

The aim of our study was to evaluate the extent of statin indication at discharge in ACS patients, the selection of agents and doses prescribed, and the outcome over the past 10 years using the information provided by the Epi-Cardio registry. The patterns of prescription among public and private institutions were also analyzed to evaluate the potential impact of patients' socioeconomic status on the use of these agents. This information aims to determine the level of clinical practice adaptation to the best scientific evidence, and to develop a hypothesis about the possible obstacles to improve it.

METHODS

Epi-Cardio is a multicenter registry of discharge summaries of cardiovascular care units (CCUs) in Argentina, focused on evaluating clinical epidemiology. (15) Between 2005 and 2014, 54 CCUs of the country participated in the registry, with a total of 106,705 patients. For the purpose of this analysis, patients with a diagnosis of ACS (with and without ST-segment elevation) were included, and as the aim of this study was the evaluation of treatments at discharge, those

deceased or without treatment indications at discharge were excluded.

The indication of statins in general and for each agent was analyzed, as well as the doses used over the 10-year study period and the influence of ezetimibe on statin doses.

The analysis of statin doses was restricted to the three agents mostly used. Statin doses were classified according to the intensity of statin therapy proposed by the 2013 American College of Cardiology/American Heart Association (ACC-AHA) guideline. (6) This guideline classifies the intensity of statin therapy as:

- Low-intensity statin: simvastatin 5-10 mg
- Moderate-intensity statin: atorvastatin 5-20 mg; rosuvastatin 5-10 mg or simvastatin 20-40 mg;
- High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg.

The temporal trend was analyzed by year, except for the period 2005-2007 when the registry started and the number of admissions was lower.

Based on previous hypotheses, a subgroup analysis was performed to investigate the influence of medical care within the public or private health care system on the variables evaluated.

Statistical analysis

Categorical data are expressed as frequency and percentage, and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Continuous variables were compared using Student's t test or the Mann-Whitney U test, as applicable. Discrete variables were compared using the chi-square test with Yates correction or Fisher's exact test with chi-square test for trends, as applicable. A two-tailed p value <0.05 was considered statistically significant for all the comparisons. All the calculations were performed using the Epi-Info 2000 3.5.3 or 7.0.9.34 software package (Centers for Disease Control and Prevention, Atlanta).

Ethical considerations

The study was carried out in compliance with the patient's right to protection of personal data. The study was approved by the institutional Ethics Committee.

RESULTS

Between 2005 and 2014, 27,475 ACS patients were discharged; 581 deceased and 3,989 patients without information about treatment at discharge were excluded. A total of 22,905 patients were included.

Median age was 61 years (IQR 53-71) and 72.1%

were men. Baseline population characteristics, use of diagnostic angiography, revascularization and treatment at discharge are presented in Table 1.

During the study period, statins were indicated to 19,335 patients (84.4%). Figure 1 shows the percentage of statin indication by year. The frequency of indication increased over the years from 83% in the pe-

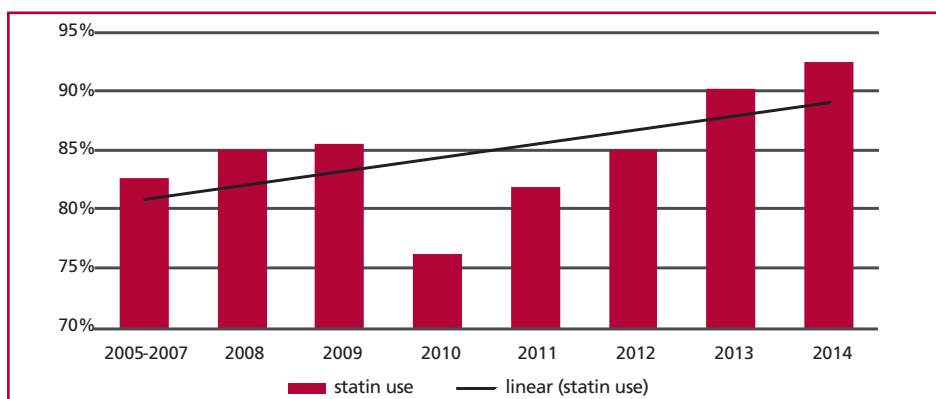
riod 2005-2007 to 92.5% in 2014 (chi-squared test for linear trend p-value < 0.01). The frequency of statin indication at discharge was significantly lower in the private health care system (83.9% vs. 85.3%; OR 0.89; 95% CI, 0.83-0.96; p<0.01), though the magnitude of this difference was small. The greater frequency of indication over time was observed in both health

Table 1. Baseline population characteristics, use of diagnostic angiography, revascularization and treatment at discharge.

	n (%)	95% CI
Cardiovascular risk factors		
Male sex	16,474 (72.1)	71.5-72.7
Hypertension	13,745 (60)	59.4-60.6
Diabetes	4,546 (19.8)	19.3-20.4
Dyslipidemia	9,992 (43.6)	43-44.3
Current smoker	6,842 (29.9)	29.3-30.5
Former smoker	5,757 (25.1)	24.6-25.7
History of coronary artery disease		
Stable chronic angina	1,578 (6.9)	6.6-7.2
Myocardial infarction	3,529 (15.4)	14.9-15.9
Previous angioplasty	2,838 (12.4)	12-12.8
Previous coronary artery bypass graft surgery	1,276 (5.6)	5.3-5.9
Type of ACS		
STEACS	5,995 (26.2)	25.6-26.7
NSTEACS	16,910 (73.8)	73.3-74.4
Angiography and revascularization during hospitalization		
Coronary angiography	14,246 (62.5)	61.8-63.1
Coronary angiography.	8,726 (38.1)	37.5-38.8
Percutaneous coronary intervention	585 (2.6)	2.4-2.8
Coronary artery bypass graft surgery		
Pharmacologic treatment at discharge		
Aspirin	20,910 (91.3)	90.9-91.7
Other antiplatelet agents	14,674 (64.1)	63.4-64.7
Clopidogrel	13,816 (60.3)	59.7-61
Clopidogrel	610 (2.7)	2.5-2.9
Prasugrel	247 (1.1)	1-1.2
Ticagrelor	19,335 (84.4)	83.9-84.9
Statins	18,795 (82.1)	81.6-82.6
Beta blockers	15,611 (68.2)	67.5-68.8
ACEI or ARB		

ACS: Acute coronary syndrome. STEACS: ST-segment elevation acute coronary syndrome. NSTEMACS: Non-ST-segment elevation acute coronary syndrome. ACEI: Angiotensin converting enzyme inhibitor. ARB: Angiotensin II receptor blocker.

Fig. 1. Frequency of statin use at discharge in acute coronary syndrome patients according to year of discharge (chi-squared test for linear trend p-value <0.01)



care systems (chi-squared test for linear trend p-value <0.01).

The most common agents used were atorvastatin 68% (n: 13,143), simvastatin 22.7% (n: 4393) and rosuvastatin 9.1% (n: 1768); other statins or combinations of two statins were indicated in < 1% of the patients (Figure 2).

Figure 3 shows the distribution of the agents used between 2005 and 2014 in all the patients. The prescription of atorvastatin and rosuvastatin increased over the last years and the use of simvastatin decreased. When the type of statin prescribed was analyzed according to the field of care, the indication of rosuvastatin was higher in the private health care system (Figure 2). Simvastatin was the agent most frequently indicated in the public health care system until 2009, when it was gradually replaced by atorvastatin; yet, it is still indicated in almost one third of

the patients with public medical coverage (Figure 3).

The analysis of the doses used is summarized in Figure 4. After classifying the doses in high intensity, moderate intensity and low intensity statin therapy, the percentage of use was distributed as follows: 27.2%, 71.1% and 1.7%, respectively. The temporal trend reveals a progressive increase in the dose of each agent and in the use of high intensity statin therapy. However, and even considering the period with the highest percentage of statin prescription, only half of the patients received high intensity statin therapy.

When the type of agents used and the intensity of statin therapy in the private and public care systems were compared, more potent and expensive agents were used in the private setting, with greater indication of high intensity therapy (33.3% vs. 16.7%; p <0.01).

The combination of ezetimibe and statins was indi-

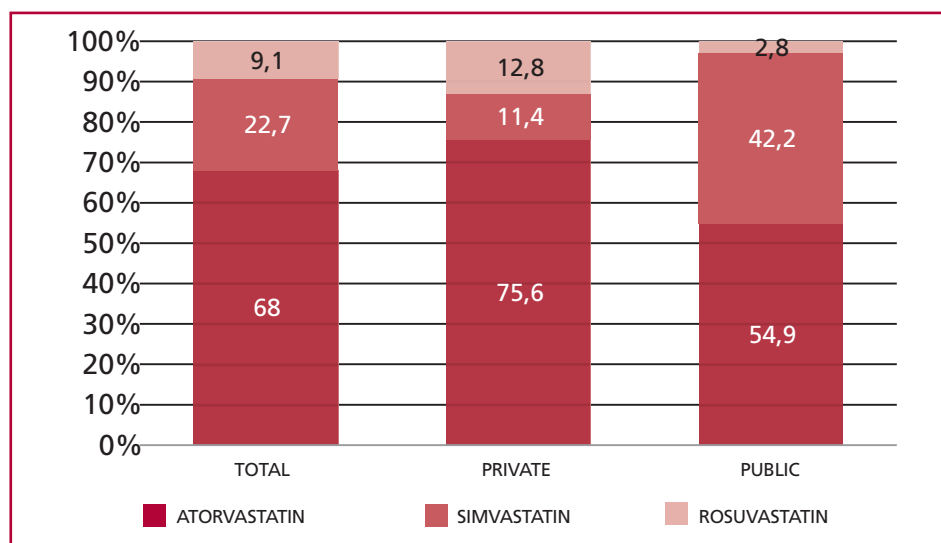


Fig. 2. Distribution of the type of drugs used globally and according to the field of care.

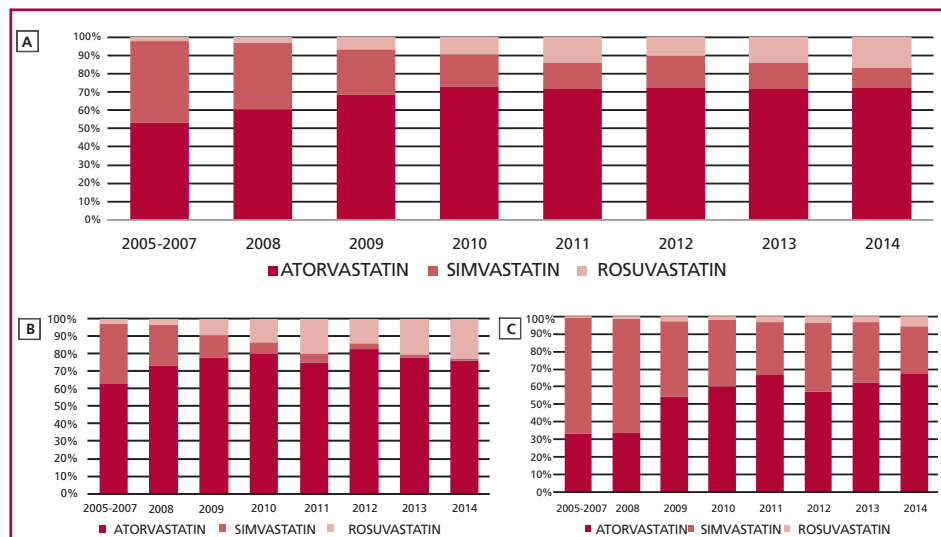
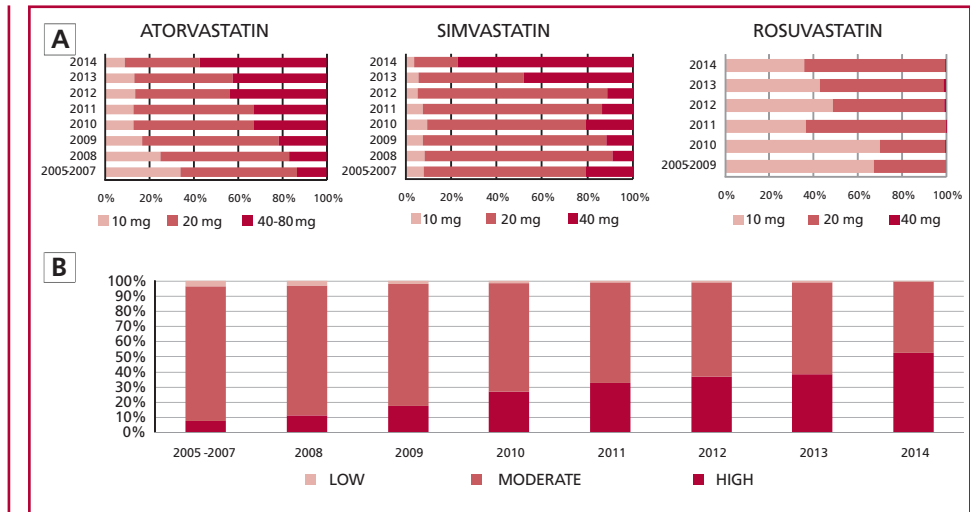


Fig. 3. Distribution of type of drugs used according to year of discharge. A. Global distribution. B. Private health care system. C. Public health care system.

Fig. 4. A. Distribution of doses of atorvastatin, simvastatin and rosuvastatin according to year of discharge. **B.** Frequency of low, moderate and high-intensity use of statin therapy according to year of discharge.



cated in 217 patients (0.94%). The use of ezetimibe was associated with lower mean dose of atorvastatin (25.3 mg without ezetimibe vs. 21.1 mg with ezetimibe; $p < 0.01$). The same trend was observed when ezetimibe was associated with simvastatin.

DISCUSSION

The results of our study show that the prescription of statins for all the patients is increasing in the network of CCUs participating in the Epi-Cardio registry, with a progressive increase in the doses of the different agents and reduction in the use of simvastatin, but with variations according to the health care system and to the use of ezetimibe. These trends are consistent with the scientific evidence, though the use of statins is still not optimal.

The evidence favoring high intensity statin therapy and early treatment in patients with ACS is solid. (16-21) The 4S study, (2) published in 1994, was the first among many trials which demonstrated significant benefits with the use of these agents in patients with coronary artery disease. The Cholesterol Treatment Trialists (CTT), (5) a meta-analysis that included 14 clinical trials of statins in primary and secondary prevention, demonstrated a reduction of 19% in coronary mortality per mmol/L (38.6 mg/dL) reduction in LDL cholesterol, with a significant 12% reduction in all-cause mortality. Several studies comparing the use of low and high intensity statin therapy (16-18) and two meta-analyses (19, 20) confirmed the benefits of high intensity therapy on cardiovascular events and mortality. Three of these four studies used atorvastatin 80 mg and one used simvastatin 80 mg as high intensity therapy. With this evidence, the current guidelines on lipid lowering treatment recommend the use of high-intensity statin therapy in all the patients with ACS and absence of contraindications. (6)

The results presented in this analysis show a progressive indication of statins over the years, reaching

levels similar to those reported in the EUROAPIRE III study (88.8%) (22) and in the French FAST-MI registry (87.9%). (23) The percentage of high-intensity statin therapy indication also increased over time, though this percentage was 52.6% during the year with the highest rate of indication. An analysis of the MINAP English registry (24) evaluated the use of high-intensity statin therapy at discharge and during a 4-year follow-up period in 6,138 patients with ACS during the period 2005-2009. A statin was prescribed at hospital discharge in 90.7% of the ACS cases, but only 30.1% received a high-intensity statin dose. These results are similar to those reported by the Get With The Guidelines (GWTG) program, (25) which evaluated the use of intensive statin therapy in a cohort of 65,396 patients diagnosed with ACS discharged from 344 centers between 2005 and 2009. Although 86.4% of the patients received statins at discharge, only one third of them were discharged with high-intensity therapy. As in our study, by the end of 2009 the authors noted a reduction in the indication of statins that was attributed to negative publications concerning statins during that year.

Although due to the study design, the results cannot identify the reasons of the incomplete implementation of high-intensity statin therapy after an ACS, other studies have identified important barriers to consider.

Firstly, costs should be considered. In patients with chronic diseases who take several drugs, treatment cost constitutes one of the main limitations for adherence, (36) and in the case of statins, high cost and low availability of drugs could limit their use. (27) In our country, the National Ministry of Health, through the REMEDIAR program, (28) provides free medications to patients without medical coverage. In the case of statins, the program incorporates only simvastatin 20-40 mg. The Emergency Obligatory Medical Program of the National Ministry of Health, (27) which

covers 70% of the reference price of medications for chronic diseases in patients with social health insurance or private medical coverage, incorporates simvastatin and atorvastatin 10-20 mg; thus, the use of high-intensity therapies or rosuvastatin could be limited. In the present analysis, we have used the field of care as representative of socioeconomic status, and although the prescription of statins was slightly higher in the public health care system, high-intensity therapies were more frequently used in the private system.

Despite the incidence of major adverse events with the use of statins is uncommon and rarely requires drug discontinuation, (30, 31) concerns about the development of adverse events with high-intensity statin therapy among physicians and patients has also been described as a barrier for its implementation. (32-33)

The impact of negative reports or debates in the media about statin therapy has remarkable consequences in their use, leading to a decrease in therapy initiation, higher discontinuation rate and lower adherence to treatment in the weeks following these publications. (34-36) As early discontinuation of treatment and switching from intensive to moderate statin therapy during follow-up have a significant impact on morbidity and mortality, (36-38) it would be convenient to improve the distribution of information regarding its safety to achieve greater adherence to the recommendations among physicians and greater adherence to treatment among patients.

Finally, the association with ezetimibe could be associated with lower use of high-intensity therapy, although in our analysis, such association occurred in <1% of the population and its global incidence was marginal. The only evidence with modest clinical benefit for the combination ezetimibe/statins was provided by the IMPROVE IT study, which added ezetimibe 10 mg to simvastatin 40 mg. (39) These results were questioned for several reasons, and in December 2015 the Food and Drug Administration voted against recommending the expanded use of ezetimibe by adding it to statin therapy in secondary prevention. (49) The use of ezetimibe in ACS should be limited to patients who do not tolerate high-intensity statin therapy, fortunately a reduced group of patients.

Study limitations

The study has several limitations that should be considered to interpret the results. The centers voluntarily participating in the Epi-Cardio registry are coronary care units or polyvalent intensive care units, and most of them have residency programs; thus, they may not be representative of all the CCUs nationwide. Fifteen percent of the records did not have indications at discharge and were excluded from the analyses, which could introduce a selection bias and thus overestimate the indication of statins in the scenario described. There is no information about contraindications for the use of statins, though it is unlikely that this might be the cause of the underutilization

of high-intensity therapies as has been demonstrated by data from other studies. (19, 20) Finally, due to the study design we did not have access to direct information about the barriers to implement the guidelines for lipid lowering treatment.

CONCLUSIONS

The results of this study demonstrate an increasingly extended use of statins after an ACS, reaching >90% of the patients over the past years. Although during the last year of the registry, half of the patients were discharged with high-intensity statin therapy, which is clearly associated with clinical benefits, this rate of prescription is still insufficient. The differences in the public health care system suggest a lower access to treatment. Additional studies are necessary to identify the barriers to implement high-intensity statin therapy in our environment.

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Conflicts of interest

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

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Appendix: Participating centers

Institution	City	Province	Researcher
CEMIC	C. A. de Buenos Aires	C.A.B.A	Dr. Javier Guetta
Centro Gallego	C. A. de Buenos Aires	C.A.B.A.	Dr. Sergio Varini
Clínica 25 de Mayo	Mar del Plata	Buenos Aires	Dr. Jorge Tévez
Clínica Bazterrica	C. A. de Buenos Aires	C.A.B.A.	Dr. Carlos Barrero
Clínica Colón	Mar del Plata	Buenos Aires	Dr. Miguel García
Clínica Constituyentes	Morón	Buenos Aires	Dr. Daniel Null
Clínica de Nefrología y Cirugía Cardiovascular	Santa Fe	Santa Fe	Dr. Guillermo Heredia
Clínica del Sol	C. A. de Buenos Aires	C.A.B.A.	Dr. Juan Gagliardi
Clínica Independencia	Vicente López	Buenos Aires	Dr. Horacio Pomés Iparraguirre
Clínica Santa Isabel	C. A. de Buenos Aires	C.A.B.A.	Dr. Adrián Charask
Fundación Médica de Río Negro	Río Negro	Río Negro	Dr. Iván Martín
Hospital de Clínicas Gral José de San Martín	C. A. de Buenos Aires	C.A.B.A.	Dra. Sandra Swieszkowski
Hospital Delicia Concepción Masvernat	Concordia	Entre Ríos	Dr. Carlos Pedroza
Hospital Dr. Cosme Argerich	C. A. de Buenos Aires	C.A.B.A.	Dr. Alfredo Piombo
Hospital Dr. Eduardo Castro Rendon	Neuquén	Neuquén	Dra. Mariana Gutiérrez
Hospital Dr. Felipe Glasman	Bahía Blanca	Buenos Aires	Dr. Fernando Sierra
Hospital Dr. Horacio Cestino	Ensenada	Buenos Aires	Dr. Adrián Lamarque
Hospital Dr. Teodoro Álvarez	C. A. de Buenos Aires	C.A.B.A.	Dra. Karina Palacios
Hospital Donación F. Santojanni	C. A. de Buenos Aires	C.A.B.A.	Dr. José Suárez
Hospital El Cruce-Néstor Kirchner	Florencio Varela	Buenos Aires	Dr. Carlos Tajer
Hospital Escuela Gral. San Martín	Corrientes	Corrientes	Dr. Julio Ibáñez
Hospital Español	C. A. de Buenos Aires	C.A.B.A.	Dra. Liliana Nicolosi
Hospital Español	La Plata	Buenos Aires	Dr. Daniel De Sagastizábal
Hospital Evita Pueblo	Berazategui	Buenos Aires	Dr. Néstor Gorini
HIGA Dr. Luis Güemes	Haedo	Buenos Aires	Dra. Silvia Ferreira
HIGA Eva Perón	San Martín	Buenos Aires	Dr. Alejandro Saied
HIGA San Martín de La Plata	La Plata	Buenos Aires	Dr. Néstor Ruiz
Hospital José Penna	Bahía Blanca	Buenos Aires	Dr. Gustavo Carrasco
Hospital Juan A. Fernández	C. A. de Buenos Aires	C.A.B.A.	Dr. Simón Salzberg
Hospital Lucio Molas	Santa Rosa	La Pampa	Dr. Mario Kohan
Hospital Regional de Río Grande	Río Grande	Tierra del Fuego	Dr. Raúl Maltez
Hospital Vélez Sarsfield	C. A. de Buenos Aires	C.A.B.A.	Dr. Lucas Corradi
INCOR	La Rioja	La Rioja	Dr. Pablo Santander
Instituto Alexander Fleming	C. A. de Buenos Aires	C.A.B.A.	Dr. Marcelo Zylberman
Instituto Cardiovascular San Luis	San Luis	San Luis	Dr. Juan Albisu
Instituto Médico Central	Ituzaingó	Buenos Aires	Dr. Mariano Ferrer
ITEC	S. M. de Tucumán	Tucumán	Dr. Esteban Ávila
Policlínico Rafaela	Rafaela	Santa Fe	Dr. Eduardo Marzioni
Sanatorio Anchorena	C. A. de Buenos Aires	C.A.B.A.	Dr. Miguel González
Sanatorio Belgrano	Mar del Plata	Buenos Aires	Dr. Héctor Moreno
Sanatorio Boratti	Posadas	Misiones	Dra. Mariela Fontana
Sanatorio de la Mujer	Rosario	Santa Fe	Dr. Pablo Milanesio
Sanatorio de la Providencia	C. A. de Buenos Aires	C.A.B.A.	Dr. Esteban Carfagna
Sanatorio de la Trinidad Mitre	C. A. de Buenos Aires	C.A.B.A.	Dr. Carlos Pellegrini
Sanatorio Dupuytren	C. A. de Buenos Aires	C.A.B.A.	Dra. Paula Pérez Terns
Sanatorio El Carmen	Salta	Salta	Dr. Edmundo Falú
Sanatorio Franchin	C. A. de Buenos Aires	C.A.B.A.	Dr. Rafael DiZeo
Sanatorio Garat	Concordia	Entre Ríos	Dr. Ezequiel Forte
Sanatorio Güemes	C. A. de Buenos Aires	C.A.B.A.	Dr. Álvaro Sosa Liprandi
Sanatorio Municipal Dr. Julio Méndez	C. A. de Buenos Aires	C.A.B.A.	Dra. Ada Abad Monetti
Sanatorio Las Lomas	C. A. de Buenos Aires	C.A.B.A.	Dr. Raúl Etchepare
Sanatorio Otamendi	C. A. de Buenos Aires	C.A.B.A.	Dr. Carlos Rodríguez Pagani
Sanatorio San Carlos	Bariloche	Río Negro	Dr. Mariano Trevisán
Unidad Asistencial Dr. César Milstein	C. A. de Buenos Aires	C.A.B.A.	Dr. Rafael DiZeo