



RESEARCH ARTICLE

**THROMBUS: A PROSPECTIVE, MULTICENTRE STUDY: DIAGNOSTIC CONCORDANCE OF EMERGENCY DOCTOR-PERFORMED BEDSIDE ULTRASONOGRAPHY VERSUS SPECIALIST-PERFORMED ECHO-DOPPLER ULTRASONOGRAPHY, IN STANDARD CLINICAL PRACTICE, IN THE DIAGNOSIS OF DEEP VEIN THROMBOSIS OF LOWER LIMBS**

**Penedo Alonso JR<sup>1</sup>, Sánchez Pérez M<sup>2</sup>, Roldán Moll F<sup>3</sup>, Ly-Pen D<sup>4</sup>, Zamorano Serrano M<sup>5</sup>, Díaz Vidal L<sup>6</sup> and Justo Gil S<sup>7</sup>**

<sup>1,2,3,4,5,6</sup> Emergency Ultrasound, Alcala University Medical School, Madrid, Spain. Emergency Department, Hospital Universitario "Ramón y Cajal", Ctra. de Colmenar Viejo km. 9,100, Madrid28034, Spain

<sup>4</sup>Emergency Department, Doncaster Royal Infirmary, Thorne Road, Doncaster, Yorkshire, DN2 5LT.UK

<sup>7</sup>Preventive Medicine and Public Health Department, Hospital Universitario "Infanta Leonor" Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Ctra. de Colmenar Viejo km. 9,100, Madrid28034, Spain

ARTICLE INFO

**Article History:**

Received 06<sup>th</sup> September, 2015

Received in revised form 14<sup>th</sup> October, 2015

Accepted 23<sup>rd</sup> November, 2015

Published online 28<sup>st</sup> December, 2015

**Key words:**

Deep Venous Thrombosis, Emergency Ultrasound, Doppler, Diagnostic concordance

ABSTRACT

**Introduction:** Deep venous thrombosis (DVT) is an increasing cause of morbidity and mortality. Current evidence suggest that Emergency doctors can perform Bedside Ultrasound (EUS) to diagnose DVT, in a quick, inexpensive and accurate way in comparison with "gold standard" studies by the specialist doctor-performed Doppler Ultrasound (SDUS). Nonetheless, important concerns have been raised about the interpretation of these studies: small sample sizes, very different experience of the emergency doctors performing, highly skilled and lack of details involving patient enrolment

**Objectives:** To ascertain the diagnostic concordance of a homogeneous group of novice emergency doctor performing EUS of the lower extremities, with SDUS in the diagnosis of DVT, in routine clinical practice.

**Methods:** In this prospective, multicenter study, adult patients (>18 years old) with clinical suspicion of DVT, with high or moderate risk (on Wells scoring) or low risk with increased D-dimer levels, were eligible. From September 2013 to September 2014, 328 patients were enrolled. Fifty-one investigators from seven hospitals performed the EUS. Each patient had the EUS and SDUS both in femoral and popliteal areas. The final result was considered non-concordant if one or both of the EUS did not match with the SDUS. For inter-rater agreement analysis, we used the Kappa statistic, and confidence intervals (CIs) of 95% were computed using a jack-knife re-sampling procedure.

**Results:** Of 326 ultrasound studies, 35 were discordant. The percentage of agreement between EUS and SDUS was 89%. The kappa index was 0.76 (95% CI = 0.69–0.84), which means a "substantial agreement."

Thorough study of the mismatched EUS/ SDUS performances, revealed that:

- 56% of non-concordant results were in the first two performances.
- 83% occurred in the first five performances.

**Conclusions:** There is "substantial agreement" between the EUS and SDUS in the diagnosis of DVT in routine clinical practice.

Thorough examination of the THROMBUS data, suggests that it seems quite reasonable (if not mandatory), that Emergency doctors performing US in the diagnosis of DVT should be shadowed by senior staff experienced in US, at least during their first five performances. This will decrease the mismatch in relation to SDUS (from 89% to 95%).

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INTRODUCTION

The incidence of deep vein thrombosis (DVT) of lower limbs is increasing in developed countries.[1,2] Evidence suggests that as many as 50% of people in whom a blood clot in the leg is left untreated will go on to develop a blood clot in their lung.[2] Even if blood clots are non-fatal, they can still result in long-term illness, including venous ulceration and

development of a post-thrombotic limb (chronic pain, swelling, and skin changes in the affected limb) and have a significant impact on quality of life.[2] Failure to quickly diagnose and properly treat DVT can worsen the patient's prognosis. However, the erroneous diagnosis of DVT can lead to unnecessary treatment with anticoagulation and will increase the risk of hemorrhage.[3] The value of vein ultrasonography for diagnosis of symptomatic DVT is widely

accepted (excluding isolated calf or pelvic thrombosis). [4] Good correlation between an emergency doctor-performed ultrasound (EUS) and specialist doctor-performed echo-Doppler (SDUS) was demonstrated.[4] Other studies have also confirmed these results[5] and even good correlation between EUS and CT venography.[6] Not only EUS, but also there is a recently published study with good correlation between nurse-diagnosed compression ultrasonography versus that performed by specialist doctors in DVT diagnosis.[7]

A systematic review of pooled data from six studies also suggests that EUS may be accurate for the diagnosis of DVT compared with SDUS.[8] However, some concerns have been raised: these studies included small sample sizes and methodological issues.[8] Most of the reviewed studies lacked details involving patient enrollment and used a small number of highly skilled ultrasonographers to perform examinations. [9] Bearing these considerations in mind, we conducted our THROMBUS study to ascertain not only the diagnostic concordance of EUS with SDUS in a homogenous population of emergency doctors (volunteer specialty registrars, non-trained beforehand in ultrasonography for DVT) in a multicenter study in standard clinical practice, but also to study possible reasons of non-concordant data. This aspect has not been previously studied.

## **PATIENTS AND METHODS**

For our study, 130 emergency doctors (volunteer specialty registrars) were trained. None of them had previously attended a formal ultrasonography course for DVT. They were from seven different tertiary level hospitals (of the Spanish National Health System), all of them with availability of a specialty doctor (either radiologist registrar or vascular surgeon registrar, depending on each hospital's protocol) to perform Doppler ultrasonography. In Spain, vascular surgery registrars are fully licensed to perform this technique, and in some hospitals where there is a vascular surgeon on guard, they usually perform the Doppler ultrasonography. All enrolled emergency doctors in the THROMBUS study performing EUS received the same induction course (theoretical/practical) of basic ultrasonography of 15 teaching hours (2 days), with special attention to simplified compression technique (4 hours) in femoral and popliteal areas of the deep venous system of the lower limbs. All the ultrasonography devices used in these courses were exactly the same as those used when performing the THROMBUS study ("General Electric LOGIC e": able to save and export images). No further training was given, and after the course the emergency doctors performed their studies by themselves.

### ***Study population and environment***

Between September 2013 and September 2014, 51 emergency doctors from seven hospitals collected data from 328 patients.

### ***Flow chart of THROMBUS study***

The patients were selected through non-probability (convenience) sampling, and the study was performed in standard clinical practice. Inclusion criteria in the THROMBUS study were patients over 18 years old with

clinical suspicion of DVT (usually non-traumatic or unexplained leg pain or discomfort in the previous 2 weeks or unilateral leg swelling) and middle (1 or 2 points) or high risk (3 or more points) according to the Wells score [10] or having a low (0 or less points) Wells score with simultaneously elevated D-dimer levels. Patients could be self-referred or sent by general practitioners or community emergency services. Exclusion criteria of the study were patients with a low (0 or less points) Wells score and normal D-dimer levels, previous diagnosis (less than 1 year) of DVT in the same limb or chronic DVT, presence of indwelling femoral vascular catheter or dialysis vascular shunts in the symptomatic leg, if the inclusion could be an additional risk for the patient (e.g., critical patients, patients with skin lesions on points of ultrasound examination), patient on which, for any reason, EUS could not be performed, and if the patient did not sign the informed consent. For each patient, demographic data were collected (date of birth, gender, height, and weight), risk factors for DVT (recent immobilization of lower limbs, bed bound for 3 or more days, diabetes mellitus, major surgery with general or regional anesthesia in the previous 12 weeks, cancer of any location, previously documented DVT, coagulopathy), and the results of physical examination.

Each enrolled patient had two separate, blinded ultrasonography studies performed. First, the EUS was performed, as the emergency doctor that was attending the patient considered at that moment that a DVT must be ruled out, always according to the clinical guidelines explained above.[10] At that moment, the emergency doctor explained to the patient (in simple language and giving a leaflet with the information) about the THROMBUS study. All patients' questions about this study were immediately and clearly answered by the emergency doctor. If after the explanation and answering patients' questions, the patient signed the informed consent for our study (along with all usual examinations and investigations) an EUS was performed in the femoral and popliteal area (following the simplified compression technique; see below). All this usually took approximately 5 to 10 minutes. After the EUS was performed according to each hospital's protocol, the SDUS was performed. Both the patient and the specialist doctor did not know the results of the EUS. However, all historical and physical examination data were of course made available to the specialist doctors.

### ***Simplified compression technique***

For the evaluation of DVT in both femoral and popliteal areas, a high-frequency linear probe was used (5–10 MHz). The patient was in a supine decubitus position, and the probe was placed in a transverse view with the marker towards the patient's right side. In the femoral area, on the inguinal crease, the lower limb was placed in external rotation with a slightly flexed knee; both the common femoral vein and greater saphenous vein with the common femoral artery had to be identified ("Mickey mouse's" sign). In the popliteal area, on the center of the popliteal fossa with the knee slightly flexed, both popliteal vein and popliteal artery had to be identified. If the veins were collapsible to a thin line with external pressure applied, the vein was presumed to be patent and there was no clot present. If the vein did not collapse with external pressure, there was presumed to be a clot(s) within the lumen

of the vessel preventing complete collapse. [11] The pressure needed to compress the vein was defined as that necessary to efface the adjacent artery. The emergency doctor registered the result of their EUS as “normal,” “abnormal,” or “not examined” for each of the two areas to be explored: inguinal and popliteal. The test was considered as normal, when the vein was seen to be compressed completely (100%) with the lumen disappearing from view on the ultrasound monitor. If incomplete (not 100%) collapse was seen, vein compressibility was noted to be abnormal, and this was diagnostic of a DVT.[4,11] The final result for each patient was considered as abnormal if, in any one of the two locations, the result was abnormal (even if a second examination was not performed). If only one of the two examinations was performed and considered normal, then the result was considered incomplete, and the patient was excluded from the concordance analysis. The specialty doctor who performed the SDUS registered the DVT as “positive” or “negative,” and this result was used as the reference. Any treatment was taken exclusively under the standard protocol: the SDUS.

**Statistical analysis**

Descriptive analyses of the characteristics of the population were performed using the mean and standard deviation of quantitative variables. Categorical variables were described with absolute and relative frequencies.

For inter-rater agreement analysis, we used the Kappa statistic,[12] and CIs of 95% were computed using a jack-knife re-sampling procedure.[13] A sensitivity analysis was performed, including those cases with incomplete values for EUS. A stratified concordance study was performed at a participating hospital. When a discordant EUS was observed, we also recorded the sequence number in the total of EUS performed by that emergency doctor and the total number of ultrasounds performed by each researcher. Statistical analyses were performed using Stata software version 13.1.

**RESULTS**

The characteristics of the patients of the THROMBUS study are shown in Table 1.

The rate of positive SDUS in our study was 118 out of 318 (36%). In total, 328 pairs of EUS/ SDUS were performed, of which 37 were discordant between them. Two EUS were incomplete, so the concordance analysis was conducted with 326 pairs of EUS with 35 discordant (Table 2).

Of these 35 discordant, 22 were false negative, and 13 were false positive (4 false positive in femoral area, and 10 were false positive in popliteal area: 1 patient was false in both femoral and popliteal areas).

The percentage of observed agreement between EUS and SDUS was 89%. The kappa statistic was 0.76 (95% CI = 0.69–0.84), representing a “substantial agreement”. [14]

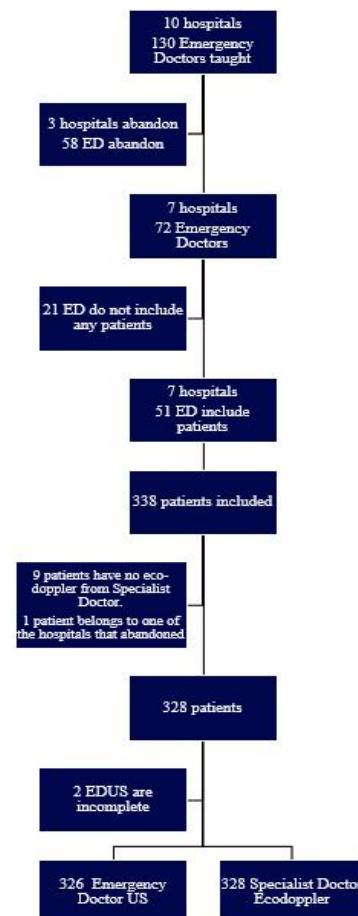
**Table 1** Characteristics of the patients of THROMBUS study.

Variable	Mean or n	SD or %*
Age, years	67.8	17.0
Gender, female %	187	57.0%
BMI, kg/m <sup>2</sup>	28.3	5.7
Lowerlimb, %		
Right	140	42.7%
Left	187	57.0%
Bilateral	1	0.3%
Symptomsduration (days)	10.5	18.0
Riskfactors, %		
Recentimmobilization	51	15.6%
Bedbound	51	15.6%
Diabetes	39	11.9%
Majorsurgery	21	6.4%
Cancer	45	13.7%
Previous DVT	46	14.0%
Coagulopathy	10	3.0%
Superficial non-varicoseveins	98	29.9%
Pain on palpation of deep veins	168	51.2%
Partialswelling of leg	237	72.3%
Complete swelling of leg	77	23.5%
Swelling of leg>3 cm.	135	41.2%
Alternative diagnosis	48	14.6
Wells score, %		
<1	53	16.2%
1-2	187	57.0%
3	88	26.8%

\* All percentages using 328 as the denominator.

**Table 2** Concordance between emergency doctor ultrasound and specialist doctor doppler ultrasound

EUS	SDUS: negative	SDUS: positive	Total
Normal	196	22	218
Abnormal	13	95	108
TOTAL	209	117	326



**Figure 1** Flow chart of THROMBUS study

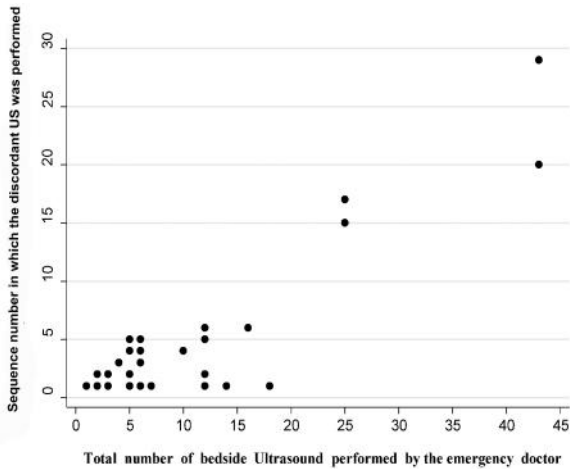
**Table 3** Classification of emergency doctors in groups according to the number of ultrasounds conducted, total of US done (and percentage), total number of discordant US in the first 5 performances (also detailed in 2 first performances in the group with 5) conducted.

Number of EUS conducted	Number of emergency doctors	Total of the EUS done (percentage)	Total number of discordants	Number of discordants in the first 5 performances (in percentage)
5	33	77 (23%)	18	18 (100%) (83% in 2 first)
6-11	9	64 (20%)	6	6 (100%)
12	9	187 (57%)	13	7 (54%)

The lower limit of the range remains within the range considered to show substantial agreement. A sensitivity analysis considering the incomplete values as both negative or both positive was performed; in both cases, they were very similar to the previous kappa index of 0.76 (95% CI = 0.68-0.83).

In the stratification by hospital, differences in the concordance among the different hospitals were observed, ranging from a minimum kappa index of 0.66 (95% CI = 0.37-0.96, n = 30) to a maximum of 0.91 (95% CI = 0.78-1, n = 75).

Table 3 shows the group of emergency doctors who conducted five or fewer EUS (n = 33), 18 discordances were observed in 77 EUS (23%); 15 of them (83%) were in the first and second performance. Of those who performed between 6 and 11 EUS (n = 9), six discordances of 64 EUS were observed; all of them (100%) were in the first five performances. In the group that performed 12 or more EUS (n = 9), 13 discordance in 187 scans (7%) were observed, with seven of them (54%) in the first five performances.



**Figure 2** Sequence number in which the US was performed by emergency doctor, according to the total number of US performed by emergency doctor

In Figure 2 we can see clearly the graphic distribution of the mentioned data. The points density is bigger in the first 5 performances and in those emergency doctors that conducted 5 US. The points density decrease as both parameters increase (the higher the sequence number and the more US performed).

**Weak Points of Thrombus Study**

For various reasons, two hospitals dropped out before starting the THROMBUS study, and one hospital could not enroll any patients. Also, of the 130 investigators initially trained, 79 of them dropped out before the beginning of the study or did not enroll any patients. This may be explained by some of them only wanting to attend the free course and some of them

changing their post before the beginning of patient enrollment.

Because of bureaucratic reasons, it took approximately 5-6 months from the teaching of theoretical courses with practical training and the beginning of enrolling patients in the THROMBUS study. As previously told, no further training was given, and after that course the emergency doctors performed their studies by themselves. Our results may have been different had we begun enrolling patients for the study just after the conclusion of the training course. Twenty one of the doctors that begun the study could no longer include more patients, because for several reasons they did not continue in their posts whilst THROMBUS was conducted. Perhaps the biggest limitation of THROMBUS is the convenience sample. Our study was performed in “standard clinical practice”. And at that time (September 2013 / September 2014), in our country (Spain), due to cuts in budgets, emergency doctors were extremely busy, and this study was not paid (neither in cash nor kind). With these premises, only convenience sample could be done: the day that the department was not as busy as to add about 15 minutes of extra work, in a DVT suspicious patient.

**DISCUSSION**

This is the first multicenter study with seven tertiary level hospitals enrolled from different cities in Spain. The population enrolled in THROMBUS reflects a nation-wide distribution, and subsequently the results can also be extrapolated to a national level. All the ultrasonography equipment used in the teaching to emergency doctors was exactly the same brand and model to the equipment used for the THROMBUS study. All researchers involved were volunteer specialty registrars, and all were trained by the same teachers following the same theoretical presentations, workshops, and books. The inclusion of patients was from September 2013 to September 2014, so on a theoretical basis, possible seasonal bias of any kind was also avoided. Basically, the results of THROMBUS confirm the findings of previous studies conducted abroad: there is substantial agreement between EUS and SDUS.[3,5]

In Blaivas *et al*, [4] the percent agreement was 98% (95% CI = 95.4% to 100%). High correlation was seen with kappa of 0.9. In Kline *et al*, [3] evaluating 56 emergency clinicians (attending physicians, residents, and midlevel providers) after didactic training showed an initial sensitivity and specificity of 70% and 89%, respectively.[3] In Crisp *et al*, [5] this sensitivity improved to 100% for clinicians who performed three or more scans.[5,8]

About the background and degree of ultrasonography experience of the emergency doctors, much has been written,

great differences have been observed, and in many studies this has not even been detailed. Several papers have described the ability of emergency doctors to perform EUS of the lower extremity in the diagnosis of DVT. In Blaiwas *et al*, [4] the five emergency doctors who participated all had significant ultrasonography experience, making this study not easily extensive because the emergency doctors were very experienced. As we saw before, most of the reviewed studies lacked details involving patient enrollment and used a small number of highly skilled ultrasonographers to perform the examinations. [9] Unlike many other previous studies, our recruiters were a quite homogeneous population: 51 volunteer specialty registrar emergency doctors who had not previously attended an ultrasonography course for DVT and received an induction course (theoretical/practical) of basic ultrasonography of 15 teaching hours (2 days) with special attention to simplified compression technique (4 hours) in femoral and popliteal areas of the deep venous system of lower limbs. We consider this fact very important because in many previous studies, either the background of the researchers emergency doctors was heterogeneous, [3] highly skilled, [4] or not specified. [8]

In THROMBUS, we dissected the results of the mismatched EUS/ SDUS and noticed very interesting results: 56% of non-concordant EUS were in the first two performances and 83% occurred in the first five performances. In our opinion, this is of crucial importance. As we discussed above, there are plenty of questions about the background of the emergency doctors performing EUS in the diagnosis of DVT in emergency departments. [3,8] After a thorough examination of the THROMBUS data, it seems quite reasonable (if not mandatory), that at least emergency doctors performing EUS in the diagnosis of DVT should be shadowed by senior staff experienced in ultrasonography during their first five EUS. This will decrease the mismatch in relation to SDUS. This situation could be extrapolated to a community setting. With a bedside ultrasonography device and a trained community emergency doctor or general practitioner, the decision of whether to begin anticoagulant drugs could be made without the need of waiting for a doppler ultrasonography the next day in a radiology or DVT clinic just to confirm if the anticoagulant treatment was properly given. [2]

As stated before we think the biggest limitation of THROMBUS is the convenience sample. We have also explained the main reasons for this: THROMBUS will never be allowed to start because clearly the main objective of every emergency department was to clear up the floor as soon as possible and the consultants will not allow to pick up patients for this study if the floor was busy. Nonetheless as stated in Valley *et al*, [15] “in Emergency Medicine, the differences between convenience sample and random samples, for many research projects may not be clinically significant”. [15]

#### **Declarations**

#### **List of Abbreviations**

DVT = deep vein thrombosis  
EUS = emergency doctor-performed ultrasound  
SDUS = specialist doctor-performed echo-Doppler

#### **Ethics Approval and Consent to Participate**

This study was approved by the Ethics Committee of University Hospital Ramón y Cajal and the Ethics Committees of all the participant hospitals (THROMBUS study, protocol code: UEU-ECO-2013-01). Informed consent was taken from all patients and collaborators of all hospitals.

#### **Consent for Publication**

Not applicable

#### **Availability of Data and Materials**

The great and most relevant data from THROMBUS are published in this article. Nonetheless, other data supporting our findings will be sent upon request with a unique and single condition: the requester’s commitment to publish that paper in an open and free journal (or other media).

#### **Competing Interests of Authors**

None of the authors, contributing authors, researchers, and collaborators, or their families have received any benefits or economic compensation from the completion of this study.

#### **Contributorship Statement**

J.R.Penedo, conceived the work, helped in the study design, selected articles for inclusion, supervised the project, assisted with data extraction and helped write the paper. M.Sánchez, helped in the study design, assisted with data extraction, integrated all hospitals’ data and helped write the paper. F.Roldán, helped in the study design, assisted with data extraction and integrated all hospitals’ data. D.Ly, helped in the study design, selected articles for inclusion, wrote the protocol, the case report form and wrote the article. M. Zamorano, helped in the study design, and assisted with data extraction L. Díaz, helped in the study design, and assisted with data extraction S. Justo, designed the statistical method, processed full data, performed statistical analysis, and helped write the paper. All the authors have revised, participated actively in the elaboration and approved the final draft.

#### **Acknowledgments**

To Laboratorios ROVI for their support with the web platform and bibliographic reference search. To Dr Claire Willis for her critical review, helpful comments and careful English revision. To Dr Andres Reyes Valdivia and Dr Cristina Gómez Olmos, for their help in reviewing the ultrasound images.

#### **List Of 51 Collaborators, Who Recruited Patients For Thrombus Study (Alphabetic Order:)**

JM Aguilar Mulet, Y Aranda García, A Baena Blancart, A Barrera Alonso, N BerradeFlamarique, JL Blázquez Díez, A Braña Cardeñosa, A Cabodevilla, M Calderón Moreno, R Caminero García, A Cantero Sandoval, C Carballo Cardona, E Contreras Murillo, F Corral Caramés, C De la Casa Resino, A Del Rey Ubago, I Estévez Lajo, MJ Estévez Rueda, M

Fernández Cardona, A Fernández González, M Gallego Alonso-Colmenarejo, P Gallego Rodríguez, JL Gálvez San Román, A García-Vicuña Meléndez, E Gargallo García, S González Del Val, S Gordo Remartínez, M Hernández Egado, A Herrero Azpiazu, D Izaguirre Diaz De Lezana, M Junquera Crespo, MA Leza, I López Isidro, L López Roldán, A Machín Muñoz, B Macías Bou, G Moreno Basarrate, M Negro Rúa, DJ Nova López, E OncalaSibajas, A Pizarro Portillo, B Sainz Berrio, ME Sánchez González, C Santiago Poveda, A Santorcuato Bilbao, N Talayero Sebastián, F Tejerina Picado, MM Torrecilla Gómez, FJ Val De Santos, N Villalba Guijorro, A Von WernitzTeleki.

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