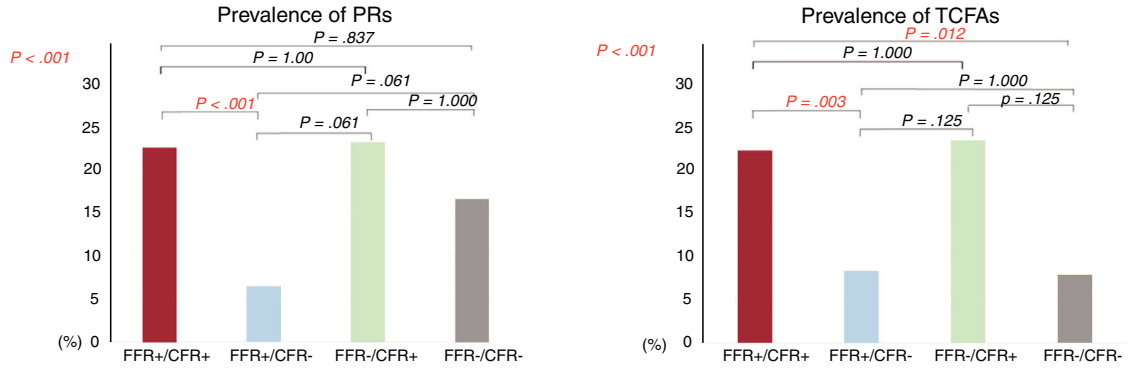

Figure 1. Prevalence of PRs and TCFAs. A: the prevalence of PRs according to FFR/CFR quadrants. B: the prevalence of TCFAs according to FFR/CFR quadrants. CFR, coronary flow reserve; FFR, fractional flow reserve; PR, plaque rupture; TCFA, thin-cap fibroatheroma.

FFR + /CFR-, the prevalence of both TCFAs and PRs tended to be higher, although, in the post hoc analysis, this difference was not significant in the FFR-/CFR + group. The net reclassification index and integrated discrimination improvement index were both significantly improved when CFR was added to the FFR-based classification for predicting PR and TCFA (PR; net reclassification index 0.462, $P < .001$, integrated discrimination improvement 0.031, $P < .001$, TCFA; net reclassification index 0.320, $P = .012$, integrated discrimination improvement 0.017, $P = .002$).

Our results indicate that physiological classifications of coronary stenosis evaluated by FFR and CFR are associated with the difference in plaque instability. Even in patients with lesions showing preserved FFR, CFR may add incremental information on plaque instability, which might be associated with worse outcomes. In the present study, we would like to address the importance of CFR in addition to FFR for evaluating plaque vulnerability. This differs from our previous report5 in which we evaluated the significance of microvascular dysfunction in addition to FFR. Further studies are needed to test the hypothesis of the possible link between physiological lesion assessment and lesion instability, and its impact on subsequent adverse cardiac events.

Masahiro Hoshino,[a] Eisuke Usui,[a] Tomoyo Sugiyama,[a] Yoshihisa Kanaji,[a] Taishi Yonetsu,[b] and Tsunekazu Kakuta[a,*]

[a]*Division of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Ibaraki, Japan*

[b]*Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan*

[*] Corresponding author:
E-mail address: kaz@joy.email.ne.jp (T. Kakuta).

Available online 28 October 2019

REFERENCES

1. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371:1208–1217.
2. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. *J Am Coll Cardiol.* 2016;67:1158–1169.
3. Taqueti VR, Everett BM, Murthy VL, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. *Circulation.* 2015;131:528–535.
4. van de Hoef TP, van Lavieren MA, Damman P, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv.* 2014;7:301–311.
5. Usui E, Yonetsu T, Kanaji Y, et al. Optical coherence tomography-defined plaque vulnerability in relation to functional stenosis severity and microvascular dysfunction. *JACC Cardiovasc Interv.* 2018;11:2058–2068.

https://doi.org/10.1016/j.rec.2019.09.008
1885-5857/
© 2019 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Differences between cardiologists' perceptions and clinical reality of the quality of anticoagulation with vitamin K antagonists in Spain

Diferencias entre la percepción de los cardiólogos y la realidad sobre la calidad de la anticoagulación con antagonistas de la vitamina K en España

To the Editor,

Evidence from clinical trials and 'real-world' studies has demonstrated that direct oral anticoagulants (DOAC) are as safe or safer than vitamin K antagonists (VKA) and at least as effective at preventing embolic events; DOACs are therefore now recommended as the first-line anticoagulation therapy in clinical guidelines.[1] Nevertheless, use of DOACs in Spain is limited and lower than that of comparable countries.[2] While this situation may be related to restrictions imposed by the Spanish health care system,[2] there is also evidence that VKA prescription is influenced by physicians' perceptions and attitudes.[3] Our aim in the present study was to analyze Spanish cardiologists' perceptions of the quality of anticoagulation with VKAs and to compare this perception with real-world evidence.

The cardiology services of all hospitals within the Spanish national health system were invited to participate in the study. In total, 171 centers agreed, and the heads of service at each hospital selected members of their teams to participate. A total of 588 cardiologists were interviewed by an external company between April and May 2018. The study participants were not forewarned of the study objectives. Each participant was asked to access his or her center's records and retrieve the medical history of a patient with nonvalvular atrial fibrillation (NVAF) who had attended the clinic that same day; the cardiologist was asked to assess the patient's international normalized ratio (INR) and time

Table 1
Time in therapeutic range by autonomous community and nationally

Canary Islands	39.0 ± 35.6%
Aragon	43.7 ± 20.6%
Community of Madrid	45.6 ± 25.2%
Castile-La Mancha	52.8 ± 18.2%
Extremadura	54.1 ± 16.4%
Valencian Community	54.3 ± 24.4%
National mean for Spain	56.2 ± 23.6%
Galicia	57.5 ± 22.4%
Andalusia	58.7 ± 22.4%
Catalonia	59.1 ± 25.4%
Basque Country	59.6 ± 21.2%
Balearic Islands	60.0 ± 16.7%
Cantabria	62.0 ± 11.6%
Castile and León	64.9 ± 17.5%
Principality of Asturias	67.8 ± 11.6%
Region of Murcia	69.5 ± 12.6%
Chartered Community of Navarre	70.8 ± 10.6%

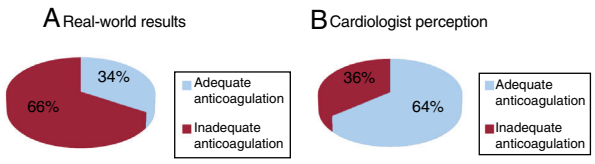

Figure 1. Proportion of patients with adequate anticoagulation (time in therapeutic range > 65%) according to (A) real-world data and (B) surveyed cardiologists' perceptions.

in therapeutic range (TTR). Participants were also asked to recall the last 4 NVAF patients treated with VKAs at their clinics and to state whether these 4 patients were correctly anticoagulated (TTR > 65% in the previous 6 months). Interviews were conducted at the end of clinics, and cardiologists gave informed consent to participate. Data calculated as means were compared by the Student *t* test and proportions were compared by the chi-square test. Differences were considered statistically significant at $P < .05$.

Interviews were conducted with 588 cardiologists from 171 cardiology services distributed across all Spanish autonomous communities. Of the cardiologists interviewed, 37% were women and 49% were younger than 40 years. Overall, 33% of the cardiologists were unable to directly access the patient's medical history and INR/TTR data, either on paper or on a computer database; moreover, access to this information varied considerably between autonomous communities ($P < .001$). The time needed to assess the INR and TTR was 1.16 ± 1.40 minutes. Mean TTR was 56.2 ± 23.6%, ranging from 39% in the Canary Islands to 70.8% in the Chartered Community of Navarre ($P < .001$; table 1). Only 36% of patients had a TTR > 65%, with the remaining 64% of patients inadequately anticoagulated (figure 1A). In contrast, according to the cardiologists' recollections of the 4 most recent VKA-treated NVAF patients in their clinics (N = 756), anticoagulation was inadequate (TTR < 65%) in only 36% of patients (272 of 756) (figure 1B). This result was similar for all autonomous communities. Neither real-world data nor cardiologist perception differed according to cardiologist sex or age range. Overall, male cardiologists believed 66.3% of their patients to be adequately anticoagulated, vs the true value of 35.4%, while the corresponding figures for female cardiologists were 63.1% and 34.8%. Cardiologists younger than 40 years believed anticoagulation to be adequate in 67.3% of patients overall, vs a real value of 35.2%, and the corresponding figures for cardiologists aged 40-55 years and >55 years were 66.3% versus 34.4% and 62.5% vs 37.8%, respectively.

Our study reveals poor anticoagulation with VKAs in NVAF patients treated in Spanish cardiology clinics; moreover, the detected quality of anticoagulation is worse than that reported in recent Spanish studies.[4,5] In those earlier studies, TTR was below 65% in 40% to 50% of patients, whereas in our study the value was 64%. Furthermore, our study shows that almost a third of cardiologists could not access INR and TTR data for patients treated at their centers. The discouraging real-world data contrast with the optimistic perceptions among the surveyed cardiologists, who believed that good control was achieved in 64% of patients, almost double the true rate. Although this study has limitations, including the lack of randomization of the participating cardiologists, there is clearly a notable discrepancy between the real and cardiologist-perceived quality of anticoagulation achieved with VKAs. Together with other likely causes noted above,[2] this discrepancy is likely to influence the underuse of DOACs in Spain.

CONFLICTS OF INTEREST

This study was carried out by the Spanish Society of Cardiology Research Agency with unconditional financial support from Daiichi-Sankyo. All the authors have received payments from the Spanish Society of Cardiology for their participation in the study scientific committee.

Manuel Anguita Sánchez,[a,b,*] Fernando Arribas Ynsaurriaga,[c] Ángel Cequier Fillat,[d] Eduardo de Teresa Galván,[e] Iñaki Lekuona Goya,[f] and José L. Zamorano Gómez[g]

[a]*Servicio de Cardiología, Hospital Universitario Reina Sofía, Córdoba, Spain*
[b]*Servicio de Cardiología, Hospital QuirónSalud, Córdoba, Spain*
[c]*Servicio de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain*
[d]*Servicio de Cardiología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain*
[e]*Servicio de Cardiología, Hospital Clínico Virgen de la Victoria, Málaga, Spain*
[f]*Servic io de Cardiología, Hospital de Galdakao, Galdakao, Vizcaya, Spain*
[g]*Servicio de Cardiología, Hospital Universitario Ramón y Cajal, Madrid, Spain*

[*] Corresponding author:
E-mail address: manuelanguita@secardiologia.es
(M. Anguita Sánchez).

Available online 24 December 2019

REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893–2962.
2. Roldán I, Marín F. Cardiovascular Thrombosis Group of the Spanish Society of Cardiology and the proposal development Committee On the way to a better use of anticoagulants in nonvalvular atrial fibrillation. Proposed amendment to the therapeutic positioning report UT/V4/23122013. *Rev Esp Cardiol.* 2016;69:551–553.
3. Mas Dalmau G, Sant Arderiu E, Enfedaque Montes MB, Sola A, Pequeño Saco S, Coello P. Patient's and physician's perceptions and attitudes about oral anticoagulation and atrial fibrillation: a quantitative systematic review. *BMC Farm Pract.* 2017;18:3.
4. Anguita Sánchez M, Bertomeu Martínez V, Cequier Fillat Áaue. CALIFA study researchers Quality of vitamin K antagonist anticoagulation in Spain: prevalence of poor control and associated factors. *Rev Esp Cardiol.* 2015;68:761–768.
5. Barrios V, Escobar C, Prieto L, et al. Control de la anticoagulación en pacientes con fibrilación auricular no valvular asistidos en atención primaria en España Estudio PAULA. *Rev Esp Cardiol.* 2015;68:769–776.

https://doi.org/10.1016/j.rec.2019.09.023
1885-5857/
© 2019 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Cardiología.

New mutation in the *ACTA2* gene (p.Met84Val) in a family with nonsyndromic familial aortic aneurysms

Nueva mutación en el gen ACTA2 (p.Met84Val) en una familia con aneurismas de aorta familiares no sindrómicos

To the Editor,

Nonsyndromic thoracic aortic aneurysms and dissections (ns-TAADs)[1] are characterized by the silent formation of aortic aneurysms and dissections without other external manifestations that facilitate their diagnosis. Familial ns-TAADs are reported to display autosomal dominant inheritance, as well as incomplete penetrance and variable expression.[2] Mutations have been found in various genes, but predominantly *ACTA2*.[3–5] Here, we present the case of a family with a novel mutation in ACTA2 causing ns-TAADs.

The index case was a man (II.9) who was treated at the age of 50 years for type A aortic dissection (AD) and had several relatives who died of sudden cardiac death (figure 1 and table 1). His mother (I.5) had a 38-mm dilatation of the aortic root (AR), whereas his brother (II.8) died of abdominal AD. The other 4 siblings were apparently healthy. The complete pedigree additionally included 2 cousins (sisters) who died of sudden cardiac death, one (II.6) at the age of 45 years without autopsy (one of her sons died at the age of 17 years of autopsy-confirmed AD), the other (II.4) at the age of 47 years from ascending AD.

A genetic study was performed using next-generation sequencing of a panel including 41 genes related to aortic disease (*ACTA2*, *ADAMTSL4*, *B3GAT3*, *CBS*, *COL1A1-2*, *COL3A1*, *COL5A1-2*, *EFEMP2*, *ELN*, *FBN1-2*, *FLNA*, *GAA*, *GATA5*, *HRAS*, *KCNJ8*, *MED12*, *MYH11*, *MYLK*, *NKX2-5*, *NOTCH1*, *PLOD1*, *PRKG1*, *PTPN11*, *SKI*, *SLC2A10*, *SMAD3-4*, *TGFB2-3*, *TGFBR12*, *ZDHHC9*, *ATP7A*, *CHST14*, *ADAMTS2**, *B4GALT7**, *FKBP14**, and *SLC39A13**). A novel heterozygous mutation was identified in exon 3 of the *ACTA2* gene, which encodes alpha-smooth muscle actin: Met84Val (NC_000010.10:g.90707023T>C). Subsequently, 19 relatives were examined; 13 underwent a genetic study. AR dilatation was found in 4, all of whom had a positive genetic screening result. All family members were studied using echocardiography, and the screening of the affected carriers was completed using computed tomography or magnetic resonance angiography. The median age at presentation was 47 years and only 1 family member had early presentation (at 17 years). In our series, the predominant location of the dilatation was the AR and there was only 1 case of abdominal aneurysm.

The patients were recommended strict control of cardiovascular risk factors and to avoid isometric exercises and competitive sports. All patients were treated with angiotensin receptor blockers and 1 was managed with prophylactic surgery.

AD in young patients is often the result of a genetic aortopathy. The paradigmatic example is Marfan syndrome. However, there are other genetic aortopathies lacking external signs, characterized by the silent formation of thoracic aortic aneurysms and dissections, known as ns-TAADs.[1] Mutations identified in the *ACTA2* gene would explain 14% of these patients.[3–5] The *ACTA2* gene, located on chromosome 10 (10q23.31), encodes alpha-actin, the most abundant protein in the smooth muscle of vascular cells. Its deficiency decreases the contractibility of these cells and can cause type A and B AD.[4,5] The variant identified in this family has not been described in the literature or in public genotyping databases of the general population and also involves a highly conserved residue. Variants associated with the development of thoracic aortic disease have been identified in nearby amino acids, such as p.Asp82Glu and p.Glu85Lys. Family members with ns-TAAD exhibit variable expression.[2] In this family, the median age at presentation was 47 years, similar to that described in the literature. Another characteristic of the phenotypic variability of ns-TAADs is the site of aortic involvement; in our family, the AR predominated. Penetrance has been reported to be incomplete; in our case, of the 6 patients with a positive genetic study, 5 had AR dilatation, indicating that the variant identified probably has elevated penetrance. Although the penetrance has been reported to be lower in women, cases were found in both sexes in this family. Other mutations described in *ACTA2* are associated with livedo reticularis, iris flocculi, and bicuspid aortic valve.[4] However, these conditions were not present in any of our patients, which may indicate a low frequency of association, as suggested in previous studies.[4]

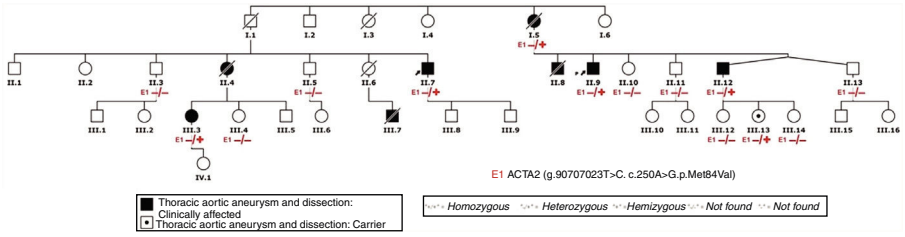

Figure 1. Pedigree.