Diagnosis and treatment of patients with antiphospholipid syndrome: a mixed-method evaluation of care in the Netherlands

Mirthe J. Klein Haneveld¹, Caro H. C. Lemmen¹, Tammo E. Brunekreef¹, Marc Bijl², A. J. Gerard Jansen³, Karina de Leeuw⁴, Julia Spierings¹, Maarten Limper¹, for the ARCH study group

1. Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands
2. Department of Internal Medicine and Rheumatology, Martini Hospital, Groningen, The Netherlands
3. Department of Haematology, ErasmusMC, University Medical Centre Rotterdam, Rotterdam, The Netherlands
4. Department of Rheumatology and Clinical Immunology, University Medical Centre Groningen, Groningen, The Netherlands

Correspondence to: Maarten Limper, Department of Rheumatology and Clinical Immunology, Heidelbergraad 100, 3584 CX Utrecht, The Netherlands. E-mail address: m.limper-2@umcutrecht.nl. ORCiD iD: https://orcid.org/0000-0002-4859-3250
Abstract

Objectives: This study aims to gain insight into the care provided to patients with antiphospholipid syndrome (APS) in The Netherlands, and to identify areas for improvement from the perspective of both patients and medical specialists.

Methods: APS care was evaluated using qualitative and quantitative methods. Perspectives on APS care were explored using semi-structured interviews with medical specialists, patient focus groups and a cross-sectional, online patient survey. In order to assess current practice, medical records were reviewed retrospectively to collect data on clinical and laboratory manifestations and pharmacological treatment in six Dutch hospitals.

Results: Fourteen medical specialists were interviewed, fourteen patients participated in the focus groups and 79 patients completed the survey. Medical records of 237 patients were reviewed. Medical record review showed that only one-third of patients were diagnosed with APS within three months after entering specialist care. Diagnostic approach and management varied between centres and specialists. Almost 10% of all patients and 7% of triple positive patients with thrombotic APS did not receive any anticoagulant treatment at the time of medical record review. Correspondingly, poor recognition and fragmentation of care were reported as the main problems by medical specialists. Additionally, patients reported the lack of accessible, reliable patient education, psychosocial support and trust in physicians as important points for improvement.

Conclusion: Delayed diagnosis, variability in management strategies and fragmentation of care were important identified limitations of APS care in this study. A remarkable 10% of patients did not receive any anticoagulant treatment.

Keywords
Antiphospholipid syndrome, quality of care, qualitative research, medical records, unmet patient needs

Key messages
1. Delayed diagnosis is common among patients with APS
2. APS treatment strategies vary between medical specialists and hospitals
3. Unmet APS patient needs include patient education, psychosocial support and trust in physicians

https://mc.manuscriptcentral.com/rheumap
Diagnosis and treatment of APS: evaluation of care

Introduction

The antiphospholipid syndrome (APS) is a rare auto-immune disease affecting approximately 1000 to 2000 patients in The Netherlands. A diagnosis of APS is generally made when a patient meets the classification criteria: vascular thrombosis and/or pregnancy morbidity, such as repeated spontaneous abortion, unexplained foetal death and preterm birth, in the repeated presence of circulating antiphospholipid (aPL) antibodies targeted at anticardiolipin (aCL) and/or β2-glycoprotein I (β2GPI) and/or lupus anticoagulant (LAC) with an interval of at least 12 weeks. APS is associated with a variety of non-criteria clinical manifestations, such as thrombocytopenia, renal microangiopathy, heart valve disease, livedo reticularis and migraine. It often occurs in isolation, but can be found in association with systemic lupus erythematoses (SLE) and other auto-immune diseases. Lifelong anticoagulation is the mainstay of therapy for thrombotic APS due to the high risk of relapse; for obstetrical APS, treatment exists of low-dose aspirin and prophylactic low-molecular-weight heparin during pregnancy. Additionally, immunomodulatory drugs such as hydroxychloroquine are recommended for secondary APS in SLE patients. Optimal care for APS is challenging due to its rare occurrence, variation in diagnostic test assays and interpretation, heterogeneous clinical manifestations and subsequent multidisciplinary character. A review of clinical practice guidelines concluded that a formal guideline covering all relevant aspects of APS diagnosis and treatment is missing. As large randomized-controlled trials for treatment of APS are rarely performed, the development of evidence-based guidelines, such as the 2019 EULAR recommendations for the management of APS, remains very challenging. As a consequence, variation in treatment strategies between medical specialists and centres is presumably high.

Few studies have investigated the experiences regarding APS care of patients and physicians. A questionnaire distributed among patients in the United Kingdom pointed out that there was a long delay between first symptoms and diagnosis, with a median duration of three years, as well as a lack of awareness of APS among general practitioners and medical specialists. Qualitative studies into experiences of APS patients described the impact of living in uncertainty and delayed diagnosis. Patient representatives highlighted the need for improved patient education and monitoring. However, these unmet patient needs require more research attention.

The Dutch Arthritis Research and Collaboration Hub (ARCH) aims to improve care for rare auto-immune diseases including APS. Using both qualitative and quantitative methods, this study aims to gain insight...
Diagnosis and treatment of APS: evaluation of care

in the care currently provided to patients with APS in the Netherlands and to identify unmet needs and areas for improvement from the perspectives patients and medical specialists from different centres and disciplines.

Methods

Design

This study employed a mixed-method design to collect qualitative and quantitative data from the perspectives of patients and medical specialists. We collected data in three stages. Firstly, qualitative data were collected from focus group sessions with patients and interviews with medical specialists. Secondly, an online survey was distributed among patients. Thirdly, medical records in university and general hospitals were reviewed to evaluate variation in patient characteristics, the diagnostic process and management between centres. Ethical approval was given by the Medical Ethical Committee of the University Medical Centre Utrecht (METC number 18-508) and all participating hospitals.

Setting and participants

Twenty medical specialists known to have a special interest in thrombotic conditions were invited to participate in individual interviews between June and September 2018. Medical specialists were selected by three ARCH APS working group members in order to reach a heterogeneous sample with regard to sex, discipline (neurology, haematology, clinical immunology, rheumatology, gynaecology and vascular medicine), patient load and type of hospital in the Netherlands. All interviews with medical specialists were held by telephone by the same researcher (JS) and lasted between 30 and 75 minutes. The researcher (female, rheumatologist, researcher) was not affiliated with the participants.

Patients with APS were recruited to participate in focus groups by the national patient organization (Nationale Vereniging voor Lupus, APS, Sclerodermie en MCTD, NVLE). Four focus group sessions, with three or four participants per group, took place between June and November 2018 at a meeting point centrally located in the country. Prior to the focus group, participants were asked to fill out a questionnaire on sociodemographic information and disease characteristics. All focus groups were moderated by one researcher (JS) in the presence of a representative of the patient organization and lasted between 120 and 150 minutes.
Medical specialists from four university hospitals (University Medical Centre Utrecht (UMCU), Erasmus Medical Centre Rotterdam (EMC), Universal Medical Centre Groningen (UMCG), Maastricht University Medical Centre (MUMC)) and three general hospitals (Diakonessenhuis Utrecht, Hospital Group Twente (ZGT) Almelo/Hengelo, Martini Hospital Groningen) invited a total of 109 patients by mail to participate in the online self-administered survey. The inclusion criterion was a clinical diagnosis of APS according to their medical specialist. Patients could sign up for participation by sending an email to the researcher with their consent. Subsequently, they received a link to the survey in Castor Electronic Data Capture (EDC). The survey was open from November 2018 until June 2019.

Between March and May 2019 medical records from four university hospitals (UMCU, EMC, UMCG, MUMC) and two general hospitals (Diakonessenhuis Utrecht, ZGT) were reviewed. Each centre compiled a list of patients for whom aPL antibody measurement was requested at the laboratory. Patients were randomly selected from this list and included into the study if the following inclusion criteria were met:

- a clinical diagnosis of APS according to the coordinating physician and;
- availability of data regarding antiphospholipid syndrome in the patient record. Inclusion of patients continued until a maximum of 50 patients was reached or no new APS patients could be identified.

**Data collection**

Two rheumatologists and a clinical immunologist formulated an interview guide for semi-structured interviews. It was tested by an advisory group consisting of patients and medical specialists of the ARCH APS working group (Supplementary Material, section Interview Guide, available at Rheumatology Advances in Practice online) A semi-structured approach was chosen, because it ensured that all topics were addressed, but left room for flexibility in pursuing participants' interests and expertise. The focus groups had a similar semi-structured approach. The diagnostic process, management after diagnosis, information provision and psychosocial support were addressed. Participants were asked to share main challenges and unmet needs and to suggest relevant process and outcome measures that should be used as quality indicators for APS care. The interviews and focus group sessions were recorded and transcribed verbatim by three independent researchers (MK, CL, CB).
Data collection for the online survey and medical record review was done in Castor EDC. The online survey was composed and tested similarly to the interview guide (Supplementary Material, section Online Survey, available at *Rheumatology Advances in Practice* online). Data for medical record review were collected using a case report form (CRF). Relevant process and outcome measures mentioned in focus groups and interviews were incorporated in the CRF (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). Collected data included demographic information, duration of illness, time until diagnosis, clinical and laboratory criteria of APS, non-criteria disease manifestations, medication use, complications of treatment and information regarding disease management.

**Data analysis**

Two independently working researchers (MK, CL) analysed the data from interviews and focus group sessions mostly deductively. The researchers first familiarized themselves with the data by thoroughly reading the transcripts and writing down initial ideas. Themes were identified using the interview guide. Additionally, topics that were frequently brought up by participants were considered as themes or subthemes. Subsequently, the two researchers discussed the identified themes and assessed their internal homogeneity and external heterogeneity. The results were summarized by the two researchers, discussed in the ARCH APS working group and used to compose the questions for the survey. The consolidated criteria for reporting qualitative research (COREQ) are reported in Supplementary Table S2, available at *Rheumatology Advances in Practice* online. Quantitative data was processed using IBM SPSS Statistics for Windows, Version 25.0.

Ethical approval was given by the Medical Ethical Committee of the University Medical Centre Utrecht (METC number 18-508) and all participating hospitals.

**Results**

*Specialist interviews, patient focus groups and patient survey*

*Characteristics of study participants*
From the 20 invited medical specialists, four did not respond and two did not want to participate due to time limitations. The characteristics of fourteen interviewed medical specialists are displayed in Table 1. For the online survey, 109 patients were invited; the response rate was 72.5%. Demographic and clinical characteristics, and experiences of fourteen focus group participants and 79 patients who filled out the digital survey are described in Table 2.

**Perspectives on the diagnostic process**

The importance of being taken seriously by medical specialists and general practitioners and the necessity of referral to expert centres were recurring themes in the focus groups and survey responses. Several patients felt that they were “being fobbed off” by physicians; two focus group participants remarked that their health problems had been initially interpreted as psychosomatic. Self-reported time to diagnosis in focus groups and survey responses varied widely, ranging from less than one month to over five years. Overall, time to diagnosis had a strong negative impact on satisfaction with the diagnostic process among the focus group participants. However, only 7.6% and 8.9% of survey respondents considered delayed diagnosis and, respectively, insufficient recognition of APS by physicians main obstacles in APS care.

According to medical specialists, main challenges in the diagnostic process are insufficient recognition of APS by medical specialists (10/14) and general practitioners (7/14) as well as the absence of evidence-based diagnostic guidelines (3/14). One specialist considered the quality of laboratory diagnostics to be a main challenge. Four medical specialists remarked that the diagnostic process of APS requires more expertise compared to the management of APS after diagnosis.

**Perspectives on management after diagnosis**

Patients felt the need to orchestrate their own care, because they experienced a lack of collaboration and communication between medical specialists and between medical specialists and medical services, i.e. the anticoagulation service (Dutch: Trombosebedienst). This made them as patients responsible for an adequate exchange of information about their disease and medication use, which could be particularly worrisome for patients when they were critically ill and required emergency care. Several participants expressed the need for a document explaining their condition to show at emergency departments. Correspondingly, limitations in exchange of patient information between hospitals was mentioned as a burden by 50% of the interviewed medical specialists.
Another main challenge in APS care reported by eight out of fourteen medical specialists was the lack of evidence-based treatment guidelines. The absence of uniform guidelines was thought to contribute to variation in treatment strategies and to negatively impact the quality of care. Patients recognized this issue and referred to uncertainty regarding the management of anticoagulation in the context of surgical procedures.

Ten medical specialists agreed that multidisciplinary consultation should be possible for all patients, however, only six reported that this was actually available at their hospital. Twelve medical specialists agreed to the statement that APS care is fragmented; eight agreed that improved communication is necessary to improve cooperation between physicians.

**Perspectives on information provision, psychosocial support and daily functioning**

Patient education was considered to be insufficient by eight out of fourteen interviewed medical specialists, eleven out of fourteen focus group participants and 41.8% of survey respondents. Patients identified this as a big challenge in APS care and a good measure for quality of care. Patients particularly needed information about the wide range of symptoms attributed to APS, the impact of APS on daily life and prognostic information. A key provider of patient information and support is the patient organization for APS, although three out of fourteen medical specialists and 38.0% of survey respondents were unfamiliar with this organization. Some patients and medical specialists proposed that specialized nurses may assist in patient education.

A minority of focus group participants and survey respondents (16.5%) was offered psychological assistance after diagnosis, although more than half of respondents would have welcomed this support. According to interviewed medical specialists, a lack of time, not being the coordinating physician and no apparent need for psychosocial assistance were barriers to provide psychosocial support.

The last unmet need identified in APS care was the need for support in coping with limitations in daily functioning (reported by 54.4% of survey respondents) and support with occupational hurdles. Focus group participants therefore included employment status and satisfactory daily functioning as important outcomes to measure in APS care.

*Figure 1* summarizes the relevant areas for improvement as reported by medical specialists and survey respondents. Participant quotations are provided in Supplementary Table S3, available at [Rheumatology Advances in Practice online](https://mc.manuscriptcentral.com/rheumap).
Diagnosis and treatment of APS: evaluation of care

Medical record review

Clinical and laboratory criteria and diagnostic process

Medical records of 237 patients were reviewed. Demographic, clinical and laboratory characteristics are displayed in Table 3. Of all patients, 70.9% had thrombosis, 40.2% experienced obstetric complication(s), and 22.4% experienced both. In 9.3% there were no thrombotic or obstetric events but a diagnosis of APS was made because of non-criteria manifestations. The median number of recorded non-criteria manifestations was 1.0 (IQR 0.0-2.0, range 0.0-5.0). The most common non-criteria manifestations were thrombocytopenia (25.3%), pre-eclampsia/HELLP (13.4% of female patients), livedo reticularis (12.7%), migraine (11.8%) and valvular heart disease (10.1%).

Antiphospholipid (aPL) antibodies were elevated in 92.4% of patients: aCL, LAC and anti-β2GPI antibodies were detected in 75.1%, 51.9% and 48.1% respectively. In 7.6% seronegativity for all measured aPL was described. 55 patients (23.6%) were ‘triple positive’, of which 42 experienced thrombotic manifestations and 13 had obstetric APS. In 84.3% of laboratory measurements aPL status was assessed in at least two separate samples.

The median duration between the first recorded disease manifestation and receiving specialist care was zero months. The median time until diagnosis after entering specialist care was six months (IQR 2 months – 24 months). In 32.1% of patients, diagnosis of APS was established within three months.

Management after diagnosis

In 81.8% of patients, the coordinating physician could be identified from medical case records; this was most often a rheumatologist/internist-clinical immunologist (39.7%) or general internist (28.7%). In 18.2% the coordinating physician could not be identified from the medical record or patients were not under regular follow-up with any medical specialist. Gynaecologists, neurologists and haematologists were frequently involved in the diagnostic process and management (in 36.7%, 34.6% and 23.2% respectively), but were less often the coordinating physician (in 4.2%, 0.4% and 4.2%, respectively). The number of medical disciplines involved in diagnosis and management was one in 19.4%, two in 38.4%, three in 21.9% and four or more in 20.3% of patients. In 45.6%, patients were discussed in a multidisciplinary consultation meeting. A specialized nurse was involved with 14.8% of patients.
In Figure 2 pharmacological management is displayed. Most patients were treated using vitamin K-antagonists, hydroxychloroquine and/or carbasalate calcium/ascal. No anticoagulant treatment was provided in 9.3% of all patients. This was the case in five out of 42 triple positive patients, of which three had thrombotic APS (7.1%) with an indication for lifelong anticoagulation.

In 26.2% of patients a next thrombotic or obstetric event occurred after diagnosis. Complications of treatment occurred in 25.4%: bleeding and intolerance of medication were reported in 20.3% and 12.5% respectively. End-organ damage, including permanent ischemic events, neurological damage, amputation, catastrophic APS, and heart or renal failure, was described in 24.5%.

Fitness for work was often not reported in medical records (47.2%). Respectively 28.7%, 11.4% and 12.7% of all patients were demonstrably fully, partly fit or unfit for work.

Discussion

In this mixed-method study, we evaluated current health care for patients with APS in the Netherlands. Delayed diagnosis, variation in management strategies and unmet needs with regard to patient education and self-management among APS patients were observed. Recommendations for improving APS care are provided in Figure 3.

Both patients and medical specialists identify poor recognition of APS and consequently delayed diagnosis as a major obstruction to quality of care. Self-reported duration between onset of any symptoms and diagnosis exceeded five years in over one third of patients. Moreover, only one-third of patients included in medical record review were diagnosed with APS within 3 months after entering specialist care. These findings are in line with previous research describing a long diagnostic delay in APS, during which patients experience uncertainty about their health.\textsuperscript{5,6} Our study found a median delay of zero months between the first recorded disease manifestation and receiving specialist care; we hypothesize that this is because the event leading to specialist referral is often registered as the first disease manifestation. A cross-sectional Mexican study including 176 APS patients found that in patients who experienced both thrombosis and a non-criteria manifestation, non-criteria manifestations predated the first thrombotic event in 28.7%.\textsuperscript{13} Non-criteria manifestations such as thrombocytopenia, pre-eclampsia/HELLP, livedo reticularis, migraine and valvular heart disease all occurred in over 10% of patients included in our study and may still be underreported; these manifestations thus may both contribute to the diagnosis of APS and significantly influence the clinical condition of patients with APS.
Another remarkable finding was a variability in management strategies. Although recent consensus papers aim to support physicians in daily clinical decision making, low quality and uptake of recommendations posed a major challenge according to interviewed medical specialists.\(^2\)\(^-\)\(^4\) In our study, a considerable percentage of patients was not treated according to the latest insights. In 9.3% of patients no anticoagulant treatment or treatment plan in case of pregnancy were provided at the time of medical record review; in particular, 7.1% of triple positive patients with thrombotic APS, bearing the highest risk of recurrent thrombosis, did not receive any anticoagulant treatment.\(^2\)\(^-\)\(^3\) Moreover, 4.2% of patients were treated with direct oral anticoagulants, which might be associated with a higher risk of recurrent thrombosis in APS.\(^14\) In our study, reasons underlying treatment decisions were not derived from medical records. As no bleeding complications were recorded in patients that did not receive anticoagulant treatment, previous adverse events are an unlikely reason for not prescribing medication. We hypothesize that unawareness among physicians may play a role in treatment variation. Furthermore, fragmentation of care results in challenges in communication between medical specialists within and between hospitals. Fragmentation of care is a well-documented problem in other rare and systemic diseases.\(^15\)

Lastly, we identified unmet patient needs in current health care. The most reported need was patient education about the disease and self-management support with regard to daily activities, work and psychological wellbeing. This need is reaffirmed by previous studies describing the impact of the disease on daily life in APS patients, and specifically how the lack of knowledge about the disease results in uncertainty and stress.\(^7\)\(^-\)\(^8\) Previous research in other rare diseases similarly highlights patient education and provision of non-pharmacological care such as psychological support as a key need.\(^4\)\(^-\)\(^15\)\(^-\)\(^17\) Although several patients and medical specialists propose that specialized nurses might play a role in providing reliable information and self-management support, nurses were involved in only a small proportion of patients. A second important unmet need of patients was trust in physicians in general, as patients experience that some medical specialists and general practitioners are unfamiliar with APS. Patients therefore felt the need to orchestrate their own care, such as taking an active role in organizing exchange of medical documentation between medical specialists, demanding diagnostic tests and proposing management strategies. This type of patient-directed interaction has been previously described as a widely experienced communication pattern among patients with rare diseases.\(^18\) Remarkably, 10 out of 14 focus group participants have received higher education; as over one-third of
the Dutch population has limited health literacy, this level of control over disease management may not be achievable for all patients, potentially resulting in decreased quality of care.\textsuperscript{19} Initiatives were proposed to bridge knowledge gaps, such as providing a document which explains APS and that can be used in emergency situations.

Our study has some limitations. Firstly, there could be selection bias, because a large proportion of included patients completed higher education and was treated at university hospitals. Secondly, only patients who were either familiar with the patient organization and able to travel, or able use electronic communication methods, could participate in the focus groups and survey, respectively. Therefore, the results may not be generalizable to all patients with APS. Thirdly, only medical specialists known to have a special interest in thrombotic conditions were interviewed. Lastly, we had to deal with missing or limited data and potential underreporting in medical records. The strength of our study, however, is that we uniquely combined qualitative and quantitative research methods to evaluate care. To our knowledge, this is the first study of its kind in the field of APS. By integrating perspectives of patients and medical specialists and medical record data from university and general hospitals across the country, it provides a comprehensive overview of current APS care in The Netherlands.

In conclusion, main challenges in APS care in The Netherlands include delayed diagnosis, low quality and uptake of evidence-based recommendations, fragmentation of care and a burden placed on patients to orchestrate their own care. Unmet patient needs include patient education, support in daily functioning and trust in physicians. Despite high risk of recurrent thrombosis, 7.1\% of triple positive patients with thrombotic APS did not receive any anticoagulant treatment. Probable underlying factors for these challenges include the rare occurrence and heterogeneous character of APS. Future research should evaluate the clinical decision-making process in APS care and continue to address unmet patient needs. National and multidisciplinary collaboration and continuing education of physicians is required to improve APS care.
Funding: This work was supported by the Arthritis Research and Collaboration Hub (ARCH) Foundation.

Acknowledgements: We are grateful towards all patients and medical specialists who participated in our study; members of the ARCH APS working group: Titia Lely, Renate van der Molen, Rolf Urbanus, Nyika Kruyt, Marcel van de Ree, Judith Potjewijd, Gerrie Brandts and Jamy Scheerhoorn-Pullen; Carolijn de Bresser and Sander Otter for their contribution to the focus groups; Julia Berentschot and Nicole Hulsebosch for their contributions to medical record review; and Rita Schriemer for her contributions to the manuscript. The authors would like to thank the Dutch Arthritis Foundation (ReumaNederland) for funding the ARCH initiative.

Disclosure statement: The authors have declared no conflicts of interest.

References:
1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Hemost. 2006;4:295-306.
2. Limper M, de Leeuw K, Lely AT, et al. Diagnosing and treating antiphospholipid syndrome: a consensus paper. Neth J Med. 2019;77:98-108.
3. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019; Epub ahead of print. doi: 10.1136/annrheumdis-2019-215213
4. Limper M, Scirè CA, Talarico R, et al. Antiphospholipid syndrome: state of the art on clinical practice guidelines. RMD Open. 2018;0:e000785. doi: 10.1136/rmdopen-2018-000785
5. Donnan PT, McDonald MJ. Patients’ experiences of a diagnosis of Hughes’ syndrome. Clin Rheumatol. 2009;28:1091.
6. Mathew S, Cesario S, Symes L. Explaining “unexplained” perinatal loss: experiences of women with antiphospholipid syndrome. J Perinat Neonatal Nurs. 2008;22:293-301.
7. Georgopoulou S, Efraimidou S, MacLennan SJ, Ibrahim F, Cox T. Antiphospholipid (Hughes) syndrome: description of population and health-related quality of life (HRQoL) using the SF-36. Lupus 2015;24:174–179.
8. Zuily S, Rat AC, Regnault V, et al. Impairment of quality of life in patients with antiphospholipid syndrome. Lupus. 2015;24:1161–1168.
9. Castor EDC. (2019). Castor Electronic Data Capture. [online] Available at: https://castoredc.com.
10. DiCicco-Bloom B, Crabtree BF. The qualitative research interview. Med Educ. 2006;40(4):314-321.
11. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77-101.
12. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-357.
13. Hernandez-Molina G, Maldonado-Garcia C, Cabral AR. Non-criteria clinical manifestations in antiphospholipid syndrome: clinical behavior and association with damage accrual [abstract]. *Arthritis Rheumatol.* 2015;67(suppl 10).

14. Sato T, Nakamura H, Fujieda Y, et al. Factor Xa inhibitors for preventing recurrent thrombosis in patients with antiphospholipid syndrome: a longitudinal cohort study. *Lupus.* 2019; Epub ahead of print. doi: 10.1177/0961203319881200

15. Spierings J, van den Ende C, Schriemer R, et al. Optimal care for systemic sclerosis patients: recommendations from a patient-centered and multidisciplinary mixed-method study and working conference. *Clin Rheumatol.* 2019;38(4):1007-1015.

16. Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotrophic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. *Orphanet J Rare Dis.* 2014;9:83.

17. EURORDIS. The voice of 12,000 patients: Experiences and expectations of rare disease patients on diagnosis and care in Europe. Boulogne-Billancourt, France: Eurordis; 2009. 324 p.

18. Budych K, Helms TM, Schultz C. How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient–physician interaction. *Health Policy.* 2012;105(2-3):154-164.

19. Heijmans M, Brabers A, Rademakers J. Health literacy in Nederland. Utrecht, The Netherlands: Nivel; 2018. 4 p.

**Tables and figures:**

*Table 1: Demographic characteristics of interviewed specialists (n=14)*

| Specialty: n (%)         | Clinical immunologist | 3 (21.4%) |
|--------------------------|-----------------------|-----------|
| Internist-vascular medicine | 3 (21.4%)             |           |
| Rheumatologist           | 3 (21.4%)             |           |
| Neurologist              | 2 (14.2%)             |           |
| Haematologist            | 2 (14.2%)             |           |
| Gynaecologist            | 1 (1.2%)              |           |

| Age in years: median (range) (n=12) | 44 (37-58) |
|-------------------------------------|------------|

| Hospital type: n (%)                     | University hospital | 9 (64.3%) |
|-----------------------------------------|---------------------|-----------|
| General hospital                        | 5 (35.7%)           |           |

| Number of patients per year: n (%)      | <5 | 3 (21.4%) |
|-----------------------------------------|----|-----------|
| 5-10                                    | 2  | (14.2%)   |
| 10-30                                   | 3  | (21.4%)   |
| >30                                     | 6  | (42.9%)   |

| Sex: n (%)                               | Male | 10 (71.4%) |
|------------------------------------------|------|------------|
|                                         | Female | 4 (28.6%) |
### Table 2: Characteristics and experiences of focus group participants (n=14) and survey respondents (n=79)

| Demographic and clinical characteristics | Focus group participants | Survey respondents |
|----------------------------------------|--------------------------|-------------------|
| **Age: median (range)**                | 46 (27-65)               | 53 (26-77)        |
| **Sex: n (%)**                         |                          |                   |
| Female                                 | 13 (92.9%)               | 68 (86.1%)        |
| Male                                   | 1 (7.1%)                 | 11 (13.9%)        |
| **Highest completed education: n (%)** |                          |                   |
| Secondary vocational training or less  | 4 (28.6%)                | 45 (57.0%)        |
| Higher professional or university education* | 10 (71.4%)            | 34 (43.0%)        |
| **Treatment centre: n (%)**            |                          |                   |
| University hospital                    | 7 (50.0%)                | 67 (84.8%)        |
| General hospital                       | 5 (35.7%)                | 6 (7.6%)          |
| Other/do not know                      | 2 (14.3%)                | 6 (7.6%)          |
| **Duration of disease in years: median (range)** | 6.5 (0-22)             | 7 (1-27)          |
| **Duration of symptoms before diagnosis: n (%)** |                      |                   |
| >5 years                               | 3 (21.4%)                | 29 (36.7%)        |
| 3-5 years                              | 0 (0.0%)                 | 4 (5.1%)          |
| 2-3 years                              | 3 (21.4%)                | 3 (3.8%)          |
| 1 year                                 | 0 (0.0%)                 | 5 (6.3%)          |
| 6 months                               | 1 (7.1%)                 | 8 (10.1%)         |
| <6 months                              | 4 (28.6%)                | 11 (13.9%)        |
| Do not know                            | 3 (21.4%)                | 19 (24.1%)        |
| **Other rheumatological disease: n (%)** |                          |                   |
| No, primary APS                        | 7 (50.0%)                | 33 (41.7%)        |
| SLE                                    | 6 (42.8%)                | 21 (26.6%)        |
| Other/do not know                      | 1 (14.2%)                | 26 (31.6%)        |
| **Manifestations of disease: n (%)**   |                          |                   |
| Deep venous thrombosis                 | 3 (21.4%)                | 37 (46.8%)        |
| Cerebrovascular accident               | 5 (35.7%)                | 23 (29.1%)        |
| Transient ischemic attack              | 3 (21.4%)                | 18 (22.7%)        |
| Obstetric manifestation                | 3 (21.4%)                | 30 (38.0%)        |
| Thrombocytopenia                       | 1 (7.1%)                 | 11 (13.9%)        |
| Livedo reticularis                     | 5 (35.7%)                | 10 (12.7%)        |
| Endocarditis                           | 1 (7.1%)                 | 5 (6.3%)          |
| Migraine                               | 6 (42.8%)                | 12 (15.2%)        |
| Other                                  | 7 (50.0%)                | 18 (22.8%)        |
| **Experienced limitation due to APS: n (%)** |                      |                   |
| Work                                   | 6 (42.8%)                | 40 (50.6%)        |
| Travel                                 | 8 (57.1%)                | 34 (43.0%)        |
| Daily functioning                      | 6 (42.8%)                | 43 (54.4%)        |

---

*a* Higher professional or university education is defined as Dutch higher vocational training (HBO) or university level. Secondary vocational training or less is defined as Dutch secondary vocational training (MBO), secondary education (VWO, HAVO, VMBO) or primary education.

*b* Not under treatment at any medical hospital or shared care between multiple hospitals

*c* Amongst others: Sjogren’s syndrome, rheumatoid arthritis.
Table 3: Demographic, clinical and laboratory characteristics of patients included in medical record review

| Patient characteristics | University hospitals (n=192) | General hospitals (n=45) | All patients (n=237) |
|-------------------------|------------------------------|--------------------------|---------------------|
| Age (mean, SD)          | 46                           | 13                       | 47                  |
| Duration of disease in years (median, IQR) (n=235) | 6                            | 2-14                     | 3                   |
| Sex (%)                 | Male                         | 15.1                     | 31.1                |
|                        | Female                       | 84.9                     | 68.9                |
| Type APS (%)            | Primary APS                  | 61.5                     | 86.7                |
|                        | Secondary APS                | 38.5                     | 13.3                |
|                        | Of which SLE                 | 76.5                     | 80.0                |
| Treatment centre (%)    | University hospital          | 81.0                     | 19.0                |
|                        | General hospital             |                          |                     |
| Deceased (%)            | 2.1                          | 2.2                      | 2.1                 |
| Time until diagnosis    |                              |                          |                     |
| Duration under specialist treatment until diagnosis in months | All patients | 6.0 | 2.0-24.0 | 218 |
|                        | University hospital          | 7.0                      | 2.0-24.0            |
|                        | General hospital             | 4.0                      | 1.0-12.0            |
| Diagnosed with APS within 3 months after entering specialist care (%; n) | All patients | 34.9% | 218 |
|                        | University hospital          | 32.6%                    | 175                 |
|                        | General hospital             | 44.2%                    | 43                  |
| Clinical and laboratory criteria | University hospital (n=192) | General hospital (n=45) | All patients (n=237) |
| Vascular thrombosis (%) | 72.9                         | 62.2                     | 70.9                |
| Obstetric complication(s) | Number of events: median (IQR) (n=168) | 2.0 (1.0-3.0) | 1.0 (1.0-2.0) | 2.0 (1.0-3.0) |
| Obstetric complication(s) | Number of events: median (IQR) (n=100) | 1.0 (1.0-2.0) | 2.0 (1.0-3.0) | 1.0 (1.0-3.0) |
| Both thrombosis and obstetric complication(s) (%) | 25.5 | 22.4 |
| Neither thrombosis nor obstetric complication(s) (%) | 6.8 | 9.3 |
| Thrombocytopenia (%)    | 26.0                         | 22.2                     | 25.3                |
| Livedo reticularis (%)  | 14.1                         | 6.7                      | 12.7                |
| Migraine (%)            | 12.0                         | 11.1                     | 11.8                |
| Pre-eclampsia/HELLP syndrome (%; % females) | 13.0; 15.3 | 2.2; 3.2 | 11.0; 13.4 |
| Valvular heart disease (%) | 10.9                  | 6.7                      | 10.1                |
| Cutaneous ulceration (%) | 8.9                        | 2.2                      | 7.6                 |
| Insult (%)              | 7.8                          | 2.2                      | 6.8                 |
| aPL-related nephropathy (%) | 4.7                        | 4.4                      | 4.6                 |
| Chorea (%)              | 3.1                          | 0                       | 2.5                 |
| Superficial venous thrombosis (%) | 2.6 | 2.1 |
| Intra-uterine growth retardation (%; % females) | 2.6; 3.1 | 0 | 2.1; 2.6 |
| Laboratory criteria     |                              |                          |                     |
| LAC                     | Prevalence (%)               | 53.1                     | 44.4                | 51.5                |
|                        | Assessed in ≥2 samples (%) (n=122) | 78.4 | 85.0 | 79.5 |
| aCL                     | Prevalence (%)               | 79.2                     | 57.8                | 75.1                |
|                        | Assessed in ≥2 samples (%) (n=178) | 89.5 | 84.6 | 88.8 |
| Anti-β2GP               | Prevalence (%)               | 47.9                     | 48.9                | 48.1                |
|                        | Assessed in ≥2 samples (%) (n=114) | 85.8 | 72.7 | 82.5 |
| Seronegative for all 3 aPL (%) | 7.8 | 6.7 | 7.6 |
| Total number of positive criteria | Total number of elevated aPL: median (IQR) | 2.0 (2.0-2.5) | 1.0 (1.0-2.0) | 2.0 (1.0-2.0) |
|                        | Total number of positive clinical and laboratory criteria: median (IQR) | 3.0 (2.0-4.0) | 2.0 (2.0-3.0) | 3.0 (2.0-4.0) |

Abbreviations: SLE: systemic lupus erythematosus. IQR: interquartile range. HELLP: haemolysis, elevated liver enzymes and low platelets. aPL: antiphospholipid antibodies. LAC: lupus anticoagulant. aCL: anticardiolipin antibodies. β2GPI: Anti-β2-glycoprotein I antibodies.
Figure legend

Figure 1: Areas for improvement in APS care according to medical specialists and patients resulting from survey

Figure 2: Pharmacological management of patients included in medical record review

Patients who received multiple medication types for management of APS count towards all received mentioned medications. Abbreviations: VKA: vitamin-K antagonist. HCQ: hydroxychloroquine. LMWH: low-molecular-weight heparin. DOAC: direct oral anticoagulant. Pregnancy treatment plan: documentation of plan to start treatment in case of pregnancy. Other: amongst others plasmapheresis, intravenous immune globulin (IVIG).

Figure 3: Recommendations for APS care in The Netherlands
Figure 3: Recommendations for APS care in The Netherlands
### Areas for improvement in APS care according to medical specialists and patients

| Medical specialists                          | Patients                                           |
|----------------------------------------------|----------------------------------------------------|
| 1. Recognition of APS by physicians         | 1. Patient education                               |
| 2. Integrated care                           | 2. Confidence about future                        |
| 3. Information exchange and cooperation      | 3. Recognition of APS by physicians                |
| 4. Evidence-based guidelines                 | 4. Non-pharmaceutical management after diagnosis (psychosocial support, occupational health) |
| 5. Patient education                         | 5. Experienced recognition of complaints by coordinating physician |

68x25mm (300 x 300 DPI)
Figure 2: Pharmacological management of patients included in medical record review

140x124mm (300 x 300 DPI)
Recommendations for APS care in the Netherlands

1. Improve awareness among general practitioners and medical specialists
2. Increase dissemination of current guidelines to improve adherence
3. Enable cooperation between physicians through shared care and improved electronic information exchange
4. Introduce a comprehensive document on APS that patients can present in cases of emergency or in consults with new physicians unfamiliar with APS
5. Involve specialized nurses who can provide reliable information and support patients in coping with APS-related problems in daily functioning