

## CONFLICT OF INTEREST

K. Davis, L. Zografos, D. McSorley, and E. Andrews are full-time employees of RTI Health Solutions, which received funding from Bayer Pharma AG to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI conducts work for government, public, and private organisations, including pharmaceutical companies. A. Asiimwe is a full-time employee of Bayer Pharma AG.

## BACKGROUND

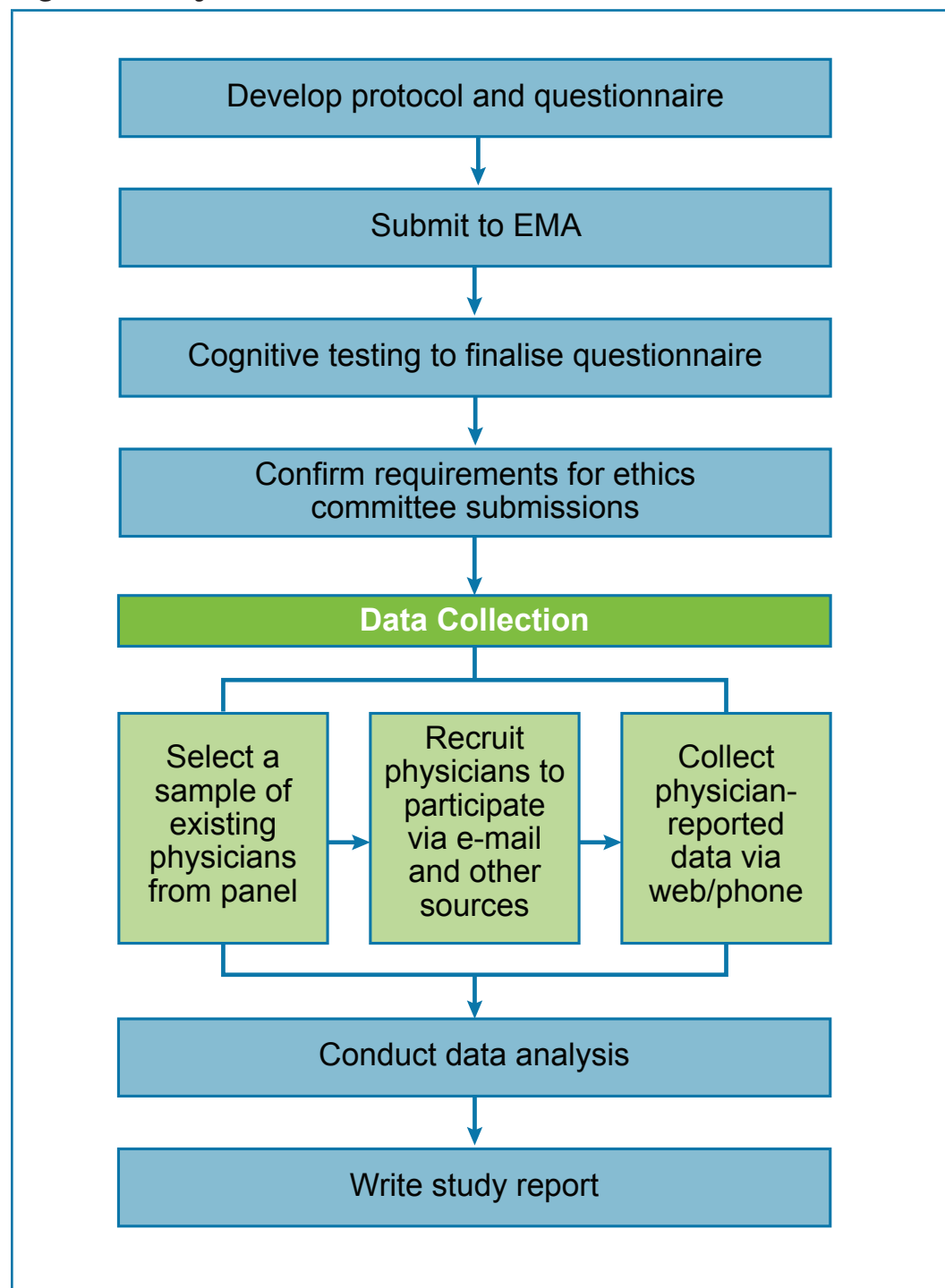
- One of the most important factors in prescribing an oestrogen/progestogen treatment is physician knowledge of the risks associated with the potential development of thromboembolism and appropriate communication to patients.
- Diane-35 (cyproterone acetate 2 mg/ethinylestradiol 35 µg) and its generics (CPA/EE) are indicated for the treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age.
- At the request of the European Medicines Agency (EMA), a patient information card and a prescriber checklist were developed and distributed to physicians to increase awareness and understanding about risks associated with CPA/EE.<sup>1</sup>
- The current study was conducted to address the EMA's request to evaluate the receipt and understanding of these materials.

## OBJECTIVES

- The objectives of this study were to assess whether physicians received the educational materials and measure physician knowledge and understanding of the key safety information.
- Specifically, the study investigated physicians' knowledge of contraindications for prescribing CPA/EE, risk factors of thromboembolism, and signs and symptoms of thromboembolism.

## METHODS

Figure 1. Project Overview



## Study Design

- The study was an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour amongst a sample of physicians with recent experience with CPA/EE in Austria, the Czech Republic, France, the Netherlands, and Spain.
- Based on CPA/EE prescribing patterns in each country, the following physician specialties were recruited, and the study specifically targeted inclusion of up to 25% dermatologists in each country:
  - Austria and the Czech Republic: gynaecologists and dermatologists
  - The Netherlands: general practitioners (GPs) and dermatologists
  - France and Spain: GPs, gynaecologists, and dermatologists
- In France, Spain, and the Netherlands, a random sample of potentially eligible physicians in each speciality of interest was recruited by e-mail from an online physician panel.
- In Austria and the Czech Republic, all physicians in each speciality of interest on the panels were invited to participate, and additional physicians were recruited via telephone from a proprietary database and publicly available sources.
- The study aimed to recruit 60 to 120 physicians each in Austria, the Czech Republic, and the Netherlands, and 100 to 200 physicians each in France and Spain.
- To participate, physicians must have been a licensed and practising dermatologist, gynaecologist, or GP and prescribed CPA/EE to at least one patient in the past 6 months.

## Survey Design and Administration

- The 24-item questionnaire was developed using best practices for instrument development and was tested through in-person cognitive interviews with physicians in each country.
- The questionnaire contained screener questions to confirm eligibility; an informed consent question; closed-ended, multiple-choice questions to measure study objectives; questions to characterise the physicians and their practices; and questions to investigate physician receipt and use of any educational materials related to CPA/EE.
- All physicians were given the option to complete the survey via the web, and physicians in Austria and the Czech Republic had the added option of completing it by telephone.
- Physicians were not able to go back and change answers to previous questions. This restriction minimised the likelihood of the respondent searching for answers via the Internet or other sources.
- The physician survey was initiated in each country after a period sufficient to allow prescribers to have received the prescriber educational materials and use the information in their practice.
- Data collection ran from 26 June 2015 to 21 February 2016.

## REFERENCE

- European Medicines Agency (EMA). Assessment report cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing medicinal products. 24 May 2013. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referalls\\_document/cyproterone\\_ethinylestradiol\\_107/Recommendation\\_provided\\_by\\_Pharmacovigilance\\_Risk\\_Assessment\\_Committee/WC500144130.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referalls_document/cyproterone_ethinylestradiol_107/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144130.pdf). Accessed 4 May 2016.

## ACKNOWLEDGEMENTS

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## RESULTS

### Demographics and Clinical Practice Characteristics

- A total of 11,102 physicians were invited to participate in the survey. The survey was completed by 759 physicians, and all physicians opted to complete the survey via the web (Table 1). The response rate was 7% (759/11,102).
- The study participants consisted of more males (62.6%) than females (37.4%), and most participants (98.0%) were aged 30 to 69 years.

Table 1. Summary of Physician Specialty by Country

Specialty	Country, n (%)					
	Czech Republic (n = 120)	Netherlands (n = 121)	Spain (n = 200)	Austria (n = 118)	France (n = 200)	Overall (N = 759)
General medicine or family practice	0	71 (58.7)	117 (58.5)	0	131 (65.5)	319 (42.0)
Dermatology	6 (5.0)	50 (41.3)	34 (17.0)	31 (26.3)	34 (17.0)	155 (20.4)
Obstetrics and gynaecology	114 (95.0)	0	49 (24.5)	87 (73.7)	31 (15.5)	281 (37.0)
Internal medicine	0	0	0	0	4 (2.0)	4 (0.5)

### Knowledge Questions

- Across countries, knowledge was highest (≥ 80% of physicians reported correct responses) on the following information:
  - Selecting individual symptoms of a possible deep vein thrombosis
  - Selecting individual symptoms of a possible pulmonary embolism
  - Selecting individual symptoms of a possible cerebrovascular accident
  - Identifying the most important risk factors for thrombosis from a list
  - Identifying that women who are older than 35 years of age should strongly be advised to stop smoking or use a nonhormonal treatment for her acne and/or hirsutism
  - Understanding that CPA/EE should not be used for contraception alone
- For the overall sample, knowledge varied on the following sub-items and for the questions presented in Figure 2 through Figure 6.
  - Physicians' knowledge of the time period during the first year of use in which the risk of thrombosis is highest was 89.3% overall and consistent across countries. Physicians' knowledge of the time period when restarting use after a break of 1 month or more was 65.2% and varied across countries.
  - Physicians' knowledge of situations when a patient may show symptoms of a thrombosis was high overall (95.5%-98.9%) for three of the four situations (i.e., just after having an operation, been off feet for a long time, during or after a long journey) and consistently high across countries. Knowledge was 75.5% for one of the situations (i.e., when initiating treatment with CPA/EE within a few weeks after having a baby), and responses varied across countries.

- 73.8% reported practising in a general setting, 37.5% reported practising at a hospital-based clinic, and 2.4% reported practising in another type of setting.

- Physicians' experience was categorised into 5-year increments up to 25 years of practice. 35.2% had been in practice more than 25 years, with durations fairly evenly distributed across the increments less than 25 years.

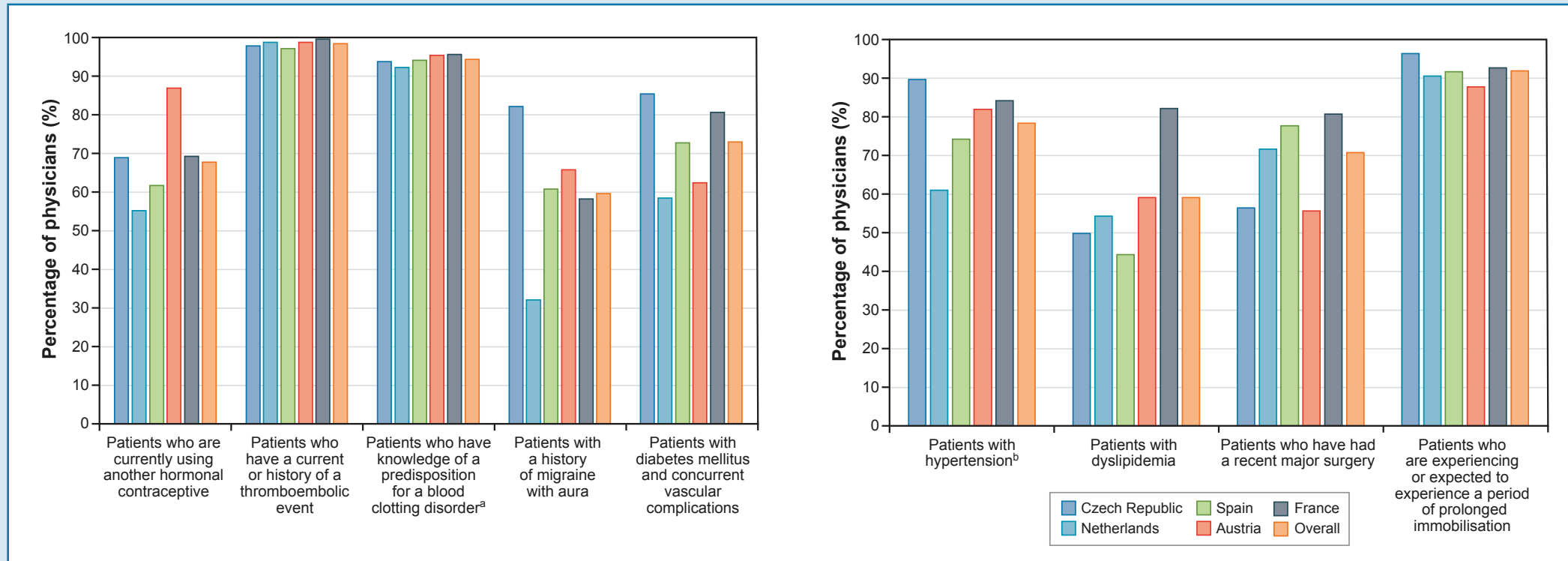
### Knowledge of Indications

- Correct knowledge that CPA/EE is indicated for moderate to severe acne related to androgen sensitivity (with or without seborrhoea) was reported by 92.0%.
- Correct knowledge that CPA/EE should not be used for contraception alone in women of reproductive age was reported by 81.4%.
- Correct knowledge that CPA/EE is contraindicated in patients who are currently using another hormonal contraceptive was reported by 68.0%.
- A smaller percentage of physicians (69.2%) were aware that CPA/EE was indicated for hirsutism.
- Approximately one-third of physicians (34.0%) were aware that androgenic alopecia was no longer an indication.
- Approximately half of physicians (47.7%) were aware that CPA/EE should be prescribed for acne only after topical therapy or systemic antibiotics have failed.

### Receipt of Educational Materials

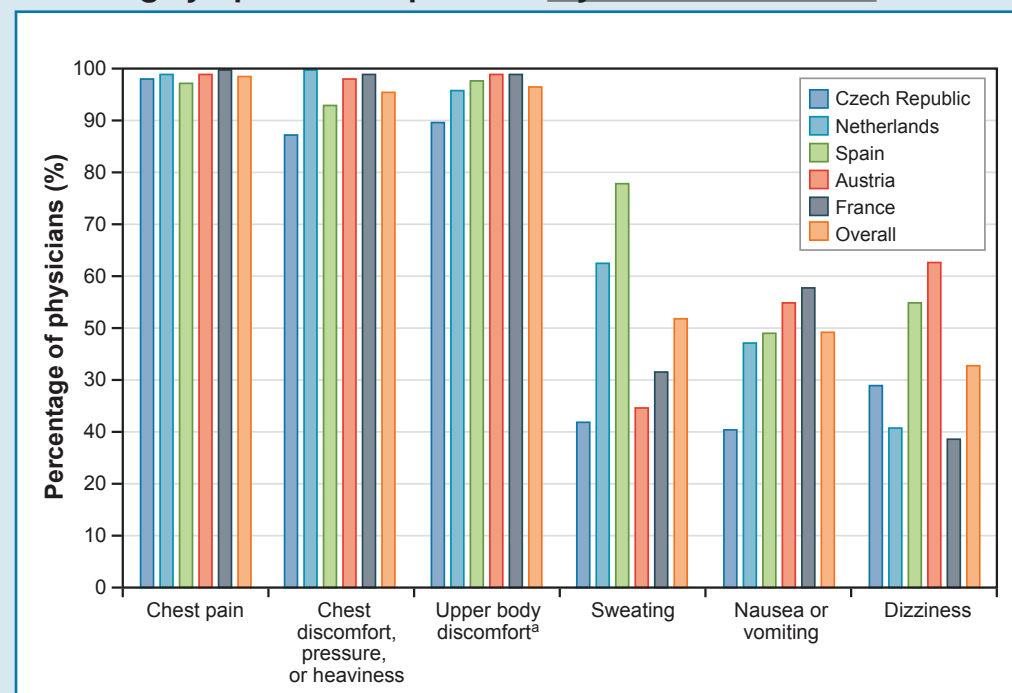
- The percentage of physicians who reported receiving at least one of the three educational materials was 51.0%.
  - 45.5% reported receiving the dear health care provider letter
  - 16.2% reported receiving the patient card
  - 16.9% reported receiving the prescriber checklist
- Most of the physicians (81.0%) who received at least one of the CPA/EE materials found it helpful or extremely helpful.

Figure 2. Correct Responses to Question: Diane-35 and its generics are contraindicated in which of the following patient populations?



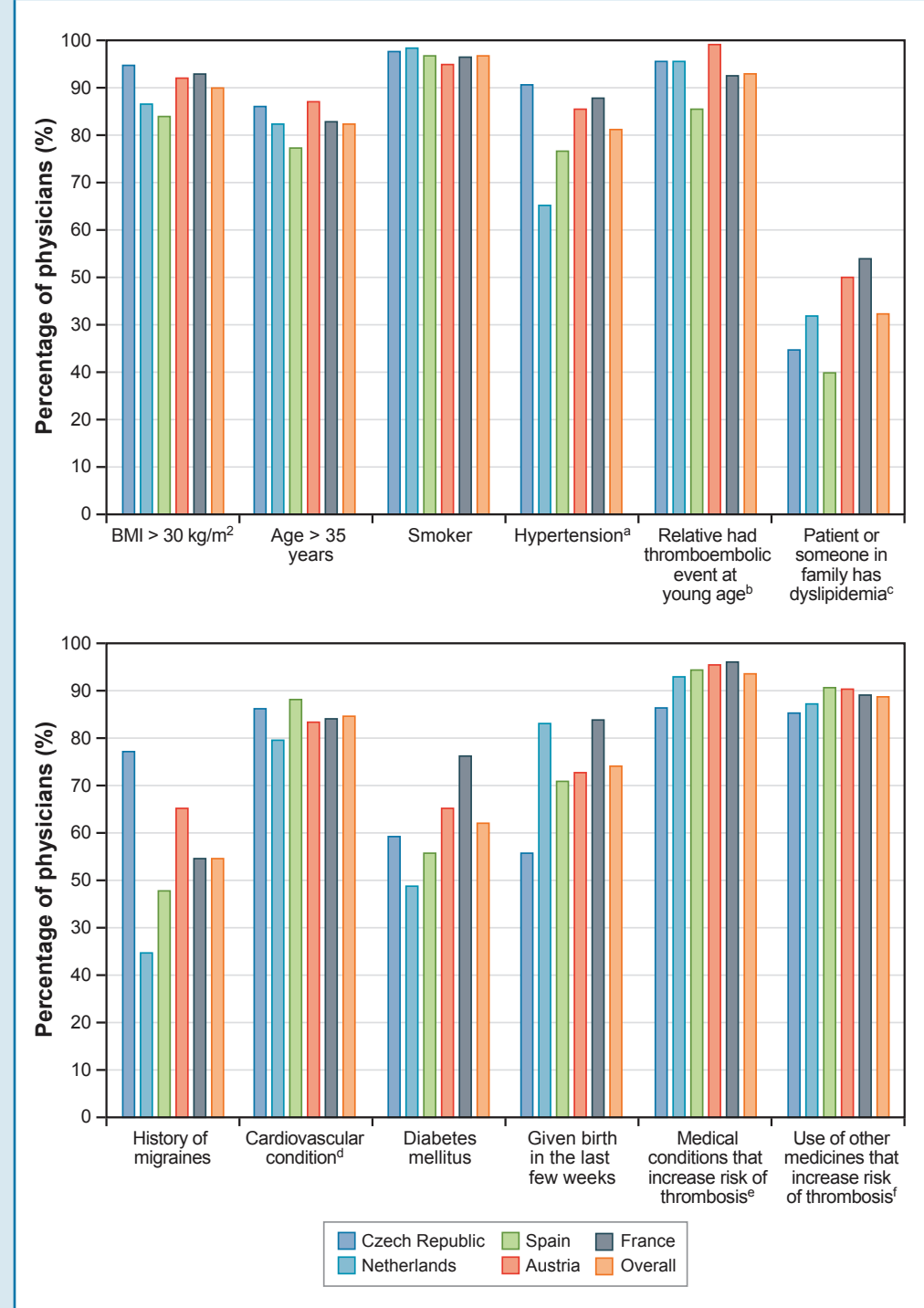
<sup>a</sup>Blood clotting disorders included deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident, transient ischemic attack, and angina pectoris.  
<sup>b</sup>Hypertension is defined as systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg.

Figure 3. Correct Responses to Question: A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible myocardial infarction?



<sup>a</sup>Upper body discomfort described as radiating to the back, jaw, throat, and arm together with a feeling of fullness associated with indigestion or choking.

Figure 4. Correct Responses to Question: Which of the following risk factors for the development of thrombosis should be considered prior to prescribing Diane-35 and its generics?



BMI = body mass index.  
<sup>a</sup>Hypertension defined as systolic blood pressure of 140-159 mm Hg or diastolic blood pressure of 90-99 mm Hg.  
<sup>b</sup>Answer choice was worded as "The patient has a close relative (e.g., parent or sibling) who has had a thromboembolic event at a young age (e.g., before 50)."  
<sup>c</sup>Family was described as "immediate family."  
<sup>d</sup>Cardiovascular conditions included atrial fibrillation, arrhythmia, coronary heart disease, and cardiac valve disease.  
<sup>e</sup>Medical conditions included cancer, systemic lupus erythematosus, sickle cell disease, Crohn's disease, ulcerative colitis, and haemolytic uraemic syndrome.  
<sup>f</sup>Medicines included corticosteroids, neuroleptics, antipsychotics, antidepressants, and chemotherapy.

Figure 5. Correct Responses to Question: What instructions should patients taking Diane-35 or its generics receive regarding the potential need for a major surgery, or occurrence of an injury or condition that may also require a period of prolonged immobilisation?

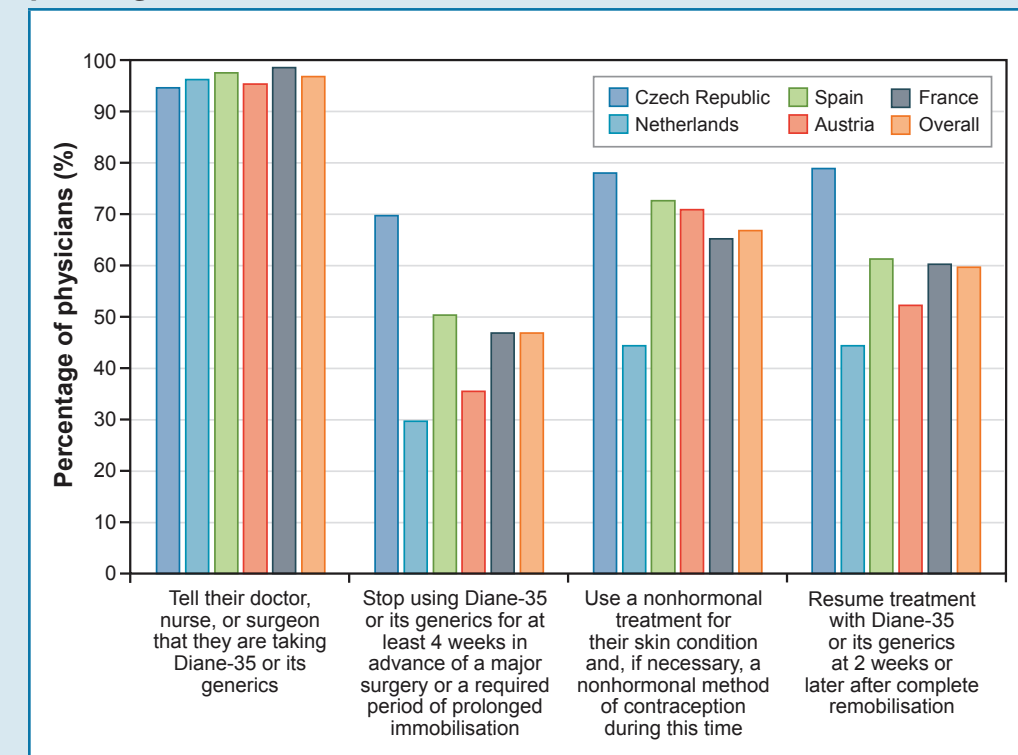
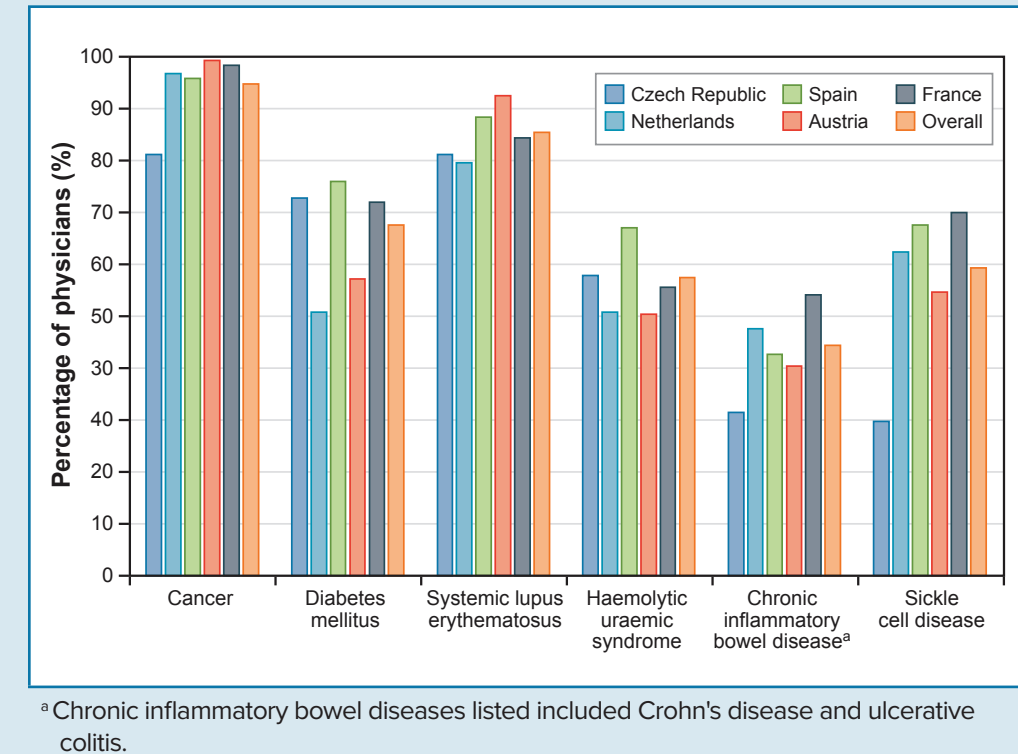


Figure 6. Correct Responses to Question: Which medical conditions can increase the risk of thrombosis?



<sup>a</sup>Chronic inflammatory bowel diseases listed included Crohn's disease and ulcerative colitis.

## DISCUSSION AND CONCLUSIONS

- In general, knowledge of thromboembolism risk and most important topics was high.
- Knowledge varied for topics that were more complex or less frequently encountered, for which physicians might consult additional references.
- For most questions in the survey, knowledge did not vary by physician speciality, receipt of educational materials, number of patients prescribed CPA/EE in the last 3 months, or number of years practising medicine.
- Although almost half of the physicians did not report receiving the educational materials, the high level of knowledge amongst treating physicians suggests that the key safety information is available to the treating physician through other sources (e.g., product label, social media, seminars, or symposia).

## CONTACT INFORMATION

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