



EUROPEAN MEDICINES AGENCY
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PASS information

Title	Prescription patterns of combined hormonal contraceptives with 3 rd or 4 th versus 2 nd generation progestogens in France, Germany and the UK during 2002- 2011: A retrospective analysis of the IMS Disease Analyser databases
Protocol version identifier	1.0
Date of last version of protocol	15 February 2013
EU PAS register number	ENCEPP/SDPP/3712
Active substance	Combined hormonal contraceptives containing any of the following progestogens: desogestrel, gestodene, norgestimate, etonogestrel, drospirenone, dienogest, chlormadinone, nomegestrol, levonorgestrel, norethisterone, norgestrel, norelgestromin
Medicinal product(s)	Multiple
Procedure number	EMA/H/A-31/1356
Marketing authorisation holder(s)	Multiple
Joint PASS	No
Research question and objectives	To describe the changes over time in prescription of 3 rd or 4 th versus 2 nd generation progestogen-combined contraceptives in three large EU countries in the period 2002-2011
Country(-ies) of study	France, Germany, the UK
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2. List of abbreviations

EMA: European Medicines Agency

EU: European Union

GP: General Practitioner (Family Doctor)

PRAC: Pharmacovigilance Risk Assessment Committee

UK: United Kingdom

VTE: Venous Thromboembolism

3. Responsible parties

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4. Abstract

Title: Prescription patterns of combined hormonal contraceptives with 3rd or 4th versus 2nd generation progestogens in France, Germany and the UK during 2002- 2011: A retrospective analysis of the IMS Disease Analyser databases.

Rationale and background: The PRAC is currently reviewing under Article 31 of Directive 2001/83/EC the risk of venous and arterial thromboembolic events and risk minimisation in users of all formulations of 3rd or 4th generation combined hormonal contraceptives. In the context of such a review, a comparative description of prescribing patterns of these medicinal products versus 2nd generation combined hormonal contraceptives in three large EU countries over a 10 year period can further inform on drug utilisation and thereby support regulatory decision-making from a public health perspective.

Objectives: To describe the prescription of 3rd or 4th versus 2nd generation progestogen-containing combined hormonal contraceptives in France, Germany and the UK in the period 2002-2011.

Study design: Retrospective database analysis.

Population: The study includes women 15 - 49 years old who are recipients of at least one prescription of combined hormonal contraceptives containing 2nd, 3rd or 4th generation progestogens as recorded during the study period in the IMS Disease Analyser data of France, Germany and the UK.

Study period: From 1st January 2002 to 31st December 2011.

Variables: The selection of prescriptions for combined hormonal contraceptives is based on the following progestogens:

- **2nd generation** - Levonorgestrel, Norethisterone, Norgestrel

- **3rd or 4th generation** – Desogestrel, Gestodene, Norgestimate, Etonogestrel, Drospirenone, Dienogest, Chlormadinone, Nomegestrol, Norelgestromin

The age of recipient at the time of prescription is computed from the year of birth.

Data sources: Patient medical records maintained in the electronic databases of IMS Disease Analyser of France, Germany and the UK. The French and UK databases include anonymised patient-level data collected through a representative sample of GPs in each country. In Germany data are collected through a representative sample of GPs and non-hospital based specialist physicians, including gynaecologists and internists.

Study size: The study included all women with relevant prescriptions in the chosen databases.

Data analysis: In each study country the number and proportion of women being prescribed 3rd or 4th versus 2nd generation combined hormonal contraceptives are computed and stratified by age, time in calendar years, and by 'new user' versus 'switcher'.

Results: Throughout 2002-2011 prescribing of 3rd or 4th versus 2nd generation contraceptives was to between 30% and 40% of women in France and the UK, while it was between 50% and 70% of women in Germany. The ratio of 3rd or 4th versus 2nd generation contraceptives varies more with age in Germany and the UK than in France and across all countries an increased prescribing of 3rd or 4th generation contraceptives is observed over time.

Conclusions: This study shows lower usage of 3rd and 4th versus 2nd generation combined hormonal contraceptives in France and the UK throughout a 10 years period and in all age groups. Nonetheless the high level of prescribing in Germany, and a consistent pattern of increasing usage across all study countries in more recent years is relevant to the assessment of risk and risk minimisation of these products.

5. Rationale and background

Following notification from France to initiate an Article 31 referral to the European Medicines Agency (EMA) on combined hormonal contraceptives and the risk of venous thromboembolism (VTE) the Pharmacovigilance Risk Assessment Committee (PRAC) at EMA has started a review of combined hormonal contraceptives authorised in the EU containing the following 3rd and 4th generation progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Combined_hormonal_contraceptives/Procedure_started/WC500138611.pdf).

In the context of the referral procedure the Pharmacovigilance and Risk Management Sector of the EMA in liaison with the PRAC Rapporteurs for the Article 31 procedure planned to conduct an analysis of prescription patterns of combined hormonal contraceptives in three large European countries, namely France, Germany and the UK, and to compare patterns of prescriptions of 3rd or 4th with 2nd generation combined contraceptives over a 10 year period from 2002 to 2011. In 2001 a major safety review of combined hormonal contraceptives was conducted with changes to the product information as a result. The selected observation period allows a description of prescription patterns after this regulatory intervention, and up to the most recently available data in the three databases.

By reason of the large populations in the three study countries, which approximate to 40% of the total EU population, these population-based data may contribute to the assessment of the public health impact of any safety concern in relation to the use of combined hormonal contraceptives in the EU.

6. Study objectives

The objective of this analysis is to describe the pattern of prescriptions of 3rd or 4th versus 2nd generation progestogen-combined contraceptives in France, Germany and the UK in the period from 1st January 2002 to 31 December 2011.

7. Research methods

7.1. Study design

Retrospective database analysis.

7.2. Study Population

The study includes women recipients of prescriptions of all formulations of 2nd, 3rd or 4th generation progestogen- combined hormonal contraceptives recorded in the IMS Disease Analyser of France, Germany and the UK from 1st January 2002 to 31st December 2011. Since exploratory counts indicated that in Germany contraceptives are mostly prescribed by Gynaecologists and Internists, only women from these practices in the German database are included in the study population.

For consistency with the target population of the Article 31 referral and in order to exclude use of combined hormonal products for the purpose of hormonal replacement therapy in older women, only women 15-49 years old have been included in the study population. However, the results of a stratification of users of 3rd or 4th generation versus 2nd generation contraceptives by 5 year age groups which includes women recipients of all ages of any of the study products is also shown for completeness of information on the overall use of the study products.

7.3. Setting and data sources

The IMS Disease Analyser databases of France, Germany and the UK include anonymised patient medical records collected through a representative panel of GPs in France and the UK and in Germany data are collected through a representative panel of specialist physicians working outside hospitals, including gynaecologists and internists (www.imshealth.com).

The GPs contributing to the French IMS Disease Analyser are representative of the GPs universe in the country with respect to gender, age, Doctor SNIR (National official indicator of GP' volume of activity in terms of visits and consultations) and geographical region. The age distribution of the patient population in the database is comparable to that of the French National Statistics. The database currently encompasses approximately 4.5 million patient's medical records. Registration of patients with a GP is not a requirement of the universal national healthcare system in France. However, GPs are increasingly regarded as the primary point of contact for patients and their records can provide substantial information on the patient's medical history managed at primary care level. The French healthcare service provides contraceptive counselling and prescribing through GPs or gynaecologists. Therefore the French IMS Disease Analyser database can be considered as a suitable source of data for the purpose of this study.

The German IMS Disease Analyser includes data collected through a panel of over 3000 doctors of different specialties. The subset of the German IMS Disease Analyser database included in this study (panel of gynaecologists and internists) encompasses a total of approximately 8 million patient's medical records. Since the German healthcare insurance system allows patients to visit a specialist of choice whenever a medical need emerges, information gaps in the patient's medical records

maintained by the contributing physicians are to be expected in the IMS Disease Analyser database. In Germany contraceptives are mostly prescribed by gynaecologists; however, internists, who can be equated to GPs in other countries, may also be expected to prescribe contraceptives. Both specialties are represented in the German database.

Approximately 5 million patient medical records are available in the IMS Disease Analyser in the UK. The role of gatekeeper that the GP plays in the national healthcare system in the UK, including registration of each UK resident person with one GP, makes the UK database a reliable resource for population-based longitudinal analyses. The patient's file maintained by the GPs in the UK includes also medical information from services provided outside of the GP clinic, such as referral to specialists or hospital discharge information. Since in the UK the GP represents the primary point of contact for any healthcare service, including contraception, the IMS Disease Analyser is an adequate data source for this study.

A comprehensive bibliography of the studies conducted with IMS Disease Analyser databases, including validation studies in selected therapeutic areas is available at:

http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Researchers/IMS_bibliography.pdf

7.4. Variables

In each study country, women recipients of prescriptions for combined hormonal contraceptives of 3rd or 4th and of 2nd generation progestogens are used as the analysis unit. Prescription selection is based on the following progestogen:

- **2nd generation** - Levonorgestrel, Norethisterone, Norgestrel
- **3rd or 4th generation** – Desogestrel, Gestodene, Norgestimate, Etonogestrel, Drospirenone, Dienogest, Chlormadinone, Nomegestrol, Norelgestromin

The full listing of substance combinations in each country is provided in Annex I.

In the absence of patient registration records in the French and German databases, the total number of women in the database for each country is estimated as the number of women with at least one prescription record for any medicinal product in the study period. For consistency, the same approach is used to identify the female population in the UK database.

Patient age at prescription is computed as the difference between year of prescription and year of birth.

For a combined hormonal contraceptive 'generation' (i.e. 3rd or 4th generation and 2nd generation) 'new use' is defined when both of the following conditions are fulfilled:

1. no previous prescription of the same 'generation' in the 365 days before the prescription date;
2. at least one prescription for any other medicinal product any time before the 365 days which precede the prescription date so that we know the patient was actively under observation.

Based on this definition, a new user can in reality be a repeat user with a prescription gap in the record e.g. because of pregnancy or because an interim prescription has been obtained from a different prescriber.

Switching from one combined hormonal contraceptive 'generation' (i.e. 3rd or 4th generation and 2nd generation) to the other is defined by a prescription of the other 'generation' in the 365 days after the prescription date.

7.5. Study size

This study is a descriptive analysis of available IMS data from the UK, France and Germany. No sample size or statistical precision calculation was performed.

7.6. Data management

Data extraction and management is performed in IMS Disease Analyser.

7.7. Data analysis

The analyses conducted are descriptive in nature. In each country the following was computed:

- Proportion of women (all ages) receiving prescriptions for 3rd or 4th versus 2nd generation combined hormonal contraceptives stratified by 5 year age groups;
- Proportion of women (15–49 years old) receiving prescriptions for 3rd or 4th versus 2nd generation combined hormonal contraceptives throughout the observation period and by calendar year 2002 through 2011.

7.8. Strengths and limitations of the research methods

- The IMS Disease Analyser maintains data collected through a panel of physicians in each of the study countries.
- Prescription records are meticulously recorded in IMS Disease Analyser, which strengthen the analyses at prescription level. However, prescriptions of contraceptives in hospital or clinics settings other than GP clinics in France and the UK or settings other than those represented in the German data are missing.

8. Protection of human subjects

This analysis is based on the secondary use of anonymised patient level data collected for the purpose of managing patients in routine clinical practice. Relevant ethical clearance is in place at source in order to allow the use of these data for research purposes.

Such a setting is not considered to pose any harm to human subjects.

9. Plans for disseminating and communicating study results

The study results are to be submitted for consideration of the PRAC Rapporteur and the PRAC within the timeframe of the referral procedure and PRAC review and will be publically available in the EU PAS Register.

10. Study results

This study describes the prescription patterns of combined hormonal contraceptives of 3rd or 4th versus 2nd generation progestogens in France, Germany and the UK during 2002-2011. The time distribution of prescriptions in the IMS Disease Analyser databases shown in **Figure 1** confirms the feasibility of the planned analyses throughout the study period in that all databases are active in collecting a growing number of prescription records.

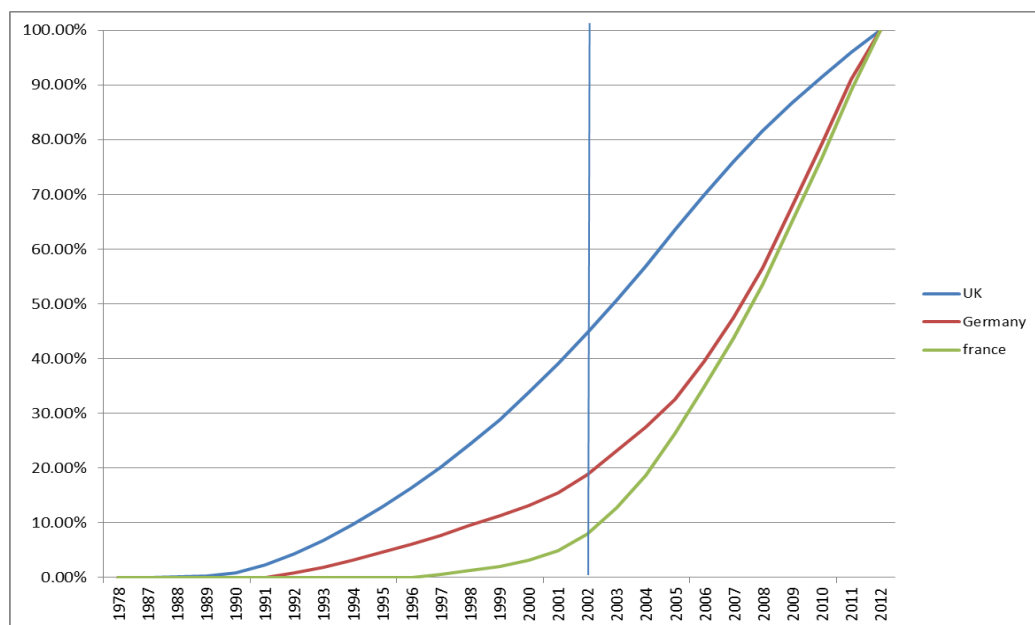


Figure 1. Cumulative time distribution of prescriptions for any medicinal product (i.e. not only combined hormonal contraceptives) in a random sample of 10,000 patients in each of the three study countries

Overall the source population in the 3 databases includes more than 6 million women (i.e. women with at least one prescription of any medicinal product). The distribution of the study population and prescriptions by 'generation' of combined hormonal contraceptives in each country is provided in **Table 1**.

Table 1. Study population and prescription records of combined contraceptives of 3rd or 4th and 2nd generation in France, Germany and the UK in 2002-2011

	France	Germany	THE UK
Number of women with at least one prescription for any medicinal product (i.e. source population)	1,776,967	3,888,932	913,402
Number of women with at least one prescription of any study product	170,195	637,723	332,685
Number of women aged 15-49 at time of prescription	163,055	573,974	299,472
– Number of women with at least one prescription of 3 rd or 4 th generation	64,174	407,590	118,958
– Number of women with at least one prescription of 2 nd generation	110,741	216,292	222,966
– Number of prescriptions of 3 rd or 4 th generation per woman	2.66	5.03	5.09
– Number of prescriptions of 2 nd generation per woman	3.41	4.71	6.35

The feasibility of assessing recording of known risk factors for VTE was explored in each database. However, relevant clinical data were available only for a very small number of women, which could not

allow conclusive evidence on the distribution of VTE risk factors in users of 3rd or 4th compared with 2nd generation combined hormonal contraceptives.

10.1 Study results in IMS Disease Analyser in France

The French IMS Disease Analyser database includes a total of 1,776,967 women, of which 163,055 (9.2%) are women 15-49 years old with at least one prescription for any of the study products.

As depicted in **Figure 2A** the women receiving 3rd or 4th generation combined contraceptives account for almost 35% of women receiving any 2nd, 3rd or 4th generation combined hormonal contraceptive across all age groups. In the age group 50+ only 20% of women are prescribed 3rd or 4th generation combined contraceptive prescriptions, with the large majority receiving 2nd generation combined contraceptives.

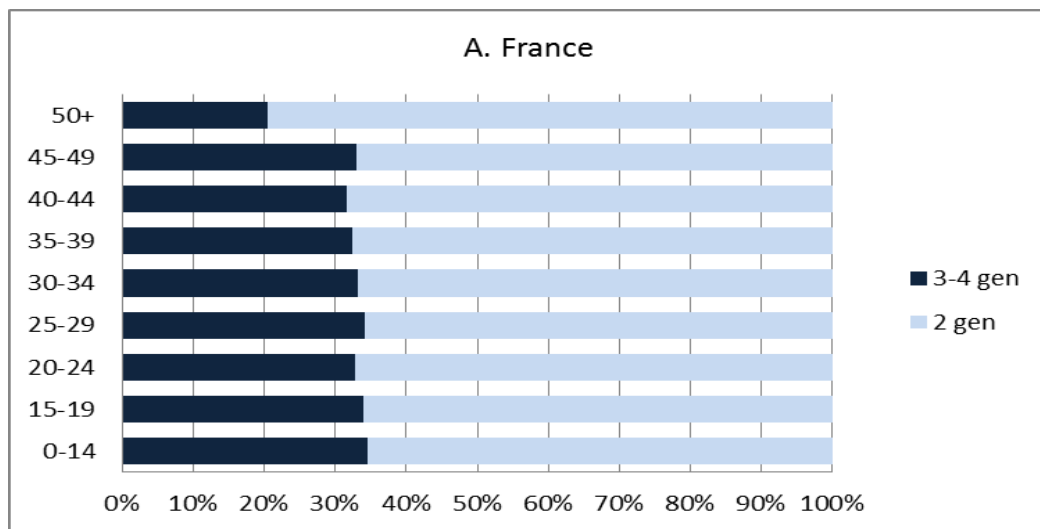


Figure 2A. Proportion of women receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives throughout 2002-2011 by 5-year age groups in France

Figure 3A depicts the proportion of the study population receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives by calendar year across the study period. Approximately 30% of women receive 3rd or 4th generation combined contraceptives in the years 2002-2007, with a small increase in more recent years up to approximately 40% in 2011.

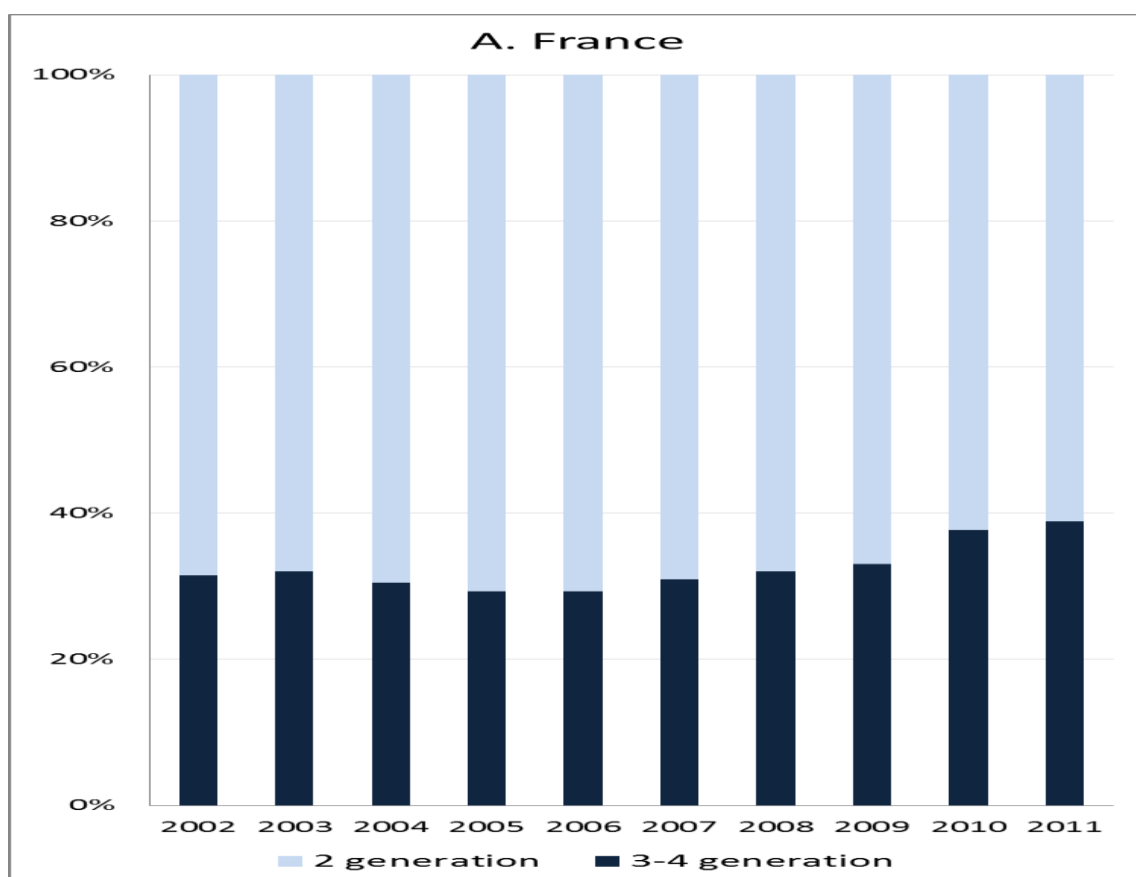


Figure 3A. Proportion of women receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives in each calendar year through 2002-2011 in France

New users account for 25% and 30% of all women receiving 3rd or 4th and 2nd generation combined contraceptives, respectively. Switching between 'generation' classes of combined hormonal contraceptives affects only a small proportion of users (**Table 2A**).

Table 2A. Number and percentage of users of 3rd or 4th versus 2nd generation combined contraceptives in France, grouped by new use or switching

France	
New use of 2 nd generation	33,427 (30%)
New use of 3 rd or 4 th generation	16,055 (25%)
Switching from 2 nd to 3 rd or 4 th	4,897 (5%)
Switching from 3 rd or 4 th to 2 nd	3,787 (6%)

Overall the prescription patterns of combined hormonal contraceptives in France shows a predominant use of 2nd generation products across age groups and throughout the study period with a small decrease in more recent years.

10.2 Study results in IMS Disease Analyser in Germany

The German IMS Disease Analyser database includes a total of 3,888,932 female patients treated by a panel of gynaecologists and internists. Of those, 573,974 (14.8%) are women 15-49 years old with at least one prescription for any of the study products.

Figure 2B shows that women receiving 3rd or 4th generation combined contraceptives accounts for over 60% of users in all age groups up to the age of 39. Such a proportion decreases gradually in older women to less than 30% in women 50+.

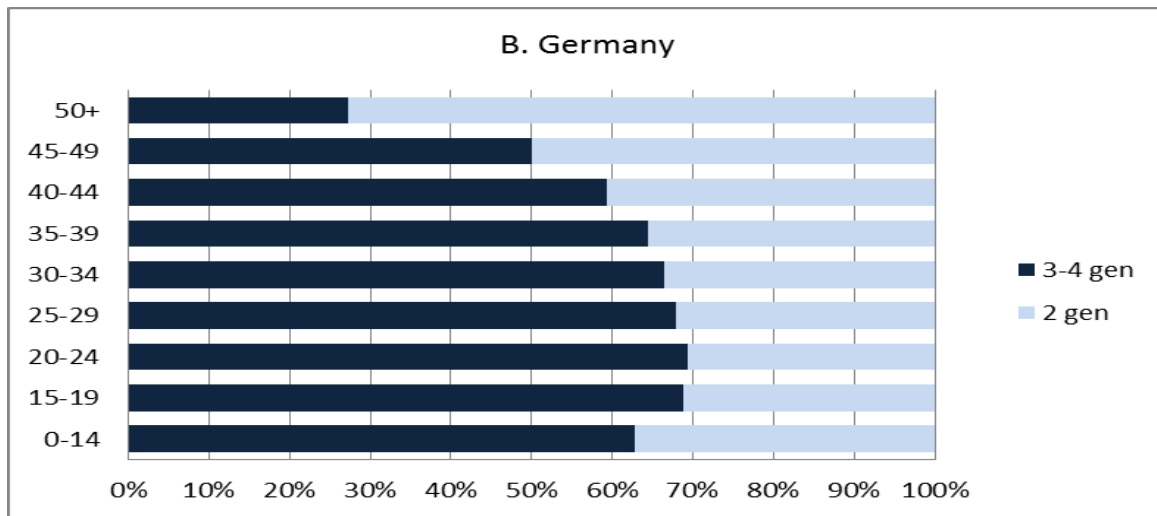


Figure 2B. Proportion of women receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives throughout 2002-2011 by 5-year age groups in Germany

As described in **Figure 3B**, the proportion of women 15-49 years of age receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives increases throughout the study period, with approximately 50% in 2002 and 70% plateau in 2008-2011.

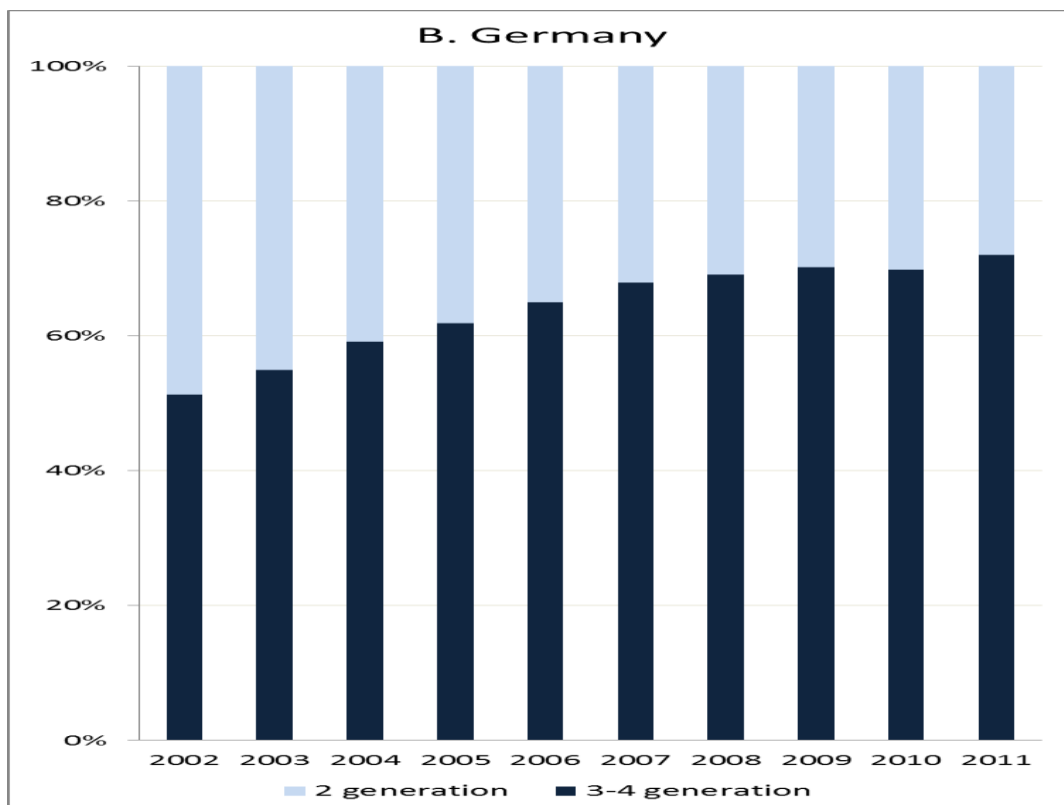


Figure 3B. Proportion of women receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives in each calendar year through 2002-2011 in Germany

Switching from 2nd to 3rd or 4th generation combined contraceptives represent 13% of users, while switching from 3rd or 4th to 2nd generation contraceptives only involves 5% of users (**see Table 2B**).

Table 2B. Number and percentage of users of 3rd or 4th versus 2nd generation combined contraceptives in Germany grouped by new use or switching

Germany	
New use of 2 nd generation	40,733 (19%)
New use of 3 rd or 4 th generation	87,684 (22%)
Switching from 2 nd to 3 rd or 4 th	28,632 (13%)
Switching from 3 rd or 4 th to 2 nd	19,373 (5%)

Overall the prescription patterns of combined hormonal contraceptives in Germany shows an increasing predominance of 3rd or 4th compared with 2nd generation combined contraceptives through the study period. Higher use is particularly evident in younger women.

10.3 Study results in IMS Disease Analyser in the UK

The UK IMS Disease Analyser database includes a total of 913,402 women, of which 299,472 (32.8%) are women 15-49 years old with at least one prescription for any of the study products.

Figure 2C shows lower prescribing of 3rd or 4th compared with 2nd generation combined contraceptives across all age groups. However, users of 3rd or 4th generation combined contraceptives account for approximately 40% in women aged 25-34, and account for smaller proportions in younger or older age groups.

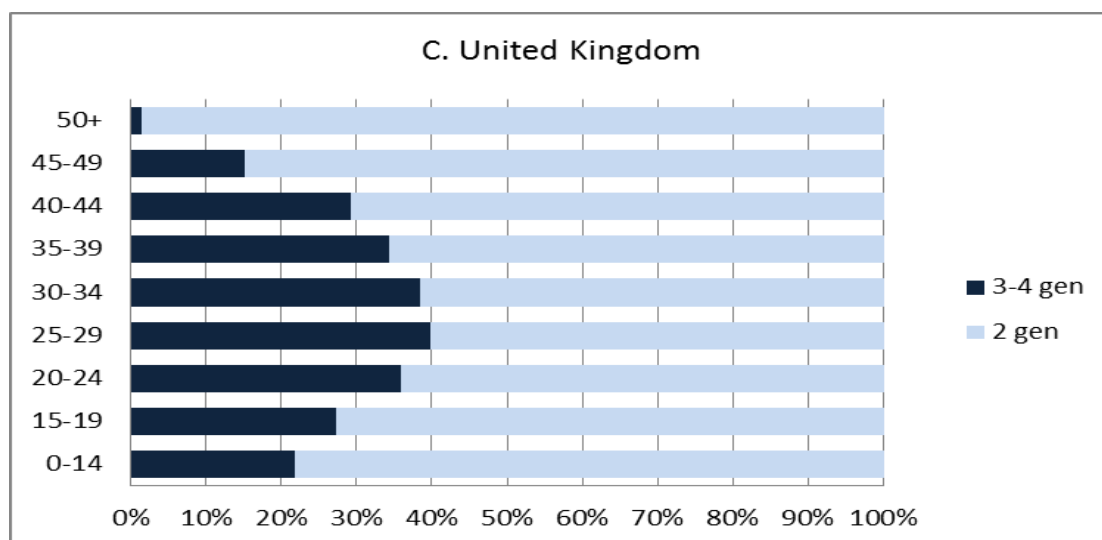


Figure 2C. Proportion of women receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives throughout 2002-2011 by 5-year age groups in the UK

Among recipients of 3rd or 4th and of 2nd generation combined contraceptives the new users account for 31% and 21% respectively (**Table 2C**).

Table 2C. Number and percentage of users of 3rd or 4th versus 2nd generation combined contraceptives in the UK grouped by new use or switching

UK	
New use of 2 nd generation	46,531 (21%)
New use of 3 rd or 4 th generation	37,346 (31%)
Switching from 2 nd to 3 rd or 4 th	26,411 (12%)
Switching from 3 rd or 4 th to 2 nd	14,357 (12%)

Figure 3C describes the proportion of women 15-49 years of age receiving 3rd or 4th generation versus 2nd generation combined hormonal contraceptives by calendar year across the study period. Only 29% of women receive a prescription for 3rd or 4th generation combined contraceptives in 2002 and this proportion increases constantly through the observation period to plateau at approximately 39% of women in 2008-2011

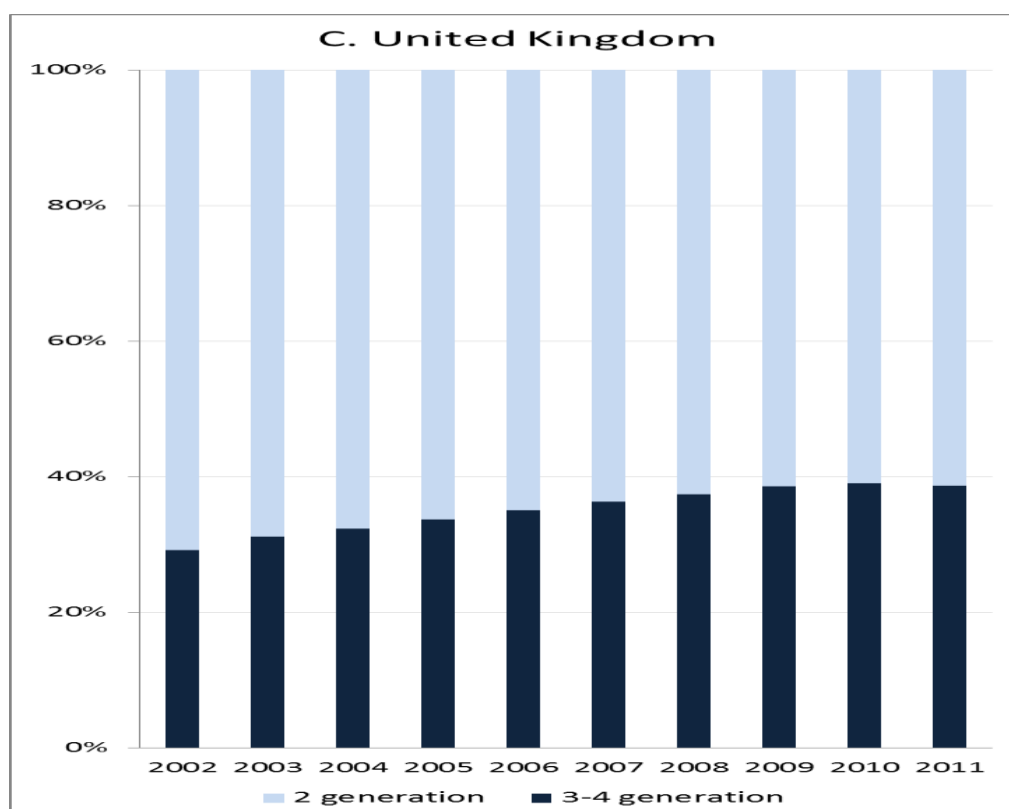


Figure 3C. Proportion of women receiving 3rd or 4th versus 2nd generation combined hormonal contraceptives in each calendar year through 2002-2011 in the UK

Overall the prescription patterns of combined hormonal contraceptives in the UK shows a predominant use of 2nd generation combination contraceptives across age groups and throughout the study period.

11. Conclusions

This study describes prescription patterns of 3rd or 4th versus 2nd generation combined hormonal contraceptives in France, Germany, and the UK over a decade. Comparisons across countries would require a careful consideration of healthcare delivery systems, national guidelines, regulatory intervention and market penetration analyses, which are beyond the scope of this study. Nonetheless, these data provide an overview of prescribing of combined hormonal contraceptive in a subset of the population in three EU countries.

The results show that throughout 2002-2011 GPs in France and the UK have prescribed 3rd or 4th generation contraceptives less frequently than 2nd generation contraceptives, while gynaecologists and internists in Germany have prescribed 3rd and 4th generation contraceptives more frequently. Across all countries an increased relative prescribing of 3rd or 4th generation contraceptives is observed over the past decade. This might be partially explained by a higher percentage of new users of 3rd or 4th generation in the UK (and to a lesser extent in Germany), together with a high number of patients switching from 2nd to the 3rd or 4th generation products in Germany.

Age-related differences in prescribing 3rd or 4th versus 2nd generation combined contraceptives are more pronounced in the UK and Germany than in France and overall would suggest that age can be a contributing factor in the choice of 3rd or 4th versus 2nd generation combined contraceptives.

In all countries the IMS Disease Analyser databases collect data from a panel of physicians. However, in this study each country-specific population represents a different proportion of the female source population ranging from 9.2% in France to over 30% in the UK. The apparently lower level of contraceptive prescribing observed in the French database suggests that in the French national healthcare system physicians other than the GPs may provide contraceptive prescriptions, which may impact on the representativeness of the study population with respect to the French general population and on the generalizability of these study results. To a greater extent the same considerations apply to the German database. On the other hand the data from the UK database would suggest a better generalizability of these results.

In conclusion, this study shows lower usage of 3rd and 4th compared to 2nd generation combined hormonal contraceptives in France and the UK throughout a 10 years period and in all age groups. Nonetheless the high level of prescribing in Germany, combined with a consistent pattern of increasing usage across all study countries in more recent years needs to be further considered in any assessment of the risk of thromboembolism associated with the use of 3rd or 4th generation combined hormonal contraceptives.

(Signature on File)

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Annalisa Rubino

Study lead

Date: 22 March 2013

Annex 1. Listing of study combined hormonal contraceptives by country

France	Germany	UK
3rd or 4th generation		
ETHINYLESTRADIOL + CHLORMADINONE	ETHINYLESTRADIOL + CHLORMADINONE	
ETHINYLESTRADIOL + DESOGESTREL	ETHINYLESTRADIOL + DESOGESTREL	ETHINYLESTRADIOL + DESOGESTREL
ETHINYLESTRADIOL + DROSPIRENONE	ETHINYLESTRADIOL + DROSPIRENONE	ETHINYLESTRADIOL + DROSPIRENONE
ETHINYLESTRADIOL + ETNOGESTREL	ETHINYLESTRADIOL + ETNOGESTREL	ETHINYLESTRADIOL + ETNOGESTREL
ETHINYLESTRADIOL + GESTODENE	ETHINYLESTRADIOL + GESTODENE	ETHINYLESTRADIOL + GESTODENE
ETHINYLESTRADIOL + NORGESTIMATE	ETHINYLESTRADIOL + NORGESTIMATE	ETHINYLESTRADIOL + NORGESTIMATE
ESTRADIOL + DIENOGEST	ESTRADIOL + DIENOGEST	ESTRADIOL + DIENOGEST
ESTRADIOL + DROSPIRENONE	ESTRADIOL + DROSPIRENONE	ESTRADIOL + DROSPIRENONE
ESTRADIOL + GESTODENE	ESTRADIOL + GESTODENE	
ESTRADIOL + NOMEGESTROL	ESTRADIOL + NOMEGESTROL	
	ETHINYLESTRADIOL + DIENOGEST	
	MESTRANOL + CHLORMADINONE	
2nd generation		
ETHINYLESTRADIOL + LEVONORGESTREL	ETHINYLESTRADIOL + LEVONORGESTREL	ESTRADIOL + NORETHISTERONE
ETHINYLESTRADIOL + NORETHISTERONE	ETHINYLESTRADIOL + NORETHISTERONE	ETHINYLESTRADIOL + LEVONORGESTREL
ESTRADIOL + NORETHISTERONE	ESTRADIOL + NORETHISTERONE	ETHINYLESTRADIOL + NORETHISTERONE
ESTRADIOL + LEVONORGESTREL	ESTRADIOL + LEVONORGESTREL	ESTRADIOL + LEVONORGESTREL

France	Germany	UK
ETHINYLESTRADIOL + NORGESTREL	ETHINYLESTRADIOL + NORGESTREL	NORGESTREL + ESTROGENIC SUBSTANCES, CONJUGATED
	ESTRADIOL + ESTRIOL + LEVONORGESTREL	NORETHISTERONE + MESTRANOL
	NORETHISTERONE + MESTRANOL	ESTRADIOL + NORGESTREL
	ESTRADIOL + NORGESTREL	ESTRADIOL + ESTRIOL + LEVONORGESTREL
	ETHINYLESTRADIOL + NORETHISTERONE + BUTAPERAZINE	ETHINYLESTRADIOL + NORGESTREL