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Patient Health Protection

PASS information

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Procedure number	
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Joint PASS	No
Research question and objectives	To study the drug utilisation of cyproterone-ethinylestradiol products in IMS electronic health record databases from UK, France and Germany
Country(-ies) of study	France, Germany, the UK
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Responsible parties

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1. Aim:

To study the drug utilisation of cyproterone/ethinylestradiol in Electronic Health Record databases from UK, France and Germany.

2. Setting

The European Medicines Agency has access to three IMS prescribing databases, Germany (25 million patients), UK (5 million patients) and France (2 million patients). All three databases are representative for their respective countries and IMS databases have been utilised for analyses of co-prescribing, duration, indication of use, time trends and age distribution of users. A comprehensive bibliography of the studies conducted with IMS databases, including validation studies in selected therapeutic areas, is available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Researchers/IMS_bibliography.pdf

3. Methods

The study period is 2002-2011. The study period was selected in order to have all three databases collecting data as well as completeness of data in each year.

For each of the three databases all patients receiving cyproterone/ethinylestradiol during 2002-2011 have been identified.

The German database contains the medical records of private specialists; here the data from internists, gynaecologist and dermatologists will be used, while the rest will be excluded. For the two other countries, the databases contain data from General Practitioners.

3.1. Co-prescribing

Co-prescribing of any of the 2nd, 3rd, and 4th generation CHC (Combined Hormonal Contraceptives) as well as isotretinoin will be investigated.

Co-prescribing is defined as any prescription done within 30 days before and after a prescription of cyproterone/ethinylestradiol. The prescribing has to be done by the same physician/General Practitioner practice.

The results will be presented as percentages of the study populations of cyproterone/ethinylestradiol users. Figures are presented for women receiving no co-prescribing, co-prescribing of CHC, co-prescribing with isotretinoin and co-prescribing of both at the same time.

3.2. Age and time distribution

Age is calculated at the time of prescription as the difference between year of prescription and year of birth. Since the study period is 10 years, the same patient might be in more than one age group and will then count towards the percentages of all age groups.

The percentage is calculated using the total number of women receiving cyproterone/ethinylestradiol in the study period as the denominator, because of the aforementioned possibility of being in more than one age group the percentages do not add up to 100%.

The time trend analysis uses number of women receiving a prescription of cyproterone/ethinylestradiol in each calendar year as the numerator and the number of women receiving any prescription in the

same calendar year as the denominator. This creates percentage prevalence of cyproterone/ethinylestradiol use in women.

3.3. Duration

Duration has been created in SAS on data extracted from IMS disease analyser. The following assumptions have been made:

Pack size: In order for each pack to match a certain number of menstrual cycles and knowing that the normal instructions would be to use for 21 days and then have a 7 day break all pack sizes have been converted from multiples of 21 to multiples of 28 (e.g. 21 -> 28, 63 -> 84 etc.).

When the quantity prescribed was 1-6 tablets, this has been treated as a mistake and been recoded to 1-6 packs of 28 tablets. All other quantities described as tablets have been treated as tablets (0.1% of prescriptions in UK, no cases in Germany or France). All quantities described as packs have been multiplied with pack size to get duration for each prescription.

Prescribing before the end date of the previous prescription has been treated by letting the duration left from the previous prescription being carried forward to the next. This means that a prescription of 84 tablets, being renewed 60 days later, would have the 24 tablets still left being added to the duration of the new prescription.

Prescribing after the end date of the previous prescription has been considered as a continued treatment episode if the date of prescription is 30 days or less after the end date of the previous prescription. This "grace period" seems to be fairly standard in duration studies and would allow for patients having less than perfect adherence.

A patient can have more than one therapy episode, all episodes have been counted.

Therapy episodes have been grouped as 0-90 days, 91-180 days, 181-365 days, 366 to 1095 days and more than 1095 days. Therapy durations might have been cut short by reaching the end of the study period or by starting before the study period.

3.4. Indication

The different electronic health record software supplying data to IMS allows for linking an indication for each prescription prescribed. In the UK this is mandatory in order for the GP to create a prescription in Germany and France this seems to be optional. Indications were grouped by level 3 and 4 of the hierarchy.

Using this link the ICD-10 codes have been analysed and grouped into main indications.

- Contraception: Z30
- Acne: L70
- Hirsutism: L68.0
- Polycystic ovarian syndrome: E28.2

In addition there are a few prominent groups of indications present as well;

- Menstrual issues: N91, N92, N93, N94
- Ovarian dysfunction: E28.9
- Androgen hypersecretion: E28.0, E29.1

- Hair loss (androgenic): L64.9, L65.9
- Unspecified (adm. codes): R69, Z76

The percentages for each country are in a single table.

4. Results

4.1. United Kingdom

In the UK the data are collected from General Practitioners (GP). GPs have a central gatekeeping role and are the primary contact for patients when prescriptions are needed. The use of private specialists is uncommon since they are not funded by the National Health System and would be more expensive to use for patients. A patient can only be registered with a single GP at any one time.

The results (**figure 1**) show that around 11% of cyproterone/ethinylestradiol users have had one or more occurrences of co-prescribing with CHC.

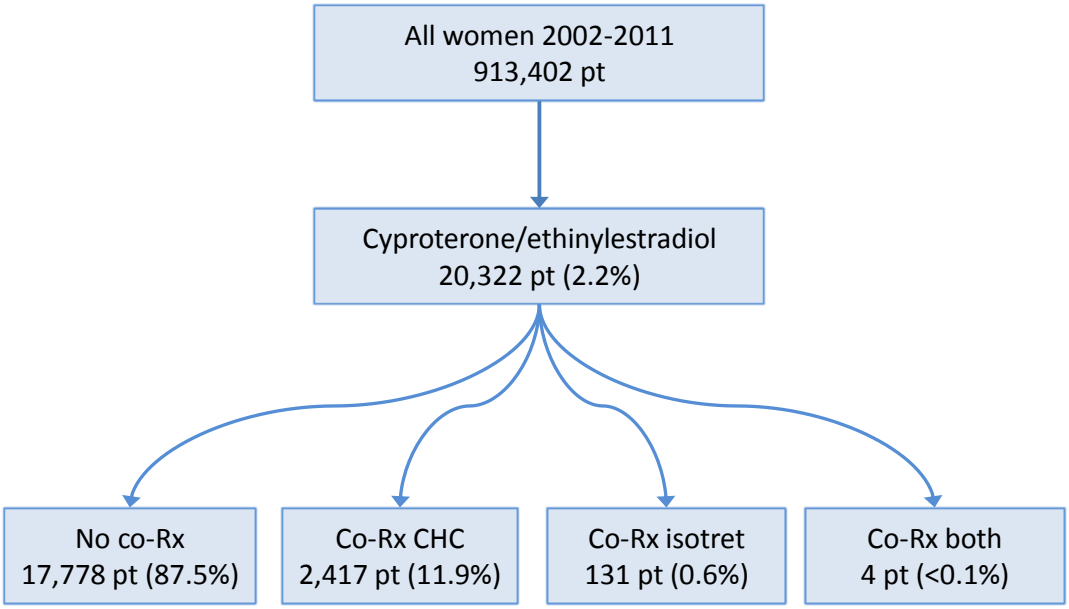

Figure 1 UK data on number of patients receiving prescriptions for cyproterone/ethinylestradiol in 2002-2011, the percentage of all women receiving any prescriptions of any drug in the same time period and the percentage of cyproterone/ethinylestradiol users co-prescribed Combined Hormonal Contraceptives (CHC) and isotretinoin (isotret).

Isotretinoin is co-prescribed to 0.6% of the users, and out of 20,322 patients receiving cyproterone/ethinylestradiol only 4 patients had one or more occurrences of co-prescribing of both CHC and isotretinoin.

In Figure 2 the age distribution of the patients is shown. Almost 60% of women received a prescription while in their twenties, 26% to younger women and 21 % to women aged 30 to 39. Very few patients aged above 50 received cyproterone/ethinylestradiol (0.2%).

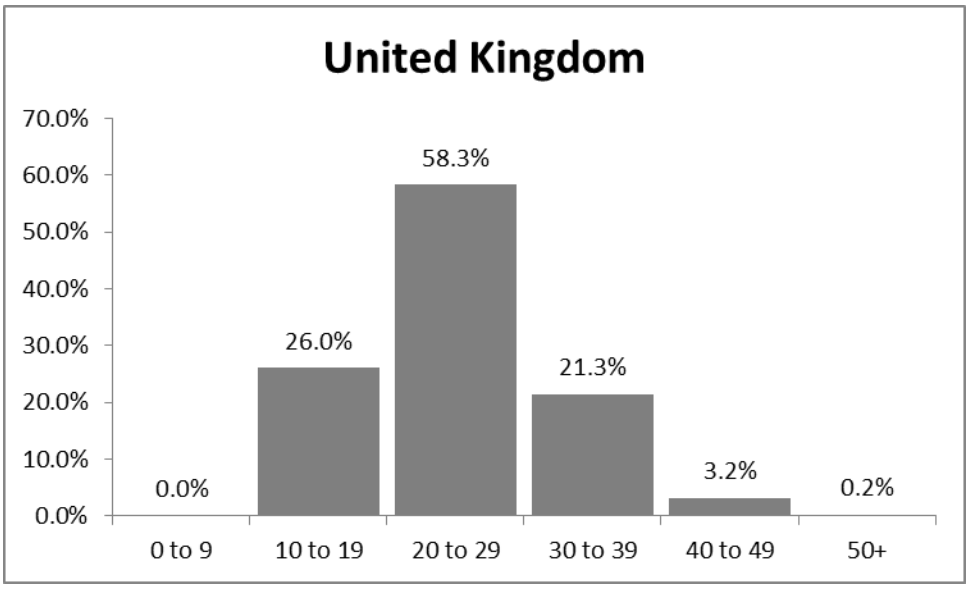

Figure 2: Distribution of patient's age when receiving a cyproterone/ethinylestradiol prescription during 2002-2011 in the UK

Figure 3 shows a drop in the prevalence of cyproterone/ethinylestradiol use in the time between 2002 and 2006. For the last 5 years of the period the prevalence has been stable.

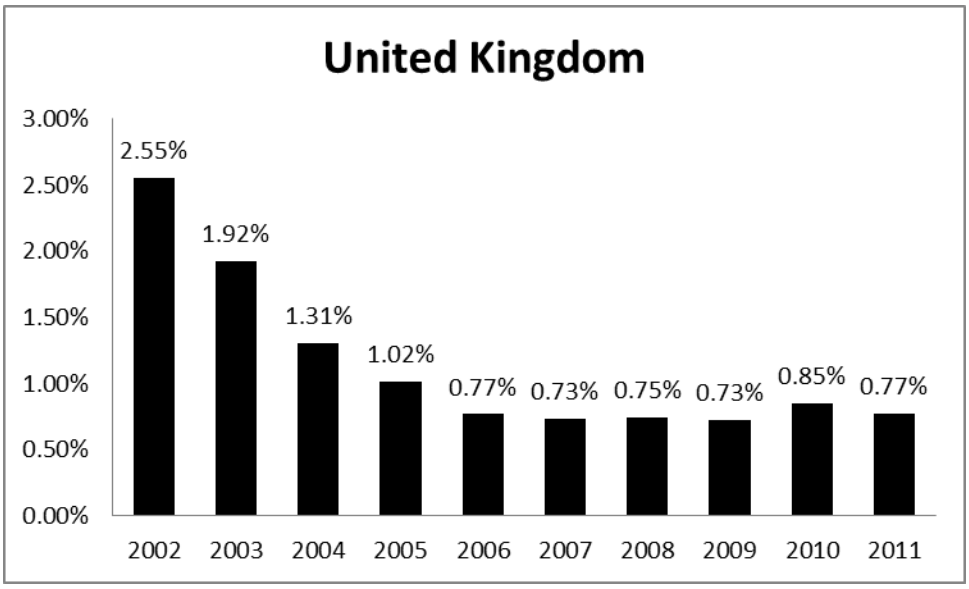

Figure 3: Cyproterone/ethinylestradiol prevalence of use 2002-2011 among all women receiving any prescription for any drug in each calendar year in UK

Duration was calculated for the 20322 patients receiving 42401 prescriptions. 50% of patients received only 1 prescription. The total number of treatment episodes was 31338.

Figure 4 displays the length of therapy with cyproterone/ethinylestradiol. It is clear that the majority (80%) of treatment is short term (less than 6 months) and that 6% of the treatment episodes were longer than one year.

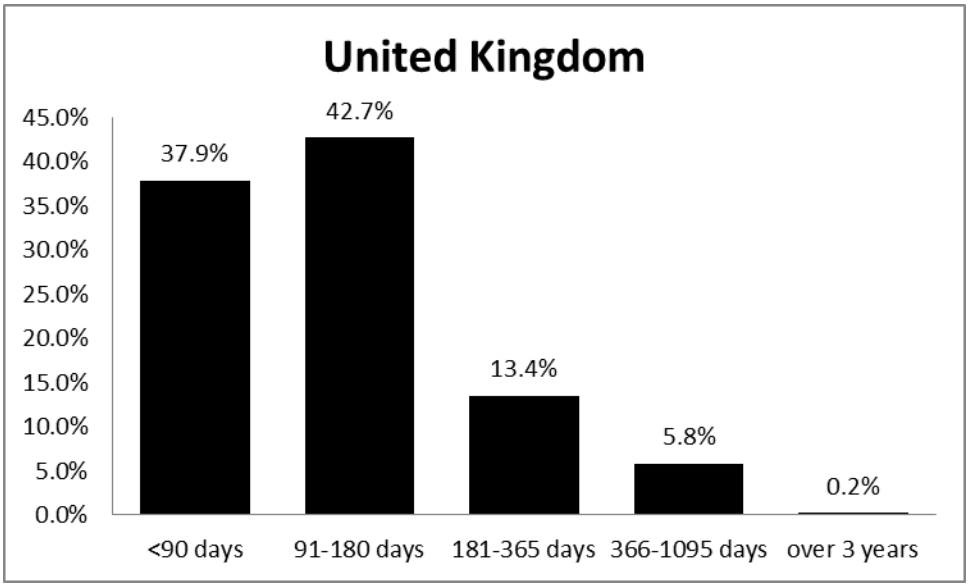

Figure 4: Duration of therapy episodes with cyproterone/ethinylestradiol in UK

4.2. Germany

In Germany the data are collected at private specialists including internal medicine specialists which are the closest to a General Practitioner in Germany. The patient can freely select to use any private specialist and it all will be funded by the national health insurance system. This means that the patient might use several physicians increasing the potential of co-prescribing by different physicians. In this analysis we have looked at three specialities, Dermatology, Gynaecology and Internal Medicine (with and without sub speciality)

The results (figure 5) show that around 5.6% of cyproterone/ethinylestradiol users have had one or more occurrences of co-prescribing with CHC. The total use of cyproterone/ethinylestradiol is at around 0.9% of all women in the dataset who have received any prescription.

Isotretinoin is co-prescribed to 0.5% the users, and out of 43,879 patients receiving cyproterone/ethinylestradiol only 5 patients had one or more occurrences of co-prescribing of both CHC and isotretinoin at the same time.

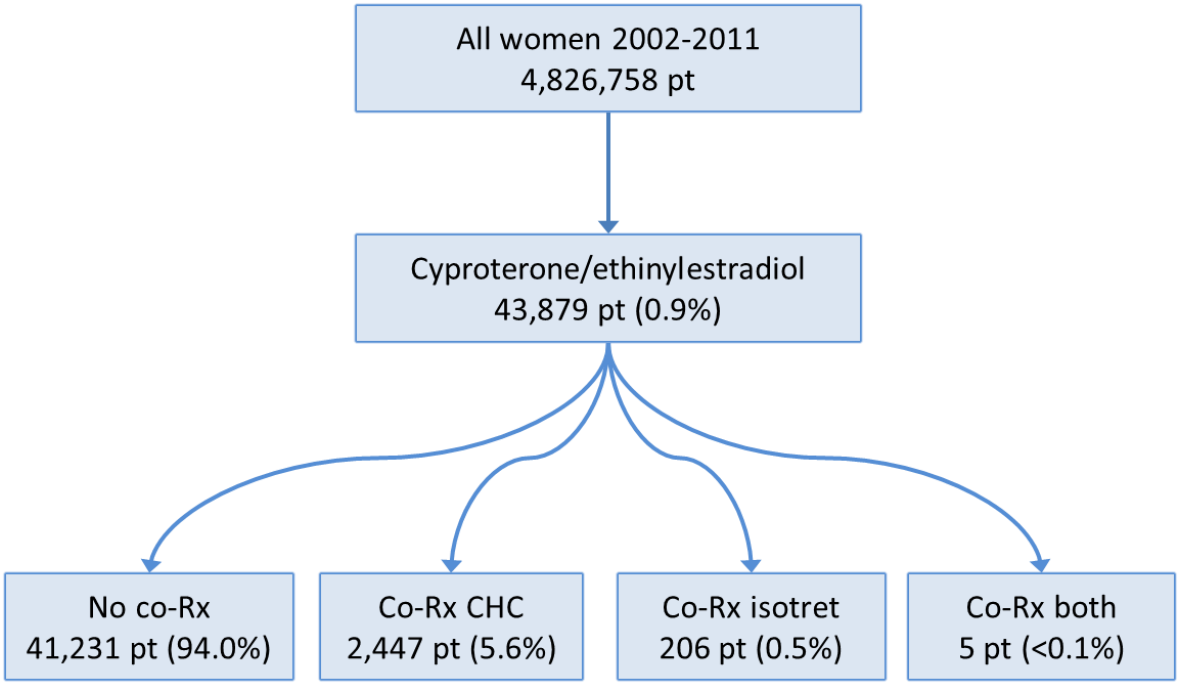

Figure 5: German data on number of patients receiving prescriptions for cyproterone/ethinylestradiol in 2002-2011, the percentage of all women receiving any prescription for any drugs in the same time period and the percentage of cyproterone/ethinylestradiol users co-prescribed Combined Hormonal Contraceptives (CHC) and isotretinoin (isotret).

In figure 6 the age distribution of the patients is shown. Over 50% of women received a prescription while in their twenties, 20% were younger and 29 % were aged 30 to 39 when they received a prescription. Around 13% of users received a prescription while in their forties. Few patients aged above 50 received cyproterone/ethinylestradiol (1.9%).

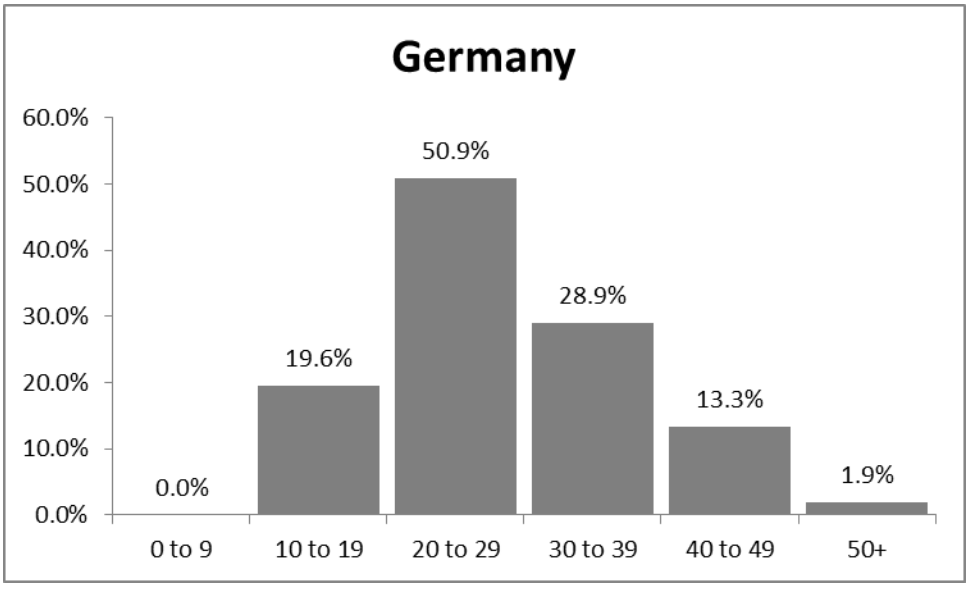

Figure 6: Distribution of patient's age when receiving a cyproterone/ethinylestradiol prescription during 2002-2011 in Germany

Figure 7 shows the prevalence of use over time. It is stable with a very slight increase from 0.58% in 2002 to 0.65% in 2011.

Duration was calculated for the 43939 patients receiving 191577 prescriptions. 38% of patients received only 1 prescription. The total number of treatment episodes was 72474.

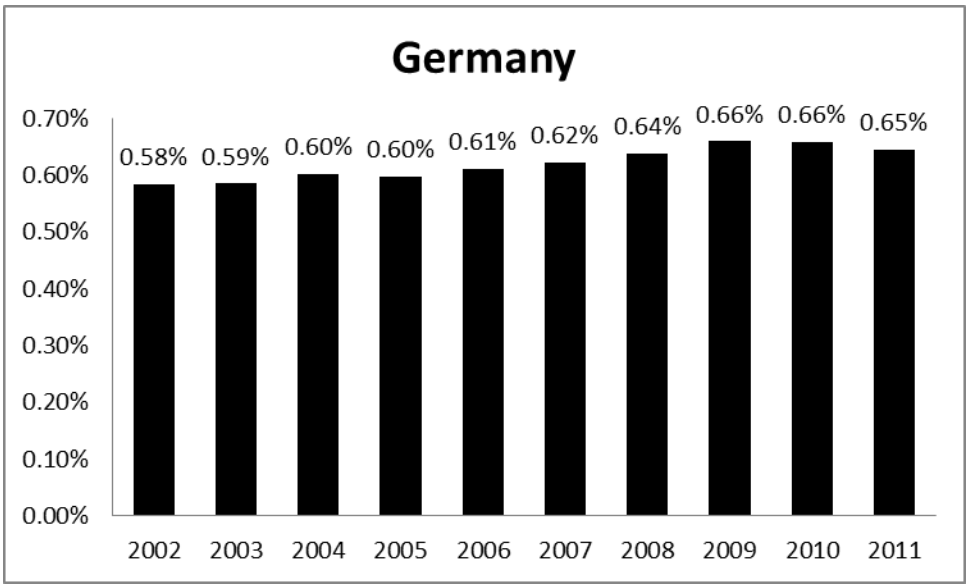

Figure 7: Cyproterone/ethinylestradiol prevalence of use 2002-2011 among all women receiving any prescription for any drug in each calendar year in Germany

Figure 8 displays the length of therapy with cyproterone/ethinylestradiol. It is clear that the majority (64%) of treatment is short term; less than 6 months, and that 20% of the episodes was longer than one year of treatment.

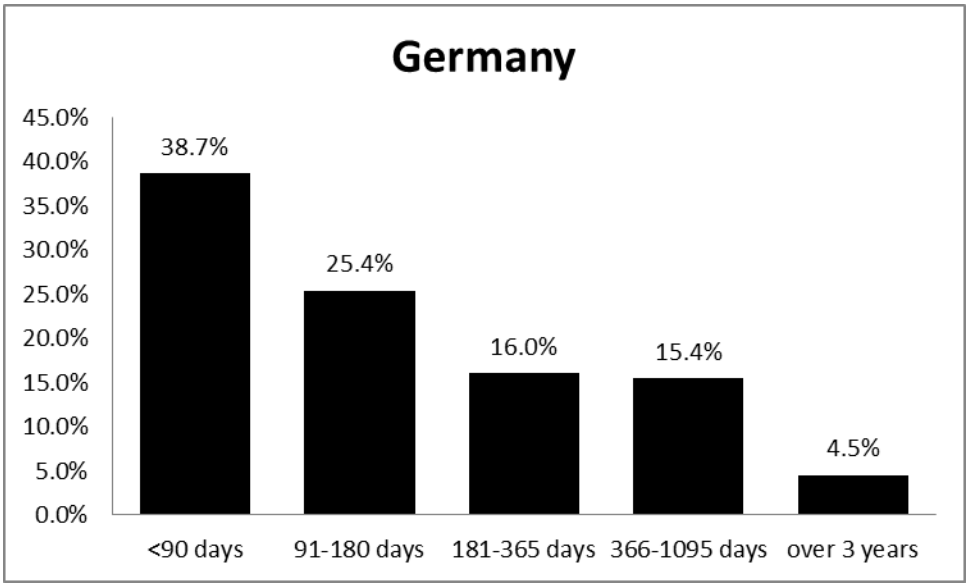

Figure 8: Duration of therapy episodes with cyproterone/ethinylestradiol in Germany

4.3. France

The French health care system is similar to the German one on the point of allowing patients to go to any private specialist. In addition the data we have only includes GPs so the extent of the use of specialists is not measurable in the data.

The results (figure 9) show that around 2.1% of cyproterone/ethinylestradiol users have had one or more occurrences of co-prescribing with CHC. The total use of cyproterone/ethinylestradiol is at around 0.8% of women, a low number compared to the other CHCs. Isotretinoin is co-prescribed to 1.0% the users, and out of 15,141 patients receiving cyproterone/ethinylestradiol only 3 patients had one or more occurrences of co-prescribing of both CHC and isotretinoin at the same time.

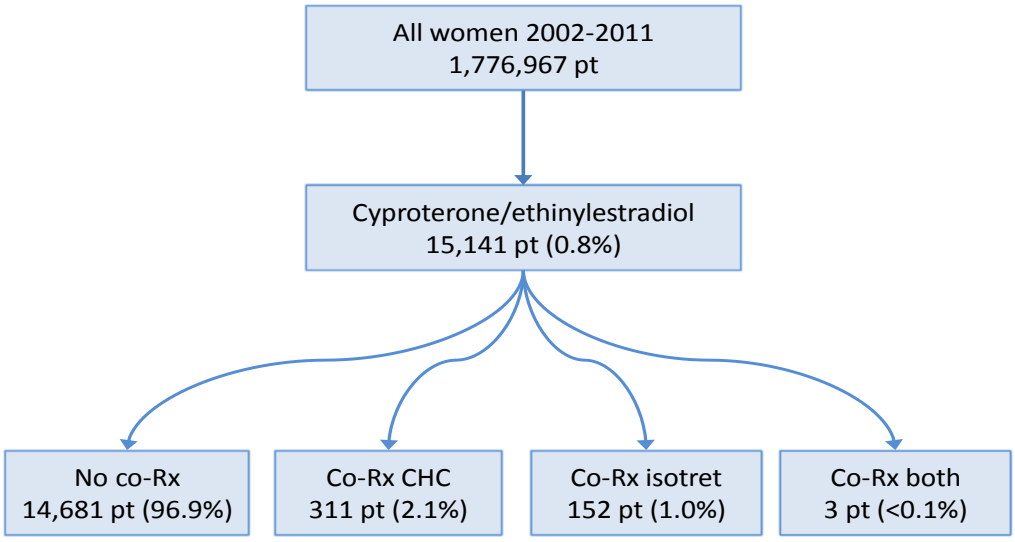

Figure 9: French data on number of patients receiving prescriptions for cyproterone/ethinylestradiol in 2002-2011, the percentage of all women receiving any prescriptions for any drug in the same time period and the percentage of cyproterone/ethinylestradiol users co-prescribed Combined Hormonal Contraceptives (CHC) and isotretinoin (isotret).

In figure 10 the age distribution of the patients is shown. About 57% of women received a prescription while in their twenties, 32% were younger and 20% were aged 30 to 39 when they received a prescription. Around 6% were aged 40 to 49 when they received a prescription and no patients aged above 50 received cyproterone/ethinylestradiol.

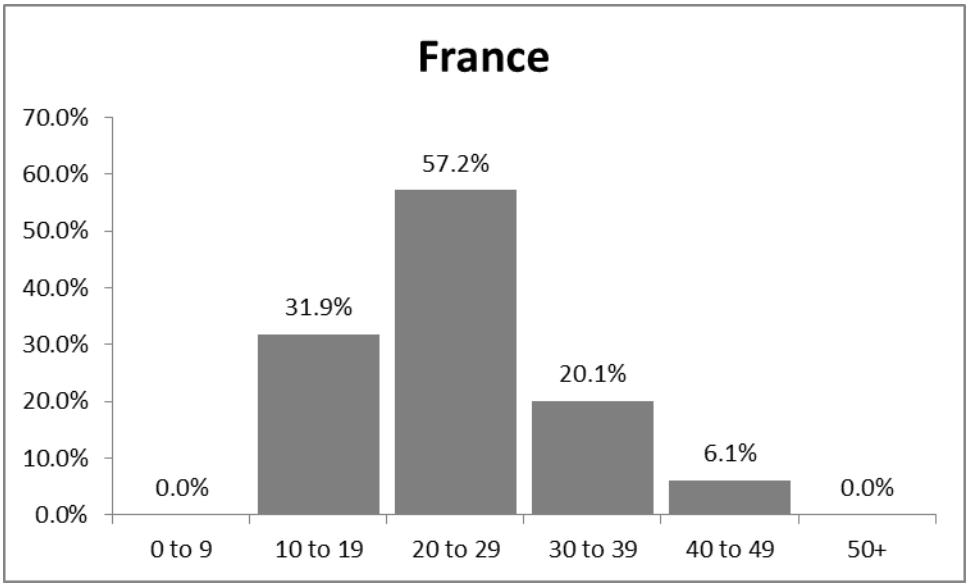

Figure 10: Distribution of patient's age when receiving a cyproterone/ethinylestradiol prescription during 2002-2011 in France

Figure 11 shows the prevalence of use over time. In France it has been stable at around 0.5% in the whole period 2002-2011. Duration was calculated for the 15141 patients receiving 36815 prescriptions. 56% of patients received only 1 prescription. The total number of treatment episodes was 28948.

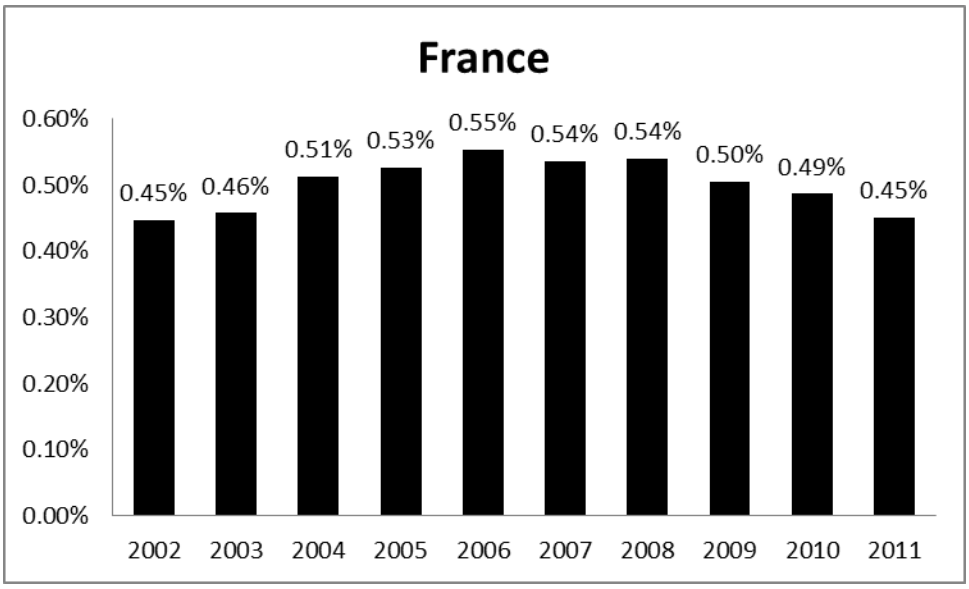

Figure 11: Cyproterone/ethinylestradiol prevalence of use 2002-2011 among all women receiving any prescription for any drug in each calendar year in France

Figure 12 displays the length of therapy with cyproterone/ethinylestradiol. It is clear that the majority (82%) of treatment recorded is short term (less than 6 months) and that 6% of the episodes were longer than one year.

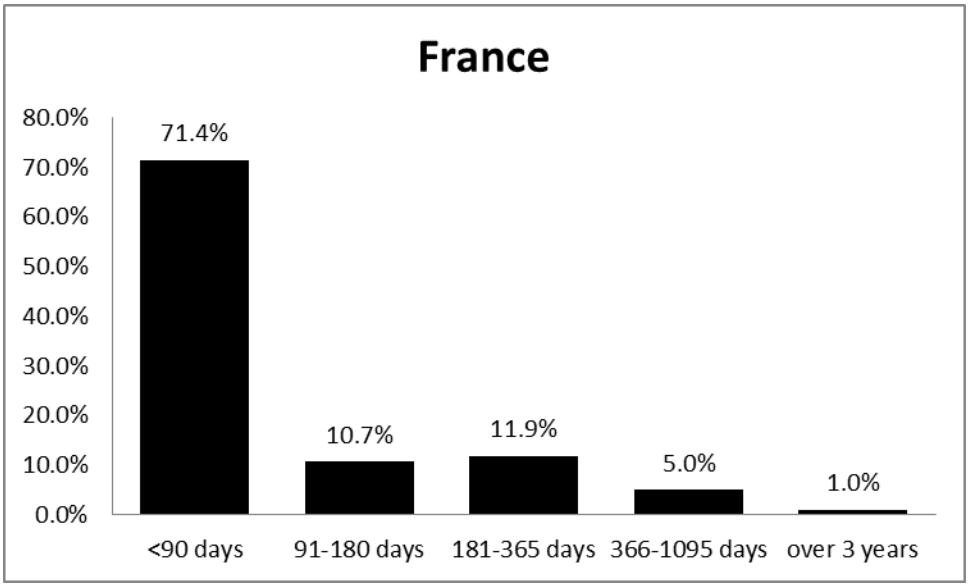

Figure 12: Duration of therapy episodes with cyproterone/ethinylestradiol in France

4.4. Indication analysis

In table 1 the results from the indication analysis is shown. What we see is that while in the UK almost all prescription had an ICD-10 code recorded while in Germany and France only about 2/3 of prescriptions recorded this.

Furthermore we see that contraception is the main indication (43-67%) but that also acne is the indication for a reasonably large percentage of prescriptions. Furthermore we see that in UK, polycystic ovarian syndrome is the indication for 2.8% of prescriptions with a lower percentage in Germany and a very low percentage in France. Hirsutism is the indication for 3% of prescriptions in Germany, 1% in UK and 0.3% in France. In other indication groups, cyproterone/ethinylestradiol is recorded as used for seems to be menstrual issues (such as bleeding, frequent and infrequent menstruation and pain), androgen hypersecretion and ovarian dysfunction in Germany only. There are a number of unspecified indications in the UK (6%) and France (34%).

There are additional indications not listed, these seem to be a mix of unspecified skin issues and genital issues as well as migraine and probably non-related indications which could be due to recording errors by the physicians.

Table 1: Indication for prescribing cyproterone/ethinylestradiol. Number of prescriptions in total and with indication. Also percentages out of prescriptions with indication recorded for selected indications

	United Kingdom	Germany	France
All Rx	42401	191577	36815
Rx with ICD-10 code (N)	**42332**	**114336**	**24674**
Contraception	66.7%	61.5%	42.6%
Acne	12.4%	13.9%	8.2%
Hirsutism	1.0%	2.9%	0.3%
Polycystic ovarian syndrome	2.8%	1.2%	0.1%
Menstrual issues	2.6%	5.1%	0.5%
Ovarian dysfunction	-	0.6%	-
Androgen hypersecretion	-	6.1%	-
Hair loss (androgenic)	0.0%	1.5%	0.1%
Unspecified (adm. codes)	6.3%	0.2%	33.5%
Other	8.2%	7.1%	14.7%

5. Discussion

The databases used have some important limitations. While in the UK the GP is the primary gatekeeper and contact point for patients this is not the case in France and Germany. This will affect the completeness of the patient's data. The way this issue would influence the results will be different for each analysis.

For time trend the effect should not be very important, also for age distribution the results should be reliable as long as the rate of missing information is constant over time and between age groups. For treatment duration the effects can, and probably are important since a missing prescription from someone other than the GP (or specialists in Germany) would be registered as a gap in the analysis and would shorten treatment durations significantly. The results and the way the health care system is

organised would suggest this to be an issue particularly in France where duration of therapy is short. However a large percentage of patients seem to only receive a single prescription and if this is accurate their duration of treatment will not be affected.

Co-prescribing might also be affected if patients receive their prescriptions from different sources such as a dermatologist for isotretinoin or a gynaecologist for combined hormonal contraceptives they will not be recorded as having any co-prescribing. These numbers would therefore be a low estimate of the total co-prescribing, especially for France and Germany.

For indications the results should be reliable, but it is important to remember that for German and French results 1/3 of prescriptions did not have an indication and in France the use of administrative codes was very high.

(signature on file)

Study lead: Kristian Svendsen

Date: 22 March 2013

Annex

Codes seen as Indication for Cyproterone/ethinylestradiol

ICD-10 CODE	Description (only IMS abbreviation)
A099	GASTRO & COLIT UNSP
A560	CHLAMYD INF LOW GU TRACT
B029	ZOSTER WO COMPLICATION
B360	PITYRIASIS VERSICOLOR
B373	CANDIDA OF VULVA/VAGINA
B379	CANDIDIASIS UNSPECIFIED
B860	SCABIES
C800	MAL NEO PRIMARY UNKNOWN
D239	OTH BEN NEOS SKIN UNSP
D485	NEO UNCERTAIN BEHAV SKIN
D508	OTH IRON DEFIC ANAEMS
D693	IDIOP THBOCYTOPEN PURPUR
E039	HYPOTHYROIDISM UNSP
E109	IDDM WITHOUT COMP
E119	NIDDM WITHOUT COMP
E282	POLYCYSTIC OVARIAN SYND
E288	OTH OVARIAN DYSFUNCTION
E301	PRECOCIOUS PUBERTY
E669	OBESITY UNSPECIFIED
E889	METABOLIC DISORDER UNSP
F321	MOD DEPRESSIVE EPISODE
F329	DEPRESSIVE EPISODE UNSP
F341	DYSTHYMIA
F402	SPECFC (ISOLATED) PHOBIA
F411	GENERALIZED ANXIETY DIS
F412	MXD ANX/DEPRSV DIS
F453	SOMATORM AUTON DYSFUNC
F454	PERSIS SOMATORM PAIN DIS
F480	NEURASTHENIA
F509	EATING DISORDER UNSP
F990	MNTL DIS NOT O/WISE SPEC
G409	EPILEPSY UNSPECIFIED
G431	MIGRAINE+AURA (CLASS)
G439	MIGRAINE UNSPECIFIED
G470	INSOMNIAS
G600	HERED MTR/SENSOR NEUROP
G933	POSTVIRAL FATIGUE SYND
H105	BLEPHAROCONJUNCTIVITIS
H603	OTH INF OTITIS EXTERNA
H608	OTHER OTITIS EXTERNA
H619	DIS EXTERNAL EAR UNSP

H811	BEN PAROXYSMAL VERTIGO
I845	EXT HAEMORR WO COMPLIC
J000	AC NASOPHARYNGITIS
J010	AC MAXILLARY SINUSITIS
J029	ACUTE PHARYNGITIS UNSP
J039	ACUTE TONSILLITIS UNSP
J069	AC UPP RESP INFECT UNSP
J209	ACUTE BRONCHITIS UNSP
J220	UNSP AC LOW RESP INFECT
J304	ALLERGIC RHINITIS UNSP
J459	ASTHMA UNSPECIFIED
J989	RESP DISORDER UNSP
K089	DIS TTH/SUP STRUC UNSP
K509	CROHN'S DISEASE UNSP
K589	IRRIT BOWEL SYND WO DIAR
K908	OTH INTEST MALABSORPTION
L010	IMPETIGO-ANY ORGNISM/STE
L029	FURUNC/CARBUNC UNSP
L032	CELLULITIS OF FACE
L033	CELLULITIS OF TRUNK
L089	LOC INF SKN/SC TISS UNSP
L208	OTHER ATOPIC DERMATITIS
L209	ATOPIC DERMATITIS UNSP
L219	SEBORR DERMATITIS UNSP
L259	UNSP CT DERM-UNSP CAUSE
L292	PRURITUS VULVAE
L293	ANOGENITAL PRURITUS UNSP
L301	DYSHIDROSIS (POMPHOLYX)
L309	DERMATITIS UNSPECIFIED
L409	PSORIASIS UNSPECIFIED
L500	ALLERGIC URTICARIA
L600	INGROWING NAIL
L630	ALOPECIA (CAPITIS) TOTAL
L639	ALOPECIA AREATA UNSP
L659	NONSCAR HAIR LOSS UNSP
L679	HAIR COL/SHAFT ABN UNSP
L680	HIRSUTISM
L700	ACNE VULGARIS
L708	OTHER ACNE
L709	ACNE UNSPECIFIED
L710	PERIORAL DERMATITIS
L718	OTHER ROSACEA
L719	ROSACEA UNSPECIFIED
L732	HIDRADENITIS SUPPURATIVA
L739	FOLLICULAR DIS UNSP
L749	ECCRINE SWEAT DIS UNSP

L858	O/SPEC EPIDERM THICKNNG
L988	O/SPEC DIS SKN/SC TISS
L989	DIS SKN/SUBCUT TISS UNSP
M436	TORTICOLLIS
M502	O/CERV DISC DISPL
M542	CERVICALGIA
M674	GANGLION
M799	SOFT TISSUE DIS UNSP
M819	OSTEOPOROSIS UNSP
M959	ACQ DEFRM M/KEL SYS UNSP
N300	ACUTE CYSTITIS
N390	URIN TRACT INF-ST UNSPEC
N399	DIS URINARY SYST UNSP
N600	SOLITARY CYST OF BREAST
N643	GALACTORR NOT+CH/BIRTH
N644	MASTODYNIA
N649	DISORDER OF BREAST UNSP
N701	CHR SALPINGIT/OOPHORITIS
N739	FM PELV INFLAM DIS UNSP
N809	ENDOMETRIOSIS UNSP
N832	OTH & UNSP OVARIAN CYSTS
N839	NONINFL-OVARY ETC UNSP
N898	O/SPEC NONINFLAM DIS VAG
N899	NONINFLAM DIS VAG UNSP
N910	PRIMARY AMENORRHOEA
N911	SECONDARY AMENORRHOEA
N912	AMENORRHOEA UNSPECIFIED
N913	PRIMARY OLIGOMENORRHOEA
N914	SEC OLIGOMENORRHOEA
N915	OLIGOMENORRHOEA UNSP
N920	EXC/FREQ MENSES+REG CYC
N921	EXC/FREQ MENST+IRREG CYC
N922	EXCESS MENSES AT PUBERTY
N923	OVULATION BLEEDING
N926	IRREG MENSTRN UNSP
N938	O/SPEC ABN UT/VAG BLDING
N939	ABN UTER/VAG BLDING UNSP
N940	MITTELSCHMERZ
N941	DYSPAREUNIA
N943	PMT SYND
N944	PRIMARY DYSMENORRHOEA
N946	DYSMENORRHOEA UNSP
N949	UNSP CND-F GN ORG/MN CYC
N951	MENOPAUS/FM CLIMAC STATE
N979	FEMALE INFERTILITY UNSP
O039	S/ABTN COM/UNSP WO COMP

O809	SINGLE SPONT DELIV UNSP
O829	DELIV C/S UNSP
O912	NONPUR MASTITIS-CH/BTH
Q840	CONGENITAL ALOPECIA
Q842	OTH CONG MALFMS OF HAIR
Q969	TURNER'S SYNDROME UNSP
R011	CARDIAC MURMUR UNSP
R050	COUGH
R060	DYSPNOEA
R068	OTH/UNS ABN BREATHING
R074	CHEST PAIN UNSPECIFIED
R102	PELVIC AND PERINEAL PAIN
R103	PAIN LOC O/PTS LW ABD
R104	OTH AND UNSP ABDO PAIN
R170	UNSPECIFIED JAUNDICE
R208	OTH/UNS DISTB SKIN SENS
R210	RASH/OTH UNSP SKIN ERUPT
R229	LOCAL SWELL MASS UNS
R238	OTH & UNSP SKIN CHANGES
R300	DYSURIA
R398	OTH/UNS SYMP IN URIN SYS
R510	HEADACHE
R530	MALAISE AND FATIGUE
R550	SYNCOPE AND COLLAPSE
R619	HYPERHIDROSIS UNSP
R629	LACK NML PHYS DEV UNSP
R635	ABNORMAL WEIGHT GAIN
R638	O/SYM/SGN CONC FD/FL INT
R688	OTH SPEC GENL SYM/SIGNS
R693	NOT STATED DIAG DOC
R694	DIOC ADMIN CODES
R698	ILL DEFINED DIAG
S522	FRAC OF SHAFT OF ULNA
T149	INJURY UNSPECIFIED
T509	POIS-O/UNS DRG ETC
Z000	GENERAL MEDICAL EXAM
Z003	EXAM ADOLESCENT DEVELOP
Z013	EXAM BLOOD PRESSURE
Z014	GYNAE EXAM ROUTINE
Z017	LABORATORY EXAMINATION
Z038	OBS OTH SUSP DIS/COND
Z039	OBS SUSP DIS/ COND UNSP
Z049	EXAM/OBS UNSP REASON
Z108	ROUT EXAM OTH DEF SUBPOP
Z124	SPEC SCR FOR NEO CERVIX
Z138	SPEC SCR OTH SPEC DIS

Z299	PROPHY MEASURE UNSP
Z300	GEN ADVICE CONTRACEPT
Z301	INSERT IUCD
Z302	STERILIZATION
Z304	SURV CONTRACEPT DRUG
Z308	OTH CONTRACEPT MANAGE
Z309	CONTRACEPT MANAGEM UNS
Z316	GEN COUNS/ADV PROC
Z318	OTH PROCREATIVE MANAGEM
Z321	PREGNANCY CONFIRMED
Z330	PREG STATE INCIDENT
Z349	SUPER NORM PREG UNSP
Z379	OUTCOME DELIVERY UNSP
Z392	ROUTINE POSTPARTUM F/U
Z408	OTH PROPHYLACTIC SURGERY
Z518	OTH SPEC MEDICAL CARE
Z519	MEDICAL CARE UNSP
Z539	PROCED NOT DONE UNS REAS
Z713	DIET COUNS/SURV
Z718	OTH SPEC COUNSELLING
Z719	COUNSELLING UNSPECIFIED
Z733	STRESS NEC
Z760	ISSUE REP PRESCRIPT
Z804	FAM HIST MAL NEO GEN ORG
Z840	F/H DIS SKIN/SUBCUT TISS
Z848	FAM HIST OTH SPEC CONDS
Z863	P/H ENDO NUTR/MET DIS
Z866	P/H DIS NRV SYS/SEN ORG
Z872	P/H DIS SKIN/SUBCUT TISS
Z874	PER HIS DIS THE GU SYST
Z915	PER HIS OF SELF HARM
Z920	PER HIS OF CONTRACEPTION
Z929	P/H MED TREAT UNS