Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints

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Note:

Tables 4a and 4b include each of the study CHCs, each of the study comparators, and two totals. The total for all comparators combined (*COMP*), is in italics. The final total is the sum of the study CHCs and the comparators. The comparators are not counted twice.

Tables 10 and 11 include separate sections in the tables for incident rate ratios for all comparators combined and for LNG2 alone.

Tables 12 – 14 include tables for all comparators combined, and LNG2 alone as the reference group.

EXECUTIVE SUMMARY

There has long been concern about the risk of both arterial and venous cardiovascular complications imparted by the use of combined hormonal contraceptives (CHCs) in large part because of the prothrombotic effects of estrogen. An increased risk of venous thromboembolism (VTE) (deep venous thrombosis [DVT] and pulmonary embolism [PE]) is well established and has been consistently reported.[1] However, there are limited data available regarding the risk of these outcomes for recently marketed CHC's, including [drospirenone/ethinyl estradiol tablet (DRSP), norelgestromin/ethinyl estradiol transdermal patch (NGMN), and etonogestrel/estradiol vaginal ring (ETON)]. Thus, we conducted a retrospective cohort study using data from four geographically diverse health plans which included 835,826 women with 898,251 person-years of CHC use to evaluate the risk of thrombotic and thromboembolic events and all-cause and cardiovascular mortality for the three newer preparations compared to four older CHC's with similar low estrogen levels.

We utilized computerized data files from two integrated medical care programs [(Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC)] and two state Medicaid programs [Tennessee State Medicaid (Vanderbilt) and Washington State Medicaid (University of Washington)] to obtain enrollment data; demographic information; ambulatory prescriptions from pharmacy records or claims; hospitalization and outpatient visit data with diagnoses from health plan records or claims; and mortality obtained from state mortality files.

We identified 835,826 women, ages 10-55 years, who had at least one prescription for a study CHC between January 1, 2001, and December 31, 2007, that was preceded by at least 6 months of continuous membership. We established study

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CHC exposure period information using data from the pharmacy records for each woman in the study and determined the number of potential endpoint cases occurring during the exposure period (hospitalized acute myocardial infarction [AMI]); hospitalized ischemic stroke; hospitalized venous thromboembolism [VTE] and outpatient deep venous thrombosis [DVT]; and total mortality including cardiovascular disease (CVD) mortality from claims and vital records. Medical records for events identified in computer databases were reviewed and adjudicated at a single site. We considered four primary study endpoints, arterial thrombotic events (ATE, includes AMI and ischemic stroke), venous thromboembolic events (VTE), CVD mortality, and total mortality.

The primary analyses were conducted on all CHC use during the 7-year time period and on new use, which was defined as CHC use during the study period which was not preceded by the use of any CHC, study or non-study, during the study period, including CHC use that may have occurred during the 6-month pre-exposure eligibility period. Cox proportional hazard modeling was used to estimate the relative risk of study endpoints associated with the 3 exposure CHCs relative to the combined comparator CHCs with adjustment for age, site, and year of entry into the study. For ATE and CVD mortality, we added the traditional cardiovascular risk factors hypertension, hyperlipidemia, and diabetes as covariates in the models. We tested a large number of other potential covariates individually but none changed the risk estimates by more than 10% (our predetermined criterion for inclusion) so all were excluded from the final models.

The final cohort included 189,210 person-years of exposure to DRSP, 67,865 person-years of exposure to NGMN, 23,910 person-years of exposure to ETON, and 617,265 person-years of exposure to the comparator CHC's. After adjudication, the

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cohort included 60 AMIs, 78 ischemic strokes, and 625 VTEs. There were also 41 CVD deaths and 267 total deaths during study CHC exposure periods.

In adjusted analyses, DRSP, NGMN, and ETON were associated with a significantly higher risk of VTE relative to low-estrogen comparators [estimates of relative risk were 1.74 (95% CI 1.42 – 2.14) for DRSP, 1.55 (1.17, 2.07) for NGMN, and 1.56 (1.02, 2.37) for ETON. For the analysis restricted to new users, only DRSP was associated with a significantly higher risk of both ATE [2.01 (1.06 – 3.81)] and VTE [1.77 (1.33 – 2.35)].

We also considered the risks associated with duration of use of the exposure CHCs relative to comparators in the new user analysis examining 4 intervals (<3 months, 3-6 months, 6-12 months, and >12 months). DRSP was associated with significantly higher risk of VTE for <3 months [1.93 (1.24, 3.00)] and 6-12 months [2.80 (1.48, 5.29), while the NGMN patch was associated with significantly higher risk for VTE at >12 months [3.05 (1.23, 7.53)].

In analyses stratified by the age groups 10-34 and 35-55 years, the risk of VTE for all 3 study CHCs were higher in the younger than in the older age group for all users and the estimate for DRSP only was statistically significant for VTE in those 35 years and older. For new users, the only significantly increased risk for VTE associated with DRSP use was in the 10-34 years age group. There was also an increased risk of ATE associated with DRSP use in those 35 years and older. Interaction terms for age were significant for DRSP for both VTE and ATE (p<0.001).

We also conducted these analyses using LNG2 alone as the comparator. This enabled us to estimate the risks of DRSP relative to LNG2, since these preparations both contained 30 µg of ethinyl estradiol. The findings with LNG2 as the comparator

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generally paralleled the findings for the combined comparators though not as many

reached statistical significance.

We conclude that the study results add to the small body of literature which

shows that the NGMN transdermal patch is associated with higher risk of VTEs

relative to standard CHC pills and provides another positive finding to the increasing

body of evidence linking DRSP to increased risk of VTE relative to standard low-dose

CHC pills. DRSP was associated with higher risk of ATE in new users overall with this

finding restricted to women in the 35-55 years age group only. The finding of

increased risk of VTE with the ETON vaginal ring relative to standard CHCs is new

and raises concern but needs to be replicated in other studies.

Introduction

There has long been concern about the risk of both arterial and venous cardiovascular complications imparted by the use of combined hormonal contraceptives (CHCs) in large part because of the prothrombotic effects of estrogen (ethinyl estradiol [EE]). An increased risk of venous thromboembolism [VTE] (deep venous thrombosis [DVT] and pulmonary embolism [PE]) is well established and has been consistently reported [1] The nature of the association of CHC use with the major arterial cardiovascular (CV) outcomes, acute myocardial infarction (AMI) and stroke is not as clear-cut, with mixed results in studies conducted during the era of low-dose estrogen CHCs. One review [2] and one meta-analysis [3] reported evidence of increased risk for these outcomes. Chan et al reported that the pooled odds ratio (OR) from 16 case-control studies showed a significant association of oral contraceptive (OC) pills with stroke [OR 2.13, 95% confidence interval (CI) 1.59-2.86] while the pooled OR from 4 cohort studies demonstrated no increased risk. The risk of stroke was significant only with thrombotic stroke and not with hemorrhagic stroke or death. Baillargeon et al reported that the summary risk estimates from a meta-analysis of 14 studies showed an increased risk of AMI (OR 1.84, 95% CI 1.38-2.44) and ischemic stroke (OR 2.12, 95% CI 1.56-2.86).

Concerns have been raised in recent years whether the risk associated with these cardiovascular endpoints may be higher in three of the newer CHC preparations, drospirenone/ethinyl estradiol tablets (DRSP), the norelgestromin/ethinyl estradiol transdermal patch (NGMN), and the etonogestrel/ethinyl estradiol vaginal ring (ETON) relative to other CHCs that are commonly used. Continuous exposure CHCs such as the NGMN patch and ETON vaginal ring potentially result in higher sustained exposure to estrogen and hence, increased thromboembolic risk. DRSP may increase cardiac

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arrhythmia risks and sudden deaths among users because it has anti-mineralocorticoid activity that may increase potassium levels.

Several studies that have examined the DRSP pill and the NGMN transdermal patch found that these place women at higher risk of CVD endpoints, primarily VTE, than standard low-dose preparations, which have been available for many years and are also available as generics. We are unaware of any prior studies examining CVD risk associated with the ETON vaginal ring.

Six published studies have examined the risk of VTE associated with DRSP-containing CHCs. The European Active Surveillance study on Oral Contraceptives (EURAS), a large prospective cohort study, found no increased risk of VTE or ATE associated with DRSP use relative to other CHCs.[4] Dinger also found no increased risk of VTE associated with DRSP use relative to levonorgestrel CHC use in a German community-based, case-control study.[5] Seeger reported no significant risk for VTE in users of DRSP CHCs relative to other CHCs in a retrospective cohort study utilizing electronic medical data from UnitedHealthcare-affiliated health plans.[6] The comparison group was composed of women selected to have demographic and health care characteristics similar to the DRSP users. Lidegaard reported on a follow-up study in Denmark linking registries for prescriptions, education, and health.[7] The risk of venous thrombosis associated with the CHCs containing DRSP was increased relative to CHCs containing levonorgestrel and with the same dose of estrogen accounting for length of use [rate ratio1.64 (95% CI 1.27 – 2.10)].[7] Van Hylckama Vlieg found that women taking CHCs containing DRSP had a substantially higher risk of venous thrombosis than those taking CHCs with levonorgestrel, though the 95% confidence intervals for the risk estimates relative to nonusers overlapped (6.3 [95% CI 2.9 – 13.7]) for DRSP and 3.6 (2.9 – 4.6) for levonorgestrel.[8] These latter two studies demonstrated that the risk of

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VTE was greatest during the earlier time period after initiation of use. Recently, two case-control studies were reported that utilized electronic data and analyzed only idiopathic cases of VTE. Parkin conducted a nested case-control study in 61 cases of idiopathic VTE and 215 matched controls utilizing the UK General Practice Research Database.[9] The odds ratios for VTE adjusted for body mass index was 3.3 (95% CI 1.4 – 7.6) in current users of DRSP relative to current users of levonorgestrel-containing CHCs. Jick conducted a nested case-control and cohort study in 186 idiopathic cases of VTE and 681 controls utilizing data from PharMetrics, a United States based company that collects information on claims paid by managed care plans.[10] The age-adjusted incidence rate ratio for venous thromboembolism for current use of DRSP containing CHCs compared with those containing levonorgestrel was 2.8 (2.1 – 3.8). Women under the age of 30 years had a higher risk than older women.

Jick has published several papers reporting on the risk of VTE associated with norelgestromin – containing CHCs (NGMN) relative to norgestimate CHCs (NGM) in a nested case-control study using data from the IMS/PharMetrics database.[11-13] The early findings showed no significant increase in risk with NGMN, but in the most recently collected set of 38 cases NGMN was associated with a 2.41 (95% CI 1.17 – 4.97) increased risk of VTE relative to NGM. However, the cumulative pooled findings for 162 total cases (including the 38 new ones) still do not show an increased risk associated with NGMN [OR 1.23 (95% CI 0.86 – 1.77)]. Jick conducted a similar study examining the risk of idiopathic VTE in users of the patch with users of levonorgestrel-containing OCs using the PharMetric/IMS and MarketScan databases. In both cases, no statistically significant increased risk of VTE was associated with the NGMN patch relative to levonorgestrel.[14] Jick also used the Pharmetrics database to examine the risk for acute myocardial infarction and ischemic stroke associated with the NGMN

patch relative to norgestimate-containing CHCs.[15] The case numbers were small (8 for

myocardial infarction and 18 for stroke) and no increased risk was found for NGMN.

Cole and later Dore conducted a retrospective cohort study to compare the incidence of

cardiovascular disease outcomes among users of transdermal patches and

norgestimate-containing CHCs utilizing data from the UnitedHealthcare database.[16, 17]

Use of the transdermal patch was associated with a two-fold increase in the risk of VTE

relative to the use of norgestimate. There was no association with risk of either acute

myocardial infarction or stroke.

In summary, the studies suggest that the NGMN transdermal patch likely

increases the risk of VTE relative to standard OC formulations. The results from studies

of DRSP are mixed. However, the majority of them (4 of 6), all conducted

retrospectively, demonstrate an increase risk of VTE with the use of DRSP-containing

CHCs suggesting that this association may be real.

None of the reported studies found an increased risk of any of these newer

CHCs with MI or stroke. We conducted this retrospective exposure cohort study to

evaluate use of contraceptive product in a population of prevalent and new users to

assess the public health impact, patterns of use, and other factors related to use that

could place a woman at greater risk for a thromboembolic event and/or death.

Consequently, the objectives were:

- To determine prevalence and incidence rates for venous and arterial
  thrombotic and thromboembolic events (VTE and ATE) and all-cause and
  cause-specific mortality in women exposed to 3 newer hormonal
  contraceptives compared to older frequently prescribed low estrogen
  hormonal contraceptives.

- Identify medical, pharmacological, and behavioral characteristics from claims and medical records to assess predictors of increased risk for VTE, ATE, and death.

Methods

Study data

Study data were obtained from the computerized files of four study sites including Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), Tennessee State Medicaid (Vanderbilt), and Washington State Medicaid (University of Washington). The study files included enrollment data (health plan or Medicaid), demographic information, ambulatory prescriptions from pharmacy records or claims, hospitalization and outpatient visit data with diagnoses from health plan records or claims, and mortality obtained from state mortality files. The study was approved by the institutional review boards at each of the four participating institutions.

Study participants

At each site except Washington, the cohort identification process outlined included the following steps:

1. Identification of all CHC prescriptions from 7/1/2000 [6 months prior to cohort inception date) through 12/31/2007 [end date for cohort identification].

2. Link membership file to CHC prescription file to create one file per member with all CHC prescriptions filled during this time period.

3. Individuals were then excluded from the data set formed by steps 1 and 2 for any of the following criteria:

    a. Gender was male;

    b. No study CHC was prescribed during the study period;

c. Age was <10 years or ≥56 years (and 0 days) on the date the first study CHC was filled during the study period;

d. Less than 182 days of continuous membership prior to the date of all study CHC prescription use during the study period (1/1/2001 through 12/31/2007).

At Washington, in order to comply with state IRB requirements, the process differed in that, first, only Medicaid membership files for the years 2000 – 2007 were analyzed. Any woman who was in the study age range at any time during 2000-2007 and had at least 5 months (plus one day) of eligibility (for medical and drug benefits) during any moving 6-month period during the time frame July 1, 2000 to December 31, 2007 was selected for possible inclusion in the study. All prescription and medical claims for the years 2000-2007 for these women were then obtained and analyzed (together with membership data) as described above.

In addition, a woman was excluded if a serious or life threatening illness (sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, severe congestive heart failure (CHF), renal failure, respiratory failure, or hospitalization for acute myocardial infarction, stroke, or venous thromboembolic disease) was documented during the pre-exposure eligibility period. Criteria for these illnesses include one (or for CHF, two) inpatient claim(s) for the exclusion disease (claims can have either ICD-9 codes or procedure codes), with the claim of interest appearing anywhere in the primary and secondary diagnoses or two outpatient claims separated by at least 30 days for the exclusion disease. [see Appendix B]

Follow-up

Follow-up was evaluated independently for each of the study outcomes (ATE, VTE, CVD death, and total mortality). End of follow-up for each woman in the cohort was defined as the first of the following dates:

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a. Last date of continuous membership. Administrative enrollment gaps of no more than one month (31 days) were allowable. Cohort members could have one or more periods of administrative eligibility during the study period. For the all user analysis, a second period of eligibility would begin if a cohort member re-enrolled after a period greater than an administrative enrollment gap.

b. 42 days after the date of the end of a period of prescription use (the period of time covered by a prescription[s]) of a study CHC (i.e., an exposure period is a prescription period plus the 42 days after the date of the end of the prescription period. As noted in "a." above, cohort members could have one or more periods of study CHC eligibility during the study period. For the all use analyses, a second period of use would begin if another study CHC prescription was filled after the first CHC period of use. Study subjects were considered censored at the end of the first exposure period for the new use analyses.

c. Development of study endpoint.

d. End of study follow-up 12/31/2007.

e. Date of 56th birthday.

f. First date of pregnancy period.

Pregnancy

Since there was no way to objectively assess when a woman was pregnant, periods of pregnancy were estimated in relation to two outcomes, abortion and delivery. Abortion outcomes were identified as ICD9 codes 630-641 and delivery codes were ICD9 codes 642.x1-649.x1, 642.x2-642.x2, 650-669, 670.x1-677.x1, 670.x2-677.x2, and V27. For each abortion, we estimated the period of pregnancy to include 120 days prior

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to the date of the abortion and we also excluded CHC exposure and events occurring within 42 days after the abortion. For each delivery, we estimated the period of pregnancy to include 270 days prior to the date of the delivery and we also excluded CHC exposure and events occurring within 42 days after the delivery.

Study Combined Hormonal Contraceptives (CHCs)

CHCs and other drugs used in the analysis were identified from pharmacy records which included drug name, date of prescription, date of dispensing, dose, quantity and days supply. Seven CHCs were identified for the evaluation of CVD risk (Table 1). Three exposure CHCs for which questions had been raised regarding increased atherothrombotic venous thrombotic risk (NGMN transdermal patch, ETON vaginal ring, and DRSP pill) were selected to be compared with 4 low estrogen content CHCs (20 – 35 µg ethinyl estradiol). We will refer to the NGMN transdermal patch, ETON vaginal ring, and DRSP pill as the exposure CHCs and the 4 other study CHCs as the comparator CHCs.

Study Definitions

1. ***Prescription period use***. The dates that are covered by a prescription or series of prescriptions for a single study CHC. The dates may be adjusted according to the considerations noted in this section.

2. ***Indeterminate use*** is the 42 day period of time immediately after a prescription period.

3. ***Exposure period*** to a CHC includes the prescription period use plus the period of indeterminate use and is also referred to as current use. The rationale to extend the exposure period for 42 days after the end of the actual prescription period is primarily to account for biological effects that might persist after use of the CHC, mostly notably increased coagulability.

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4. ***Switcher use*** refers to the filling of a prescription for a second study CHC during the indeterminate use period of another study CHC. Switcher use ends at the end of the 42 day period of indeterminate use. Since this resulted in a very small proportion of exposure (2%) and very few endpoints occurred during periods of switcher use (n=22 out of 1,071), we considered it as prescription period use in analyses rather than as a separate category of use.

5. ***Study period*** refers to the period of time over which study exposure periods and endpoints were assessed, January 1, 2001 through December 31, 2007.

6. ***Pre-exposure eligibility period*** refers to the 182 days (6 months) of continuous membership required before a study exposure period. Because the study period began on January 1, 2001, pre-exposure eligibility could be assessed as far back as 182 days prior to that date (i.e., July 3, 2000).

7. ***New use*** refers to the exposure period associated with first use of a study CHC during the study period. New use cannot be preceded by any CHC use, including non-study CHC use, during the study period or the pre-exposure eligibility period. The study subject was censored at the end of the first exposure period for the new use analysis.

8. ***All use*** (or prevalent use) refers to all study CHC exposures during the study period.

For clarification, schematic figures of definitions #1-4 are provided below for a CHC preparation. Figure 1a shows an exposure period composed of a prescription and indeterminate use periods. Figure 1b shows a period of switcher use.

Figure 1a.

```
|_____prescription period_____|__indeterminate__|
A                                   B                 C
```
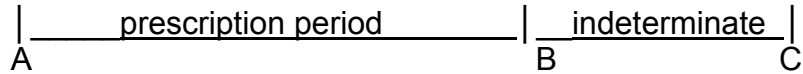
From A to B: prescription period of study CHC
From B to C: indeterminate use (42 days)
From A to C: exposure period.

Figure 1b.

```
CHC A
|_____prescription period_____|___indeterminate___|
A                                   B          D        C
```

```
                                         CHC B
                                         |switcher|prescription period

                                         D        C
```
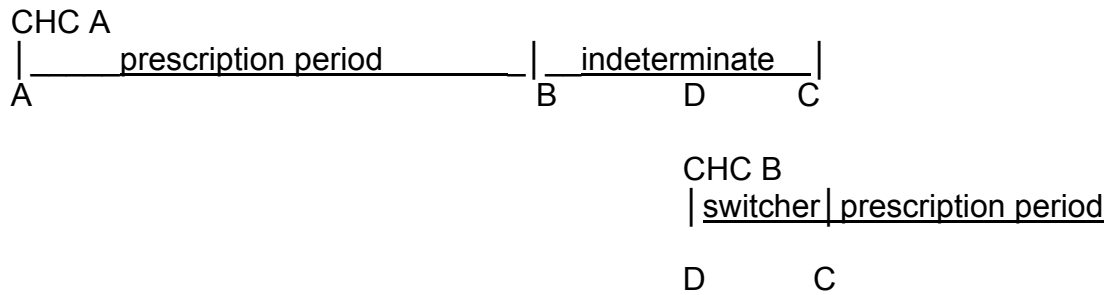
From A to B: prescription period of study CHC A
From B to C: indeterminate use (42 days) for CHC A.
From D to C: switcher use for study CHC B.

Exposure periods were calculated beginning with the fill date of the CHC prescription.   The duration of a prescription was calculated as the number of days that the prescription covered. If a second prescription for the same CHC was filled during the time period of the first prescription, then the start date of the second prescription would be adjusted to correspond to the day after the first prescription ended.   A rule was established to end the prescription period for a single study CHC no later than 14 days after the last day of the final prescription in a series for that CHC (i.e., 14 days after prescription period plus indeterminate use period). This was to prevent the possibility of very lengthy periods of time of study CHC use after the last of a sequence of prescriptions. In rare instances, these periods extended to several months after the exposure period associated with the last fill date of the prescription sequence and did not seem plausible.

If a second study CHC was filled during a prescription for another study CHC, then the first CHC prescription period was stopped and the second CHC started with the

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start date of the second CHC adjusted to a date that corresponded to the end of a normal cycle of use for the first CHC, generally 28 days. For example if the first CHC was started on February 1 for a period of 84 days and a second CHC was filled on March 14, then the first CHC would be stopped on March 28 (56 days = 28 x 2) days of use and the start date of the second CHC adjusted to March 29.   This is illustrated in figure 2 below.

Figure 2.

```
_____|_____|_____|CHC A stopped_____
   CHC A      day 28     day 42   day 56


CHC B recorded fill date   |————————————
                     day 42

CHC B adjusted start date            |_____
                              day 56
```
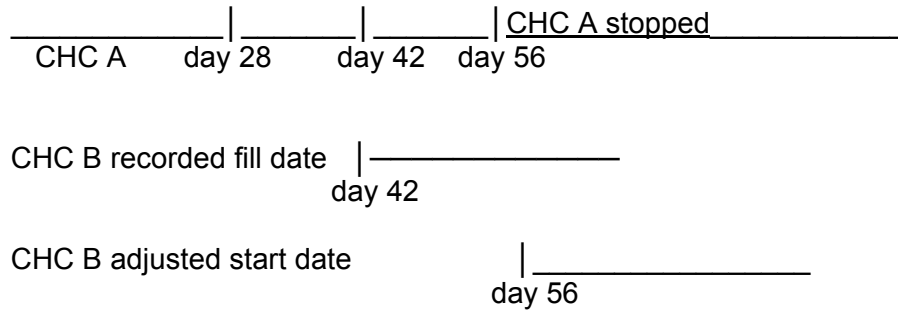
In this example, if the exposure period for first study CHC represented new use, then the new use period would end on March 28.

We did not include periods of non-study CHC exposure in the analysis dataset, but did consider them in constructing the study CHC exposure data so that non-study CHC use could impact on the actual dates of study CHC exposure by adjusting either the stop date or start date of a study CHC prescription period.

Study endpoints

The primary study endpoints were hospitalization for acute myocardial infarction, ischemic stroke, and venous thromboembolic disease (VTE) [including hospitalized deep venous thrombosis (DVT), hospitalized pulmonary embolism (PE), and DVT diagnosed as an outpatient]; and total mortality. We also assessed cardiovascular mortality.   All potential hospitalized cases were identified by the sites using the primary discharge codes as follow: AMI (410.x), stroke (430, 431, 432.0, 432.9, 433.x, 434.x, 436), and VTE (pulmonary embolism code 415.1 and DVT codes 451.1, 451.1x, 451.2,

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451.8, 451.81, 451.82, 451.84, 451.89, 453.0, 453.1, 453.2, 453.3, 453.4, 453.8, 453.9) [more detail in Appendix A]. Outpatient DVTs were identified by an outpatient diagnosis of DVT in conjunction with a first prescription for an anticoagulant (low-molecular weight heparin or warfarin) during the 30-day period subsequent to the diagnosis.

All cases were abstracted at the study sites using standardized criteria [see Appendix E for forms]. The key elements of the hospitalization medical record (e.g., admission and discharge summaries, laboratory tests, imaging study results) were de-identified and sent to KPNC for adjudication. Four physicians adjudicated the cases blinded to the CHC. A cardiologist reviewed all AMIs and a neurologist reviewed most of the stroke cases with the principal investigator doing the remaining adjudications. Cases for which the adjudication decision was not clear-cut were discussed with the principal investigator and a 10% sample of adjudicated cases was independently reviewed by another adjudicator blinded to the CHC. There were no disagreements between adjudicators on the 10% sample probably because the adjudicators were encouraged to bring difficult to adjudicate cases to discussion.

Medical records of outpatient DVTs from KPNC only were obtained and were adjudicated by the principal investigator. Of 103 potential outpatient DVTs not meeting any of the exclusion criteria, 92 met the criteria for definite / probable DVT (89.3% positive predictive value).

Mortality was assessed by linkage of membership data with state mortality files for all women in the study and for the entire study period. Cardiovascular mortality was defined by an ICD-10 code of I01 – I99 as the underlying cause of death. We also examined mortality from the main study CVD endpoints defined by the following ICD-10 codes as the underlying cause of death: acute myocardial infarction (I21.x – I23.x), ischemic stroke (I63.0 – I63.5, I65.x, I66.x), and VTE (I80.x, I81.x, I82.x).

The study endpoints that were evaluated in the statistical analyses were hospitalization for acute arterial thromboembolic event (AMI, ischemic stroke), hospitalized and outpatient VTE (all hospitalized validated VTEs, validated outpatient VTEs from KPNC, and all outpatient VTEs from the KPSC and the Medicaid sites), cardiovascular mortality, and total mortality. AMI and ischemic stroke were combined in the main analyses because of relatively small numbers of these events. We did not present most cardiovascular mortality analyses in the new user group because there was only one CVD death among the three exposure CHCs.

Covariates and confounders.

Covariates that were potential confounders or effect modifiers were ascertained from the electronic databases at each of the sites. Most of the common potential confounders for all CHCs were identified in studies where the comparison group for CHC users was compared to nonusers of CHCs. The covariates are listed along with how they were ascertained. [See Appendix A.]

Assessment of covariates of interest began during the 6-month period prior to a study CHC exposure period and continued to be assessed throughout the exposure period. Each covariate was analytically managed in one of 3 ways:

a. **Fixed (ever vs. never until end of all study follow-up):** Some medical conditions that are generally considered to be chronic were categorized as being present from the date they were first noted through the remainder of the study, i.e., from the exposure period in which they were identified through all subsequent exposure periods. For example, diabetes is a condition that fell into this category.

b. **Ever vs. never during study CHC exposure period**: Some medical conditions that were not chronic were categorized as being present from the date they were

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first noted throughout the remainder of the exposure period. For example,

cardiac arrhythmias fall into this category. These conditions would be included

as covariates for the study CHC exposure period in which they were identified

but would not be included as a covariate in subsequent study CHC exposure

periods unless they were re-identified during these exposure periods.

c. **Current vs. not current**: Some medications that may impact the risk of

cardiovascular disease endpoints (e.g. cardiovascular prevention medications

such as statins, ACE inhibitors, and warfarin) were evaluated in this manner, so

that covariate was "turned on" only during the prescription periods of these

medications and "turned off" when the prescription period was over. In addition,

some covariate exposures (major injuries and surgeries) were considered to

have an effect for only 6 weeks.

Figure 3 illustrates these analytic approaches in an individual who has 3 exposure

periods during the study.

Figure 3.

_____| Exposure 1 _____| Exposure 2 _____ Exposure 3|_____

●--
fixed until end of study follow-up (starts before exposure 1 and is present until the
end of follow-up)

●-----------------|
ever vs. never during exposure period (ends at end of
exposure 2)

●--------------------|
 current vs. non-current (ends with the end of time-varying
exposure midway during exposure 2)
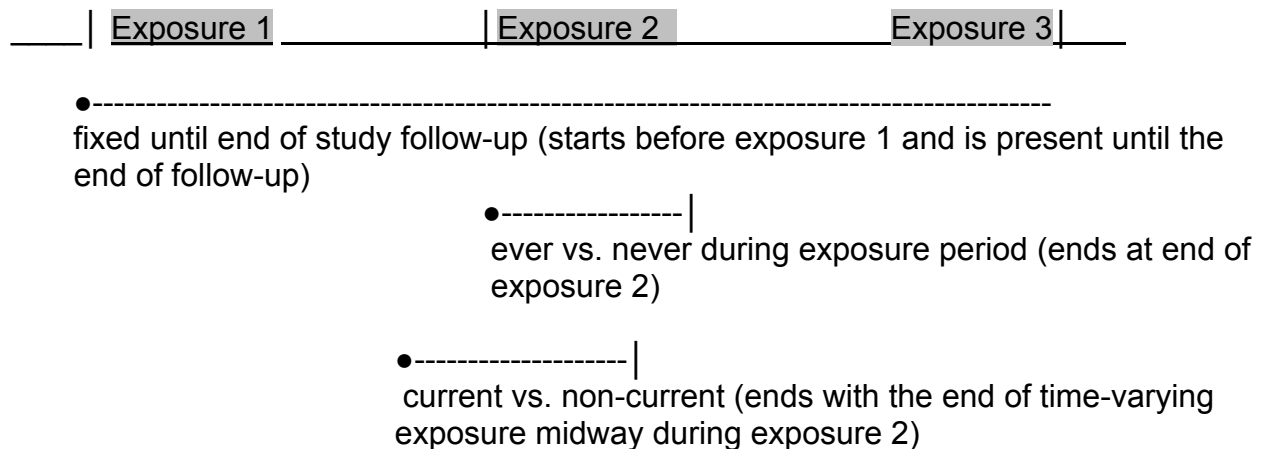
Statistical Approach

Cox proportional hazards regression was used to estimate the relative risk of

study endpoints associated with current use of study CHCs relative to the comparator

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CHCs. The Cox proportional hazards model accommodates unequal length of follow-up due to varying duration of CHC exposure, termination of health plan membership, and end of study (i.e. right censoring). Control for potential confounders at the study subject level can be implemented via inclusion of the covariate in the model, or via stratification. Changes in covariates during follow-up are also accommodated. CHC exposure was considered as a 4-level time-varying covariate, capturing current use of the NGMN transdermal patch, ETON vaginal ring, DRSP pill, and the 4 comparator CHCs combined as one category. Time since cohort entry (i.e. first day of first exposure period during study period) was the time scale in the Cox regression model. In the all users models, the periods without study CHC exposure were considered unobserved or window censored given that events were not ascertained during these periods.

We conducted age stratified Cox models, allowing for separate baseline hazards for each age category (5-year intervals), providing tight control for age and freeing us from specifying the form of the relationship between age and outcomes in the regression models. Additional control for potential residual confounding within age strata was achieved via inclusion of age as a continuous covariate in the regression model. Age, site, calendar year of entry into study were included in all models. In addition, established CVD risk factors (hypertension, hyperlipidemia, and diabetes mellitus) were included as fixed covariates in models that included ATE or CVD mortality as outcomes. Each of the other potential covariates was tested individually in these base models with a decision to include it in further model testing if the estimate of relative risk associated with any of the study CHCs (vs. comparators) was changed by 10% or more. None of the covariates met this criterion for any of the models so that none were included in final modeling. Because hypertension is in the causal pathway between CHC use and

AMI/stroke, we ran models with and without hypertension. We kept it in the models for ATE because it minimally affected the risk estimates associated with the study CHCs.

Cox proportional hazards modeling was conducted to estimate the relative risks in all users and new users. Modeling was conducted with all four of the comparators CHCs (LGN1, LGN2, NETA, and NGM) combined and with the four comparators kept separate in the model. While the main analyses were planned using the combined comparators, the separation of the comparators in the analyses enabled the estimation of the risks associated with DRSP relative to LGN2, since these preparations both contained exactly 30 µg of EE while two of the other comparators contained less than 30 µg of EE (LNG1 and NETA) while one contained more (NGM with 35 µg EE). Associations of new use and of all use of CHCs with study endpoints were examined within age strata (10-35 years and 36-55 years) and within site strata (KP and Medicaid sites).

The new user analyses were confined to the subset of women entering the cohort with exposure to any study CHC or comparator and with no previous use of any study CHC or comparator or non-study contraceptive during the prior 6 month cohort entry eligibility interval. In the new user analysis, follow-up ended for each woman at date of end of exposure to the cohort entry study CHC or comparator. The relative risk of study endpoints associated with current use of each study CHC relative to the comparator CHCs by duration of use was examined in the new user cohort (up to 3 months [1-84 days], 3-6 months [85-168 days], 6 -12 months [169-365 days], and >12 months [>365 days]). All analyses were conducted with SAS.

Age- and site-adjusted rates were calculated using direct adjustment with the age distribution of the entire study population at cohort entry as the standard (age groupings

10-24, 25-34, 35-44, 45-55 years). Age- and site-adjusted incidence rate ratios were estimated using Poisson regression modeling.

We also calculated incidence rates of study endpoints in the analysis dataset in order to compare them to published rates for this age group of women.

Results

Case identification and validation. After exclusion criteria were applied, a total of 947 potential hospitalization endpoints (92 AMIs, 241 strokes, 614 VTEs) were identified.   Of these, 543 were determined to be valid cases for the analytic datasets (60 MIs, 78 strokes, and 405 VTEs).   Additionally, 220 outpatient DVTs were included in the analytic data set after exclusions were considered. A summary of the case disposition is provided in Table 2b.

Exposure periods and length of follow-up.   There were 835,826 women in this study cohort. The age distribution of the women in this study is shown in Table 3.   The KP sites had a larger proportion of women 35 to 55 years and consequently a higher mean age (29.0 and 29.1 years, respectively) than the Tennessee and Washington sites (23.2 and 22.9 years).

The distribution of the first study CHC used during the study period by age is shown in Table 4a1 for all use. This includes all new use, and in addition includes the first use of a study CHC after use of non-study CHC or of a study CHC initiated during the pre-exposure eligibility period. Over 50% of users were younger than 25 for NGMN, DRSP, ETON, NGM, and LNG1 whereas more than 45% of NETA users (containing only 20µg EE) were 35 years of age or older.   The distribution is shown stratified by KP and Medicaid (Tables 4a2 and 4a3) and by each of the 4 sites (Tables 4a4-4a7).

Table 4b1 shows the distribution of the first study CHC used during the study period by age in new users only.   This distribution is also shown stratified by KP and Medicaid sites (Tables 4b2 and 4b3) and by each of the 4 sites (Tables 4b4-4b7). DRSP was the most commonly used exposure CHC at KP sites while the NGMN patch was the most commonly used exposure CHC at the Medicaid sites.

The distribution of the duration of new use of exposure and of comparator CHCs is shown in Table 5. There were 573,680 periods of new use, representing 68.6% of the women in the study, with total exposure time of 367,138 person-years. The mean number of days of new use for the pill preparations (DRSP and comparators) was substantially longer than that for the continuous exposure preparations, the CHC patch (NGMN) and vaginal ring (ETON).

The mean duration of cumulative use of each of the study CHCs during the study period is shown in Table 6 along with the distribution of prescription period (84.5% of all use) and indeterminate (15.5%) use. As noted, switcher use (not shown) comprised 2.0% of all use and was included in prescription period total.   835,826 women in the cohort had a total of 2,113,298 exposure periods to study CHCs (Table 2a) with total exposure time of 898,251 person-years (Table 6, mean exposure period 155 days).

The prevalence of 38 covariates in new users only and in all users is shown in Tables 7a and 7b. The prevalence of most covariates was low, with most occurring in fewer than 1% of women. In general, especially for new users, the prevalence of the covariates tended to be higher in users of comparators than in users of the study CHCs. The most highly prevalent covariate was NSAID use which ranged from about 17% to 20% among new users and from 23% to 27% for all users. The prevalence of covariates in the 10-34 years and 35-55 years age groups is included in Appendix B.

The distribution of study endpoints by current, indeterminate and switcher user status is presented in Table 8. Since only 16% of cases occurred during the indeterminate/switcher period, we did not perform further analyses on this group. As noted earlier, switcher use was re-categorized as current use for the CHC that was switched to during the period of indeterminate use (all user analyses only). Current use in the analytic models included both the prescription period and the 42 days of indeterminate use after it, as noted earlier.

The overall incidence of all endpoints is shown in Table 9 for all users (Appendix B includes overall incidence for new users). The age-specific incidence of each of the study endpoints and the age-site adjusted rates are shown in Table 10a – 10d along with the age-adjusted rates and incidence rate ratios. The incidence rate ratios (IRR) for VTE (Table 10B) were significantly higher for each of the study CHCs relative to use of the combined comparators in all users. The IRR was also significantly higher for DRSP relative to use of LNG2 in all users and to both combined comparators and LNG2 alone in new users.

Tables 11a – 11d show the age and site adjusted incidence rates for each of the study CHCs and comparators by duration of use (0-3 months, 4-6 month, 7-12 months, >12 months). For VTEs (Table 11b), The IRR for DRSP relative to the comparators was significantly higher than 1 for 0-3 months duration [IRR 1.93 (95% CI 1.26-2.95)] and for 7-12 months duration [IRR 2.90 (95% CI 1.59-5.28)] relative to the combined comparator group. With LGN2 as the comparator, there also was an increase at 7-12 months [2.11 (95% CI 1.02-4.38)]. These findings suggest that there may be an increase in risk of VTEs with DRSP during the early stages of new use relative to the risk from comparators as well as later (7-12 months). The IRRs and 95% CI for ATE

and total mortality could not be calculated with the Poisson model because the model did not converge due to small cell sizes.

Tables 12 through 14 represent a summary of the results of proportional hazards modeling. For all users, the risk of VTEs was higher than 1 with each of the study CHCs relative to the grouped comparators for all use, ranging from 1.55 (95% CI 1.17-2.07) for the NGMN patch to 1.56 (95% CI 1.02-2.37) for the ETON vaginal ring and 1.74 (95% CI 1.42-2.14) for DRSP. For new use, the risk of VTEs was only higher than 1 for DRSP. With LNG2 as the comparator, the risk of VTE was increased with DRPS in all users [OR 1.45 (95% CI 1.15=1.83)] and new users [OR 1.57 (95% CI 1.13, 2.18)] and not significantly increased with the other exposure CHCs. We also examined evaluated the risk for hospitalized VTEs only (n=405) and determined that the relative risk estimates were similar to those for all VTEs (hospitalized and outpatient combined). The risk for ATEs was increased in new users of DRSP [OR 2.01 (95% CI 1.06, 3.81)] but was not increased in the all user analysis for DRSP.

As expected, the relative risk estimates DSRP for duration of new use with all VTEs were consistent with the IRRs shown in Table 11b (Table 13b1) and were significantly higher than one for <3 months [OR 1.93 (95% CI 1.24, 3.00)] and 6-12 months [OR 2.80 (95% CI 1.48, 5.29)] relative to the grouped comparators.

For NGMN, duration of >12 months of new use was associated with a 3-fold increase in risk of VTE relative to >12 months of combined comparator use. With LNG2 as the comparator, an increased risk was present in both the <3 month and >12 months groups. For ETON, an increase in risk for ATE was found with use >12 months; however, this was based on only 1 case of ATE in the ETON users and probably should be ignored. We did not include a table for CVD mortality because many of the cells in

the table were empty due to the low number of events and no change in risk with the exposure CHCs was found for the non-empty cells.

Since the KP sites (KPNC and KPSC) and the Medicaid sites (Vanderbilt and Washington) had such large demographic differences, we performed stratified analyses within the 2 pairings of sites (Tables 14a-14d).   We did not include the CVD mortality results for the same reason noted for Table 13. The direction of the relative risk patterns for VTE were consistent between the site pairings, but the hazard ratio estimates were higher for the KP sites than the Medicaid sites for all three study CHCs and were also statistically significant only at the KP sites relative to the combined comparator group. With LNG2 as the comparator group, the above findings were also present with the exception of the increased risk of VTE for all users in ETON users. For new users, the relative risk estimates for VTE were higher and statistically significant at the KP sites for DRSP and NGMN only relative to both the combined comparator group and to LNG2. In addition, DRSP and NGMN use were associated with a higher risk of ATE relative to the combined comparator sites at KP sites only, with DRSP also associated with higher risk of ATE with LNG2 as the comparator. The test for interaction by site in new users was significant for DRSP only at the p<0.001 level in the VTE analysis with group comparators.

We performed a similar stratified analysis based on age, evaluating risk within the age strata 10-34 and 35-55.   The risk of VTE for all 3 study CHCs were higher in the younger than in the older age group for all users. With LNG2 as the comparator, the relative risk of VTE for DSRP and ETON only were increased in the 10-34 year strata for all users. For new users, the only significantly increased risk for VTE associated with DRSP use was in the 10-34 years age group relative to both the combined comparator and LNG2 groups. There was also an increased risk of ATE associated

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with DRSP use in those 35 years and older.   Interaction terms for age were significant for DRSP for both VTE and ATE (p<0.001) and for NGMN with VTE.

Discussion

The main findings of this study are that all use of the DRSP pill and each of the continuous exposure preparations, the NGMN patch and the ETON vaginal ring, are associated with an increased risk of VTE relative to the standard low-dose OCPs. New use of the DRSP pill is also associated with increase of VTE as is the first 3 months of new use relative to that of the comparators. DRSP was associated with higher risk of ATE in new users overall but this finding was restricted to women in the 35-55 years age group only, Many of the study findings also apply when LNG2 alone was used as the comparator in the analyses. None of the potential confounders that we assessed significantly impacted the risk estimates.

The KP sites and the Medicaid population sites were substantially different. The Medicaid site population was considerably younger than the KP sites and had higher rates of comorbidities (not shown).   There was a significant interaction with site (KP vs. Medicaid) for current DRSP use with VTE, with the risk estimates for DSRP higher in the KP than in the Medicaid sites. It is unclear why this is the case. It is possible that important unmeasured confounders, most notably smoking and obesity, may differ between the sites, and be higher among KP CHC users though this seems unlikely. Another possible explanation is that compliance might differ between the sites. Higher compliance should be associated with higher risk of VTE. Finally, there may be differences in prescribing patterns for which we do not have information.

There was also a significant interaction with age (<35 years vs. 35+ years) with a higher risk of VTE in younger relative to older women in current DSRP users and a

lower risk of ATE in younger relative to older women. This is consistent with a finding from Jick's study.[10] A possible contributor to this finding is the probability that older users even if defined as new users for this study, are less likely to be naïve users of CHCs or other hormone preparations and therefore are less likely to experience a cardiovascular disease endpoint while taking a CHC. The lower risk of ATE found in younger relative to older women would be inconsistent with this hypothesis.

The positive finding for the NGMN patch in relation to VTE provides an additional piece of evidence that this is a causal association, though there are few studies published that address this question (references 11-13 represent one study, while14, 16-17 represent one study). For DRSP, the positive finding regarding VTE risk in this study adds to what is becoming an increasingly clear picture. One primary reason to examine DRSP in this study was because of the possible link that has been raised between DRSP and cardiac arrhythmias and possible acute myocardial infarction or cardiovascular death. No association was found for these endpoints, in part due to the low number of MI endpoints. DRSP has anti-mineralocorticoid properties. The finding that aldosterone may modify hemostasis leading to decreased coagulabilty provides a potential mechanism by which DRSP may result in a greater thrombotic tendency than other CHCs. [20]

The main strengths of the study include the large population size and number of events for one of the outcomes, venous thromboembolic diseases; the standardized protocol; and the validation of most of the electronically identified study endpoints with the exception of outpatient DVTs. The incidence rates of MI, stroke, and VTE are consistent with other published rates.[18,19]

Limitations of the study include the reliance on electronic pharmacy data to ascertain the CHC exposures as well as the covariates, absence of data on key

covariates (obesity/BMI, smoking, family history) and the validation of outpatient DVTs by chart review was conducted at only one site though with high positive predictive value. It is difficult to make inferences from electronic medical data because of assumptions that need be made to create an analytic dataset, e.g. the exposure periods to CHCs that are calculated may not represent the actual usage patterns and the estimate of pregnancy dates may be inaccurate. Furthermore, unless an electronic data source has had adequate quality control evaluation, the validity of the data may be suspect. The relatively small number of acute myocardial infarctions and strokes limited power for analyses of these outcomes, though the rates of these outcomes were consistent with published data.

In conclusion, the study results add strength to the likelihood that the NGMN transdermal patch results in higher risk for VTEs than standard CHC pills and provides another positive finding to the increasing body of evidence linking DRSP to increased risk of VTE relative to standard CHC pills. DRSP was associated with higher risk of ATE in new users overall with this finding restricted to women in the 35-55 years age group only, The finding of increased risk of VTE with the ETON vaginal ring relative to standard CHCs is new and raises concern but needs to be replicated in other studies.

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Table 1. Study Combined Hormonal Contraceptive (CHCs)

Acronym	Combination	Dose	Generation progestin
Exposure CHCs			
DRSP	Drospirenone / ethinyl estradiol tablets	3.0 mg of drospirenone and 30 µg of ethinyl estradiol	4
NGMN	Norelgestromin / ethinyl estradiol transdermal patch	6.0 mg norelgestromin (NGMN) and 750 µg ethinyl estradiol (EE)	3
ETON	Etonogestrel / ethiniyl estradiol vaginal ring	11.7 mg etonogestrel and 2700 µg ethinyl estradiol	3
Comparator CHCs			
LNG1	Levonorgestrel / ethinyl estradiol	0.10 mg of levonorgesetrel and 20 µg of ethinyl estradiol	2
LNG2	Levonorgestrel / ethinyl estradiol	0.15 mg levonorgestrel and 30 µg ethinyl estradiol	2
NETA	Norethindrone / ethinyl estradiol	1 mg norethindrone acetate and 20 µg ethinyl estradiol	1
NGM	Norgestimate / ethinyl estradiol	0.18 – 0.25 mg of norgestimate and 35 µg of ethinyl estradiol	3

Table 2a. Accounting Eligible Women and Exclusions[1]

	Site				
	KPNC	**KPSC**	**Vanderbilt**	**Washington**	**Total**
# women and prescriptions prior to cohort formation					
# Women ages 10-55 years	356,002	335,878	162,475	104,441	958,796
# Prescriptions for study CHCs, 1/1/01 – 12/31/07*	1,996,644	1,641,482	1,279,005	645,632	5,562,763
# Women excluded prior to cohort formation					
Gender male/ other/unknown	629	0	637	0	1,266
Age $\leq$ 10 years or >55 years on date of first study CHC	1,731	261	614	33	2,639
Ineligible membership[2]	10,108	14,223	2,353	18,738	45,422
Membership < 6 months prior to all study CHC use	18,931	20,977	8,269	5,596	53,773
# Women excluded after cohort formation (# potential[3] cases excluded)					
Pregnancy	1,279 (3)	1,123 (2)	4,055 (23)	2,770 (4)	9,227 (32)
Medical exclusion[4]	5,076 (18)	1,971 (17)	3,815 (31)	1,842 (23)	12,704 (89)
Combination CHC exposure[5]	373 (0)	397 (0)	1,449 (5)	111 (0)	2,330 (5)
Analytic cohort composition					
# women in all user dataset	320,773	297,170	142,532	75,351	835,826
# exposure periods (all users)	783,977	698,097	427,652	203,572	2,113,298
# person-years (all users)	404,660	330,807	115,114	47,669	898,251
# women in new user dataset	213,487	202,167	100,235	57,791	573,680
# exposure periods (new users)	213,487	202,167	100,235	57,791	573,680
# person-years (new users)	159,431	136,096	48,267	23,344	367,138

1. Total of number of women excluded is lower than total of the exclusion categories because of overlap in the 2nd-4th exclusion criteria (not age 10-55 years, ineligible membership, membership<6 months)
2. Outside of eligible dates of follow-up or missing membership data.
3. "Potential" cases means that the cases have not been validated so may not be true cases.
4. See Appendix A for further detail on medical exclusions.
5. Only study prescription(s) are for two CHC prescriptions that exactly overlap in dates.

Table 2b. Accounting of endpoints

ENDPOINTS	KPNC	KPSC	VAND	WASH	TOTAL
ACUTE MYOCARDIAL INFARCTION					
Total # potential cases identified for review	**30**	**30**	**29**	**3**	**92**
Reason Case not Abstracted/adjudicated					
No Hospitalization	3	7	1	0	11
No Endpoint Identified	0	1	0	0	1
Medical Records Unavailable	0	2	6	0	8
Total # cases not Abstracted/Adjudicated	**3**	**10**	**7**	**0**	**20**
Total # cases adjudicated	**27**	**20**	**22**	**3**	**72**
Reasons for exclusion					
Not validated as endpoint*	2	1	7	2	12
Total # cases excluded	**2**	**1**	**7**	**2**	**12**
Total # hospitalized cases analytic dataset	**25**	**19**	**15**	**1**	**60**

*See Appendix A for further detail on case validation.

Table 2b. Accounting of endpoints (cont.)					
ENDPOINTS	**KPNC**	**KPSC**	**VAND**	**WASH**	**TOTAL**
STROKE					
Total # potential cases identified for review	**65**	**69**	**92**	**15**	**241**
Reason Case not abstracted/adjudicated					
No Hospitalization	5	6	0	0	11
No Endpoint Identified	5	3	0	3	11
Medical Records Unavailable	0	0	19	0	19
Infant Strokes	0	0	5	0	5
Trauma	0	0	9	0	9
Total # cases not Abstracted/Adjudicated	**10**	**9**	**33**	**3**	**55**
Total # Cases Adjudicated	**55**	**60**	**59**	**12**	**186**
Reasons for exclusion					
Subarachnoid hemorrhage	7	7	3	2	19
Intracerebral hemorrhage	4	3	4	1	12
Venous thrombosis / AVM	5	4	3	0	12
Other stroke	0	2	0	0	2
Head / brain trauma	3	2	3	0	8
Not validated as endpoint*	8	9	32	6	55
Total # cases excluded	**27**	**27**	**45**	**9**	**108**
Total # cases for analytic dataset	**28**	**33**	**14**	**3**	**78**
VENOUS THROMBOEMBOLISM					
Total # potential cases identified for review	**181**	**174**	**198**	**61**	**614**
Reason Case not abstracted/adjudicated					
Medical record not available	0	0	34	12	46
No Hospitalization	19	6	0	0	25
Trauma (identified at site)	0	0	7	0	7
Infant (identified at site)	0	0	0	2	2
Total # cases not Abstracted/Adjudicated					
Total # hospitalized cases adjudicated	**162**	**168**	**157**	**47**	**534**
Reasons for exclusion					
Not validated as endpoint*	38	20	57	14	129
Total # cases excluded	**38**	**20**	**57**	**14**	**129**
Total # hospitalized cases analytic dataset	**124**	**148**	**100**	**33**	**405**
Total # outpatient DVTs	**92**	**79**	**15**	**34**	**220**
Total # cases for analytic dataset	**216**	**227**	**115**	**67**	**625**

*See Appendix A for further detail on case validation.

Table 3. Distribution of Age at first study CHC use in all users.

Age Groups per Site	Number of Women										Total n
	10-14		15 - 24		25 - 34		35 - 44		45-55		
	N	%	n	%	n	%	n	%	n	%	
KPNC	4324	1.3	125695	39.2	110912	34.6	57600	18.0	22242	6.9	320773
KPSC	2843	1.0	115229	38.8	105271	35.4	52749	17.8	21078	7.1	297170
VAND	7652	5.4	90229	63.3	34437	24.2	8669	6.1	1545	1.1	142532
WASH	4362	5.8	47211	62.7	18824	25.0	4193	5.6	761	1.0	75351
Total	19181	2.3	378364	45.3	269444	31.0	123211	14.7	45626	5.5	835826

Tables 4a1. First study CHC used by age: All Users – All Sites
(COMP includes all 4 comparators in Tables 4a1-4a7)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	N	%	n	%	n	%		
DRSP	3251	2.3	67837	47.7	49359	34.7	18254	12.8	3465	2.4	142166	25.9 (8.0)
NGMN	2765	3.3	49080	59.2	24252	29.2	6122	7.4	718	0.9	82937	23.6 (6.9)
ETON	153	0.6	12141	49.7	9101	37.2	2534	10.4	516	2.1	24445	25.8 (7.2)
LNG1	2588	6.3	22137	54.1	10522	25.7	4284	10.5	1369	3.3	40900	*24.3 (8.6)*
LNG2	3615	1.8	80149	40.3	68713	34.6	35957	18.1	10405	5.2	198839	*27.9 (8.9)*
NETA	1585	1.1	34329	24.9	36896	26.7	38373	27.8	26757	19.4	137940	*33.4 (10.6)*
NGM	5224	2.5	112691	54.0	70601	33.8	17687	8.5	2396	1.1	208599	*24.5 (7.0)*
COMP	*13012*	*2.2*	*249306*	*42.5*	*186732*	*31.9*	*96301*	*16.4*	*40927*	*7.0*	*586278*	*27.7 (9.4)*
TOTAL	19181	2.3	378364	45.3	269444	32.2	123211	14.7	45626	5.5	835826	

Table 4a2. First study CHC used by age: ALL Users – KP Sites

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	n	%	n	%	n	%		
DRSP	2176	1.8	56693	45.9	44366	35.9	17011	13.8	3290	2.7	123536	26.30 (8.0)
NGMN	299	1.0	13113	43.6	12002	39.9	4140	13.8	538	1.8	30092	26.56 (7.5)
ETON	21	0.1	5492	38.9	6075	43.1	2057	14.6	456	3.2	14101	27.71 (7.4)
LNG1	61	0.9	2362	33.4	2693	38.1	1327	18.8	620	8.8	7063	29.60 (9.0)
LNG2	2254	1.4	61013	36.8	59197	35.7	33400	20.1	9974	6.0	165838	28.67 (9.0)
NETA	1028	0.8	29850	23.1	34531	26.8	37257	28.9	26339	20.4	129005	33.95 (10.4)
NGM	1328	0.9	72401	48.8	57319	38.6	15157	10.2	2103	1.4	148308	25.67 (6.4)
COMP	*4671*	*1.0*	*165626*	*36.8*	*153740*	*34.1*	*87141*	*19.4*	*39036*	*8.7*	*450214*	*29.21 (9.4)*
TOTAL	7167	1.2	240924	39.0	216183	35.0	110349	17.9	43320	7.0	617943	

Table 4a3. First study CHC used by age: ALL Users, Medicaid Sites

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	N	%	n	%	n	%	n	%	n	%		
DRSP	1075	5.8	11144	59.8	4993	26.8	1243	6.7	175	0.9	18630	22.92 (8.0)
NGMN	2466	4.7	35967	68.1	12250	23.2	1982	3.8	180	0.3	52845	21.98 (6.0)
ETON	132	1.3	6649	64.3	3026	29.3	477	4.6	60	0.6	10344	23.27 (6.0)
LNG1	2527	7.5	19775	58.4	7829	23.1	2957	8.7	749	2.2	33837	23.22 (8.1)
LNG2	1361	4.1	19136	58.0	9516	28.8	2557	7.7	431	1.3	33001	23.75 (7.2)
NETA	557	6.2	4479	50.1	2365	26.5	1116	12.5	418	4.7	8935	25.12 (7.0)
NGM	3896	6.5	40290	66.8	13282	22.0	2530	4.2	293	0.5	60291	21.65 (6.4)
COMP	*8341*	*6.1*	*83680*	*61.5*	*32992*	*24.2*	*9160*	*6.7*	*1891*	*1.4*	*136064*	*22.78 (7.3)*
TOTAL	12014	5.5	137440	63.1	53261	24.4	12862	5.9	2306	1.1	217883	

Table 4a4. First Study CHC used by age: ALL Users for KPNC Site

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	N	%	n	%	n	%	n	%	n	%		
DRSP	1348	2.0	30531	46.2	23349	35.3	9168	13.9	1731	2.6	66127	26.19 (8.1)
NGMN	154	1.7	4458	49.8	3141	35.1	1061	11.9	130	1.5	8944	25.37 (7.6)
ETON	5	0.1	1427	39.5	1653	45.7	431	11.9	100	2.8	3616	27.39 (7.0)
LNG1	11	0.7	502	30.3	677	40.9	302	18.2	163	9.8	1655	30.08 (8.9)
LNG2	1399	1.5	34527	37.0	34334	36.7	18440	19.7	4727	5.1	93427	23.89 (7.8)
NETA	540	0.8	15031	22.1	18076	26.6	20039	29.5	14283	21.0	67969	34.23 (10.4)
NGM	867	1.1	39219	49.6	29682	37.6	8159	10.3	1108	1.4	79035	25.54)7.0)
COMP	*2817*	*1.2*	*89279*	*36.9*	*82769*	*34.2*	*46940*	*19.4*	*20281*	*8.4*	*242086*	*29.11(9.4)*
TOTAL	4324	1.3	125695	39.2	110912	34.6	57600	18.0	22242	6.9	320773	

Table 4a5. First Study CHC used by age: Users for KPSC Site

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	N	%	n	%	n	%		
DRSP	828	1.4	26162	45.6	21017	36.6	7843	13.7	1559	2.7	57409	26.19 (7.9)
NGMN	145	0.7	8655	40.9	8861	41.9	3079	14.6	408	1.9	21148	27.06 (7.4)
ETON	16	0.2	4065	38.8	4422	42.2	1626	15.5	356	3.4	10485	27.83 (7.6)
LNG1	50	0.9	1860	34.4	2016	37.3	1025	19.0	457	8.5	5408	29.45 (9.0)
LNG2	855	1.2	26486	36.6	24863	34.3	14960	20.7	5247	7.2	72411	29.02 (9.3)
NETA	488	0.8	14819	24.3	16455	27.0	17218	28.2	12056	19.8	61036	33.63 (10.5)
NGM	461	0.7	33182	47.9	27637	39.9	6998	10.1	995	1.4	69273	25.81 (6.9)
COMP	*1854*	*0.9*	*76347*	*36.7*	*70971*	*34.1*	*40201*	*19.3*	*18755*	*9.0*	*208128*	*29.32 (9.4)*
TOTAL	2843	1.0	115229	38.8	105271	35.4	52749	17.8	21078	7.1	297170	

Table 4a6. First Study CHC used by age: ALL Users for VAND Site:

| CHC | Number of Women by Age with row percents. | | | | | | | | | | Total n | Mean age (sd) |
| | 10-14 | | 15-24 | | 25-34 | | 35-44 | | 45-55 | | | |
	n	%	n	%	n	%	n	%	N	%		
DRSP	711	5.3	8174	60.9	3524	26.3	874	6.5	129	1.0	13412	22.96 (7.0)
NGMN	1367	4.8	19751	69.3	6267	22.0	1010	3.5	108	0.4	28503	21.89 (5.9)
ETON	70	1.3	3508	65.8	1458	27.4	256	4.8	38	0.7	5330	23.24 (6.1)
LNG1	1876	7.3	15300	59.4	5892	22.9	2179	8.5	532	2.1	25779	23.17 (8.0)
LNG2	1103	3.8	16840	58.2	8407	29.1	2221	7.7	365	1.3	28936	23.81 (7.1)
NETA	262	5.1	2770	53.4	1367	26.3	589	11.4	200	7.3	5188	24.71 (8.8)
NGM	2263	6.4	23886	67.5	7522	21.3	1540	4.4	173	0.5	35384	21.66 (6.4)
COMP	*5504*	*5.8*	*58796*	*61.7*	*23188*	*24.3*	*6529*	*6.9*	*1270*	*1.3*	*95287*	*22.89 (7.3)*
TOTAL	7652	5.4	90229	63.3	34437	24.2	8669	6.1	1545	1.1	142532	

Table 4a7. First Study CHC used by age: ALL Users for WASH Site:

| CHC | Number of Women by Age with row percents. | | | | | | | | | | Total n | Mean age (sd) |
| | 10-14 | | 15-24 | | 25-34 | | 35-44 | | 45-55 | | | |
	n	%	n	%	n	%	n	%	N	%		
DRSP	364	7.0	2970	56.9	1469	28.2	369	7.1	46	0.9	5218	22.81 (7.3)
NGMN	1099	4.5	16216	66.6	5983	24.6	972	4.0	72	0.3	24342	22.09 (6.1)
ETON	62	1.2	3141	62.6	1568	31.3	221	4.4	22	0.4	5014	23.31 (5.9)
LNG1	651	8.1	4475	55.5	1937	24.0	778	9.7	217	2.7	8058	23.38 (8.6)
LNG2	258	6.3	2296	56.5	1109	27.3	336	8.3	66	1.6	4065	23.29 (7.8)
NETA	295	7.9	1709	45.6	998	26.6	527	14.1	218	5.8	3747	25.69 (6.4)
NGM	1633	6.6	16404	65.9	5760	23.1	990	4.0	120	0.5	24907	21.64 (6.4)
COMP	*2837*	*7.0*	*24884*	*61.0*	*9804*	*24.0*	*2631*	*6.5*	*621*	*1.5*	*40777*	*22.52 (7.5)*
TOTAL	4362	5.8	47211	62.7	18824	25.0	4193	5.6	761	1.0	75351	

Table 4b1. Study CHC by age at initiation of new use for ALL sites (new users only)
(COMP includes all 4 comparators in Tables 4a1-4a7)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	n	%	n	%	N	%		
DRSP	3000	2.8	54484	50.0	35792	32.8	13110	12.0	2684	2.5	109070	25.4 (8.0)
NGMN	2429	3.9	37302	59.9	17549	28.2	4488	7.2	548	0.9	62316	23.4 (7.0)
ETON	126	0.7	9509	49.7	7105	37.1	1954	10.2	449	2.3	19143	25.8 (7.3)
LNG1	2361	7.7	16672	54.5	7426	24.3	3101	10.1	1018	3.3	30578	23.5 (8.7)
LNG2	3099	2.3	59797	43.5	44984	32.8	22530	16.4	6901	5.0	137311	32.9 (9.0)
NETA	1397	1.5	25704	26.8	24822	25.9	26060	27.2	17923	18.7	95906	25.4 (10.7)
NGM	4403	3.7	69287	58.1	36829	30.9	7865	6.6	972	0.8	119356	25.4 (6.8)
COMP	*11260*	*2.9*	*171460*	*44.7*	*114061*	*29.8*	*59556*	*15.5*	*26814*	*7.0*	*383151*	*27.2 (9.6)*
TOTAL	16815	2.9	272755	47.5	174507	30.4	79108	13.8	30495	5.3	573680	

Table 4b2. Study CHC by age at initiation of new use for KP sites (new users only)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	n	%	n	%	N	%		
DRSP	2039	2.1	45926	48.3	32322	34.0	12219	12.9	2546	2.7	95052	25.86 (8.1)
NGMN	251	1.1	9863	44.6	8612	39.0	2969	13.4	396	1.8	22091	26.39 (7.5)
ETON	18	0.2	4381	39.1	4828	43.1	1570	14.0	394	3.5	11191	27.69 (7.5)
LNG1	56	1.0	2024	34.9	2192	37.8	1039	17.9	483	8.3	5794	29.24 (9.0)
LNG2	2000	1.7	47439	40.6	39561	33.9	21125	18.1	6662	5.7	116787	27.91 (9.1)
NETA	905	1.0	22349	25.0	23244	26.0	25302	28.3	17623	19.7	89423	33.51 (10.6)
NGM	971	1.3	39319	52.2	28051	37.2	6200	8.2	775	1.0	75316	24.95 (6.3)
COMP	*3932*	*1.4*	*111131*	*38.7*	*93048*	*32.4*	*53666*	*18.7*	*25543*	*8.9*	*287320*	*28.90 (7.3)*
TOTAL	6240	1.5	171301	41.2	138810	33.3	70424	17.0	28879	6.9	415654	

Table 4b3. Study CHC by age at initiation of new use for Medicaid sites (new users only)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	n	%	n	%	N	%		
DRSP	961	6.9	8558	61.1	3470	24.8	891	6.4	138	1.0	14018	22.51 (7.2)
NGMN	2178	5.4	27439	68.2	8937	22.2	1519	3.8	152	0.4	40225	21.79 (7.5)
ETON	108	1.4	5128	64.5	2277	28.6	384	4.8	55	0.7	7952	23.24 (9.6)
LNG1	2305	9.3	14648	59.1	5234	21.1	2062	8.3	535	2.2	24784	22.68 (8.2)
LNG2	1099	5.4	12358	60.2	5423	26.4	1405	6.8	239	1.2	20524	23.09 (7.2)
NETA	492	7.6	3355	51.8	1578	24.3	758	11.7	300	4.6	6483	24.58 (9.4)
NGM	3432	7.8	29968	68.0	8778	19.9	1665	3.8	197	0.4	44040	21.15 (6.3)
COMP	*7328*	*7.6*	*60329*	*63.0*	*21013*	*21.9*	*5890*	*6.1*	*1271*	*1.3*	*95831*	*22.20 (7.3)*
TOTAL	10575	6.7	101454	64.2	35697	22.6	8684	5.5	1616	1.1	158026	

Table 4b4. Study CHC by age at initiation of new use for KPNC (new users only)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	n	%	n	%	N	%		
DRSP	1256	2.5	24641	48.2	17191	33.7	6644	13.0	1349	2.6	51081	25.78 (8.1)
NGMN	130	1.9	3294	49.2	2375	35.5	795	11.9	104	1.6	6698	25.44 (7.6)
ETON	5	0.2	1131	38.0	1398	47.0	348	11.7	92	3.1	2974	27.59 (7.0)
LNG1	9	0.7	419	31.3	555	41.5	229	17.1	125	9.3	1337	29.79 (8.9)
LNG2	1244	1.9	26405	40.7	22910	35.3	11396	17.6	2977	4.6	64932	27.59 (8.8)
NETA	473	1.0	11154	23.7	12368	26.3	13656	29.0	9373	19.9	47024	33.77 (10.5)
NGM	635	1.6	21073	53.4	14226	36.1	3158	8.0	349	0.9	39441	24.70 (6.7)
COMP	*2361*	*1.5*	*59051*	*38.7*	*50059*	*32.8*	*28439*	*18.6*	*12824*	*8.4*	*152734*	*28.76 (9.5)*
TOTAL	3752	1.8	88117	41.3	71023	33.3	36226	17.0	14369	6.7	213487	

Table 4b5. Study CHC by age at initiation of new use for KPSC (new users only)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	n	%	n	%	n	%	N	%		
DRSP	783	1.8	21285	48.4	15131	34.4	5575	12.7	1197	2.7	43971	25.94 (8.0)
NGMN	121	0.8	6569	42.7	6237	40.5	2174	14.1	292	1.9	15393	26.81 (7.4)
ETON	13	0.2	3250	39.6	3430	41.7	1222	14.9	302	3.7	8217	27.72 (9.7)
LNG1	47	1.1	1605	36.0	1637	36.7	810	18.2	358	8.0	4457	29.08 (9.0)
LNG2	756	1.5	21034	40.6	16651	32.1	9729	18.8	3685	7.1	51855	28.30 (9.4)
NETA	432	1.0	11195	26.4	10876	25.7	11646	27.5	8250	19.5	42399	33.77 (10.7)
NGM	336	0.9	18246	50.9	13825	38.5	3042	8.5	426	1.2	35875	25.22 (6.7)
COMP	*1571*	*1.2*	*52080*	*38.7*	*42989*	*31.9*	*25227*	*18.7*	*12719*	*9.5*	*134586*	*29.06 (9.7)*
TOTAL	2488	1.2	83184	41.1	67787	33.5	34198	16.9	14510	7.2	202167	

Table 4b6. Study CHC by age at initiation of new use for Tennessee site (new users only)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		24-34		35-44		45-55			
	n	%	n	%	n	%	n	%	N	%		
DRSP	619	6.3	6085	61.8	2430	24.7	613	6.2	102	1.0	9849	22.62 (7.1)
NGMN	1206	5.8	14339	69.1	4360	21.0	758	3.7	92	0.4	20755	21.68 (6.0)
ETON	55	1.4	2567	65.5	1058	27.0	204	5.2	33	0.8	3917	23.30 (6.3)
LNG1	1706	9.2	11047	59.7	3886	21.0	1492	8.1	367	2.0	18498	22.64 (8.1)
LNG2	874	5.0	10602	60.4	4696	26.7	1191	6.8	197	1.1	17560	23.18 (7.1)
NETA	222	5.8	2099	55.3	911	24.0	412	10.9	151	4.0	3795	24.30 (9.0)
NGM	1977	7.6	17744	68.6	4990	19.3	1035	4.0	115	0.4	25861	21.18 (6.3)
COMP	*4779*	*7.3*	*41492*	*63.1*	*14483*	*22.0*	*4130*	*6.3*	*830*	*1.3*	*65714*	*22.31 (7.3)*
TOTAL	6659	6.6	64483	64.3	22331	22.3	5705	5.7	1057	1.1	100235	

Table 4b7. Study CHC by age at initiation of new use for Washington site (new users only)

CHC	Number of Women by Age with row percents.										Total n	Mean age (sd)
	10-14		15-24		25-34		35-44		45-55			
	n	%	N	%	n	%	n	%	N	%		
DRSP	342	8.2	2473	59.3	1040	24.9	278	6.7	36	0.9	4169	22.26 (7.3)
NGMN	972	5.0	13100	67.3	4577	23.5	761	3.9	60	0.3	19470	21.90 (6.1)
ETON	53	1.3	2561	63.5	1219	30.2	*180*	4.5	*22*	0.5	4035	23.19 (6.0)
LNG1	599	9.5	3601	57.3	1348	21.4	570	9.1	168	2.7	6286	22.81 (8.6)
LNG2	225	7.6	1756	59.2	727	24.5	214	7.2	42	1.4	2964	22.58 (7.7)
NETA	270	10.0	1256	46.7	667	24.8	346	12.9	149	5.5	2688	24.98 (9.9)
NGM	1455	8.0	12224	67.2	3788	20.8	630	3.5	82	0.5	18179	21.11 (6.3)
*COMP**	*2549*	*8.5*	*18837*	*62.5*	*6530*	*21.7*	*1760*	*5.8*	*441*	*1.5*	*30117*	*21.96 (7.4)*
TOTAL	3916	6.8	36971	64.0	13366	23.1	2979	5.2	559	1.0	57791	

Table 5. Number and length of new use exposure periods (#days and mean length)
(COMP includes all 4 comparators)

CHC	Number of days of use in new use exposure period					
	# of new use exposure periods	Duration of new use period				Mean # days use
		1 -90	91-180	181-365	>365	
DRSP	109,070	20,267	40,416	24,723	23,664	268.3
NGMN	62,316	23,215	20,391	11,580	7,130	176.6
ETON	19,143	6,690	6,910	3,668	1,875	167.4
LNG1	30,578	12,147	8,986	5,647	3,798	184.4
LNG2	137,311	25,555	55,579	28,833	27,344	258.6
NETA	95,906	15,817	42,267	19,933	17,889	255.1
NGM	119,356	28,391	42,362	31,843	16,760	208.9
COMP	*383,151*	*8,1910*	*149,194*	*86,256*	*65,791*	*236.3*
TOTAL	573,680	132,082	216911	126,227	98,460	

*COMP includes all 4 comparators (LNG1, LNG2, NETA, NGM)

Table 6. Total duration of cumulative CHC use

	Prescription period use			Indeterminate use (42 day period after prescription)		
	# Women	# years of ever use	Mean # days	# Women	# years of ever use	Mean # days*
DRSP	192,082	162,880	309.5	173,417	26,330	55.4
NGMN	109,287	51,683	172.6	107,751	16,182	54.8
ETON	41,549	18,462	162.2	37,857	5,449	52.5
LNG1	49,830	24,739	181.2	47,645	7,043	54.0
LNG2	236,506	211,688	326.7	220,433	32,919	54.5
NETA	167,882	139,397	303.1	156,769	21,646	50.4
NGM	228,514	150,586	240.5	220,571	29,248	48.4
TOTAL		759,434			138,817	

*Mean number of days is greater than 42 because women can have multiple exposure periods to a study CHC and therefore have multiple periods of indeterminate use.

Table 7a. Distribution of covariates for all sites by study CHCs in NEW users										
COVARIATE	DRSP N = 109,070			ETON N = 19,143			NGMN N = 62,316			Comparators N = 383,151	
	n	%	p	n	%	p	N	%	p	n	%
ACE_INHIBITORS	927	0.85	‡	185	0.97	‡	418	0.67	‡	5312	1.39
ACNE	4606	4.22	‡	157	0.82	‡	420	0.67	‡	8203	2.14
ADRENAL_INSUFFICIENCY	3	0.00	✳	2	0.01	✳	5	0.01	✳	29	0.01
AMPHETAMINE_DEPENDENCY	156	0.00	✳	37	0.19	■	133	0.21	‡	493	0.13
ANTICOAGULANTS	0	0.14	-	0	0.00	-	0	0.00	-	3	0.00
ASTHMA	3273	3.00	†	642	3.35	‡	1930	3.10	‡	10924	2.85
ATRIAL_FIBRILLATION	11	0.01	✳	6	0.03	✳	5	0.01	✳	63	0.02
BETA_BLOCKERS	1639	1.50	‡	314	1.64	‡	834	1.34	‡	8052	2.10
CHRONIC_KIDNEY_DISEASE	3	0.00	✳	1	0.01	✳	8	0.01	■	18	0.00
COAGULOPATHY	51	0.05	✳	17	0.09	■	46	0.07	■	197	0.05
COCAINE_DEPENDENCY	100	0.09	✳	21	0.11	✳	78	0.13	‡	283	0.07
COPD	170	0.16	‡	66	0.34	■	263	0.42	‡	997	0.26
DIABETES	2151	1.97	✳	387	2.02	✳	1245	2.00	✳	7621	1.99
DIURETIC_POTASSIUM_SPARIN	973	0.89	†	85	0.44	‡	269	0.43	‡	3080	0.80
DYSMENORRHEA	924	0.85	†	91	0.48	‡	381	0.61	‡	3604	0.94
EPILEPSY	143	0.13	■	27	0.14	1	142	0.23	‡	619	0.16
HEART_FAILURE	18	0.02	†	18	0.09	‡	33	0.05	■	130	0.03
HEPATIC_DYSFUNCTION	70	0.06	✳	22	0.11	‡	58	0.09	‡	213	0.06
HRT	3952	3.62	‡	839	4.38	‡	3838	6.16	‡	20389	5.32
HYPERLIPIDEMIA	1889	1.73	‡	328	1.71	‡	934	1.50	‡	8750	2.28
HYPERTENSION	2625	2.41	‡	557	2.91	‡	1368	2.20	‡	14335	3.74
LUPUS	43	0.04	✳	18	0.09	†	42	0.07	■	173	0.05
MIGRAINE	2117	1.94	✳	478	2.50	‡	1328	2.13	†	7423	1.94
NSAIDS	19752	18.11	‡	3307	17.28	‡	12657	20.31	✳	78028	20.37
OTHER_CARDIAC_DYSRHYTHMIA	224	0.21	✳	61	0.32	■	171	0.27	■	880	0.23
OTHER_ISCHEMIC_HEART_DISE	86	0.08	†	21	0.11	✳	85	0.14	■	412	0.11
PERIPHERAL_VASCULAR_DISEA	39	0.04	†	15	0.08	✳	37	0.06	✳	216	0.06
PLATLET_INHIBITORS	8	0.01	†	3	0.02	✳	17	0.03	✳	75	0.02
POLYCYSTIC_OVARY_SYNDROM	5	0.00	■	3	0.02	✳	27	0.04	‡	52	0.01
POTASSIUM	235	0.22	‡	46	0.24	†	173	0.28	‡	1399	0.37
PREMENSTRUAL_TENSION_SYN	217	0.20	‡	16	0.08	✳	26	0.04	‡	417	0.11
RENAL_INSUFFICIENCY	12	0.01	✳	2	0.01	✳	12	0.02	✳	64	0.02
STATINS	763	0.70	‡	123	0.64	‡	315	0.51	‡	4065	1.06
SURGERY_INJURY	1000	0.92	‡	153	0.80	‡	680	1.09	‡	4904	1.28
THYROID	162	0.15	‡	40	0.21	✳	131	0.21	✳	849	0.22
TIA	1	0.00	‡	4	0.02	✳	1	0.00	■	47	0.01
VARICOSE_VEINS	137	0.13	✳	25	0.13	✳	50	0.08	†	485	0.13
WARFARIN	28	0.03	■	7	0.04	✳	13	0.02	■	149	0.04

p-value of chi-square test for percentage of covariate for exposure CHC with percentage of covariate for comparator group:

✳ p-value >0.05   ■ = p-value <0.05   † = p-value <0.01   ‡ p-value <0.001

Percent refers to # of women

Table 7b. Distribution of covariates for all sites by study CHCs in ALL users (% of number of women)										
Covariate	DRSP N = 192,263			ETON N = 41,630			NGMN N = 109,480			Comparators N = 615,624	
	n	%	p	n	%	p	n	%	p	n	%
ACE_INHIBITORS	2038	1.06	‡	441	1.06	‡	931	0.85	‡	10883	1.77
ACNE	8331	4.33	‡	437	1.05	✳	961	0.88	‡	15650	2.54
ADRENAL_INSUFFICIENCY	11	0.01	✳	5	0.01	✳	9	0.01	✳	58	0.01
AMPHETAMINE_DEPENDENCY	341	0.18	✳	97	0.23	†	262	0.24	‡	1041	0.17
ANTICOAGULANTS	2	0.00	✳	0	0.00	‡	1	0.00	✳	7	0.00
ASTHMA	7312	3.80	■	1762	4.23	‡	4407	4.03	‡	22698	3.69
ATRIAL_FIBRILLATION	30	0.02	■	10	0.02	✳	10	0.01	†	154	0.03
BETA_BLOCKERS	4045	2.10	‡	852	2.05	‡	1997	1.82	‡	17839	2.90
CHRONIC KIDNEY DISEASE	12	0.01	✳	4	0.01	✳	15	0.01	†	36	0.01
COAGULOPATHY	124	0.06	✳	50	0.12	‡	106	0.10	‡	392	0.06
COCAINE_DEPENDENCY	216	0.11	✳	72	0.17	‡	191	0.17	‡	649	0.11
COPD	402	0.21	‡	204	0.49	‡	636	0.58	‡	1989	0.32
DIABETES	4502	2.34	✳	1008	2.42	■	2577	2.35	✳	13978	2.27
DIURETIC_POTASSIUM_SPARIN	2310	1.20	✳	224	0.54	‡	634	0.58	‡	7091	1.15
DYSMENORRHEA	1702	0.89	‡	264	0.63	‡	915	0.84	‡	6411	1.04
EPILEPSY	303	0.16	‡	96	0.23	✳	280	0.26	‡	1204	0.20
HEART_FAILURE	45	0.02	‡	36	0.09	‡	75	0.07	‡	251	0.04
HEPATIC DYSFUNCTION	163	0.08	✳	49	0.12	†	124	0.11	‡	488	0.08
HRT	8189	4.26	‡	2124	5.10	‡	7574	6.92	‡	37776	6.14
HYPERLIPIDEMIA	4164	2.17	‡	914	2.20	‡	2154	1.97	‡	17272	2.81
HYPERTENSION	6105	3.18	‡	1469	3.53	‡	3208	2.93	‡	28941	4.70
LUPUS	92	0.05	✳	44	0.11	‡	82	0.07	■	341	0.06
MIGRAINE	5371	2.79	✳	1392	3.34	‡	3349	3.06	‡	17169	2.79
NSAIDS	45146	23.48	‡	9516	22.86	‡	28272	25.82	‡	164450	26.71
OTHER_CARDIAC_DYSRHYTHMIA	508	0.26	‡	165	0.40	■	405	0.37	■	2009	0.33
OTHER ISCHEMIC HEART DISE	170	0.09	‡	63	0.15	✳	184	0.17	†	837	0.14
PERIPHERAL_VASCULAR_DISEA	123	0.06	✳	41	0.10	✳	100	0.09	✳	465	0.08
PLATLET_INHIBITORS	23	0.01	‡	7	0.02	✳	24	0.02	✳	160	0.03
POLYCYSTIC OVARY SYNDROM	18	0.01	✳	8	0.02	✳	49	0.04	‡	90	0.01
POTASSIUM	613	0.32	‡	150	0.36	‡	424	0.39	‡	3134	0.51
PREMENSTRUAL_TENSION_SYN	433	0.23	‡	34	0.08	†	69	0.06	‡	835	0.14
RENAL INSUFFICIENCY	33	0.02	✳	9	0.02	✳	30	0.03	✳	138	0.02
STATINS	1664	0.87	‡	308	0.74	‡	700	0.64	‡	8345	1.36
SURGERY_INJURY	2321	1.21	‡	396	0.95	‡	1551	1.42	‡	10518	1.71
THYROID	386	0.20	‡	119	0.29	✳	318	0.29	✳	1748	0.28
TIA	10	0.01	‡	6	0.01	✳	10	0.01	✳	93	0.02
VARICOSE_VEINS	320	0.17	✳	46	0.11	†	109	0.10	‡	1085	0.18
WARFARIN	77	0.04	✳	15	0.04	✳	31	0.03	†	301	0.05

p-value of chi-square test for percentage of covariate for exposure CHC with percentage of covariate for comparator group:
✳ p-value >0.05   ■ = p-value <0.05   † = p-value <0.01   ‡ p-value <0.001
Percent refers to # of women

Table 8. Number of validated study endpoints* by CHC status current, indeterminate, and switcher status (all use).

CHC/Status	All ATE (n=138)	All VTE* (n=625)	CVD Death (n=41)	All Death* (n=267)
DRSP				
Current	13	126	2	27
Indeterminate	4	15	0	8
Switcher	0	4	1	2
NGMN				
Current	7	57	1	17
Indeterminate	2	8	0	7
Switcher	0	2	0	1
ETON				
Current	4	22	1	10
Indeterminate	0	2	0	2
Switcher	0	1	0	0
NETA				
Current	38	117	10	29
Indeterminate	5	16	0	5
Switcher	0	2	0	1
NGM				
Current	10	65	5	44
Indeterminate	2	9	1	10
Switcher	0	1	0	1
LNG1				
Current	8	15	5	15
Indeterminate	1	1	1	5
Switcher	0	1	0	1
LNG2				
Current	36	149	10	62
Indeterminate	6	10	4	19
Switcher	2	2	0	1
TOTAL	138	625	41	267

 *VTE and includes validated hospitalized VTE and outpatient DVT
**All deaths include CVD mortality.

Table 9. Incidence rates for all study outcomes in all users.

Endpoint	Events	Rate (per 10K person-years)
MI	60	0.67
Stroke	78	0.87
All VTE	625	6.96
CVD mortality	41	0.46
Total mortality	267	2.97

 All denominators are 898,251 person-years.

Table 10a. Age- and site-specific incidence rates and age-adjusted rates for study CHCs for ATE

EXPOSURE		Age-specific incidence rates					
		NEW USERS			ALL USERS		
		Person-years	Events	Rate (per 10K)	Person-years	Events	Rate (Per 10K)
DRSP	Age (yrs)						
	10-24	39452	0	0.00	79590	0	0.00
	25-34	27362	3	1.10	72346	3	0.41
	35-44	10672	5	4.69	29968	8	2.67
	45-55	2684	6	22.35	7306	6	8.21
		80171	14		189210	17	
NGMN	Age (yrs)						
	10-24	17680	1	0.57	37602	2	0.53
	25-34	9424	2	2.12	22781	6	2.63
	35-44	2651	1	3.77	6515	1	1.53
	45-55	397	0	0.00	967	0	0.00
		30152	4		67865	9	
ETON	Age (yrs)						
	10-24	3913	0	0.00	10901	0	0.00
	25-34	3497	0	0.00	9601	1	1.04
	35-44	1073	2	18.64	2782	2	7.19
	45-55	301	0	0.00	626	1	15.97
		8784	2		23910	4	
LNG2	Age (yrs)						
	10-24	39977	2	0.50	80454	7	0.87
	25-34	33843	4	1.18	89057	6	0.67
	35-44	17544	3	1.71	54546	12	2.20
	45-55	5896	8	13.57	20550	19	9.25
		97260	17		244607	44	
COMP*	Age (yrs)						
	10-24	103683	5	0.48	218616	12	0.55
	25-34	77191	9	1.17	207964	19	0.91
	35-44	42631	13	3.05	121685	29	2.38
	45-55	24526	18	7.34	69000	48	6.96
		248031	45		617265	108	

*COMP includes all 4 comparators (NETA, NGM, LNG1, LNG2)

EXPOSURE	Age- and site- adjusted ATE rates and incidence rate ratios for ALL USERS (per 10K person-years)					
		IRR (ref: all comparators)			IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI		Incidence Rate Ratio	95% CI
DRSP	1.08	0.83	0.50 – 1.40		0.74	0.42 – 1.29
NGMN	1.10	1.08	0.53 – 2.21		0.94	0.44 – 2.00
ETON	1.70	1.37	0.50 – 3.77		1.19	0.42 – 3.37
LNG2	1.64				Ref	
COMP	1.44	Ref				

EXPOSURE	Age- and site-adjusted ATE rates and Incidence rate ratios for NEW USERS (per 10K person-years)					
		IRR (ref: all comparators)			IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI		Incidence Rate Ratio	95% CI
DRSP	2.55	1.68	0.91 – 3.11		1.37	0.67 – 2.79
NGMN	1.79	0.88	0.30 – 2.54		0.71	0.22 – 2.22
ETON	2.15	1.42	0.34 – 5.93		1.15	0.26 – 5.07
LNG2	2.28				Ref	
COMP	1.76	Ref				

ATE

Table 10b. Age-specific incidence rates and age-adjusted rates for study CHCs for VTE

EXPOSURE		Age-specific incidence rates					
		NEW USERS			ALL USERS		
		Person-years	Events	Rate (per 10K)	Person-years	Events	Rate (Per 10K)
DRSP	Age (yrs)						
	10-24	39452	19	4.82	79590	27	3.39
	25-34	27362	26	9.50	72346	54	7.46
	35-44	10672	18	16.87	29968	43	14.35
	45-55	2684	11	40.98	7306	20	27.37
		80171	74		189210	144	
NGMN	Age (yrs)						
	10-24	17680	11	6.22	37602	21	5.58
	25-34	9424	12	12.73	22781	26	11.41
	35-44	2651	8	30.18	6515	14	21.49
	45-55	397	2	50.39	967	6	62.04
		30152	33		67865	67	
ETON	Age (yrs)						
	10-24	3913	2	5.11	10901	9	8.26
	25-34	3497	5	14.30	9601	11	11.46
	35-44	1073	0	0.00	2782	2	7.19
	45-55	301	2	66.50	626	3	47.92
		8784	9		23910	25	
LNG2	Age (yrs)						
	10-24	39977	10	2.50	80454	20	2.49
	25-34	33843	15	4.43	89057	33	3.71
	35-44	17544	33	18.81	54546	72	13.20
	45-55	5896	16	27.14	20550	36	17.52
		97260	74		244607	161	
COMP	Age (yrs)						
	10-24	103683	32	3.09	218616	62	2.84
	25-34	77191	39	5.05	207964	80	3.85
	35-44	42631	79	18.53	121685	136	11.18
	45-55	24526	55	22.42	69000	111	16.09
		248031	205		617265	389	

*COMP includes all 4 comparators (NETA, NGM, LNG1, LNG2)

EXPOSURE	Age- and site- adjusted VTE rates and incidence rate ratios for ALL USERS				
		IRR (ref: all comparators)		IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
DRSP	10.22	1.69	1.39 – 2.06	1.49	1.19 – 1.87
NGMN	9.75	1.54	1.16 – 2.03	1.27	0.93 – 1.72
ETON	11.91	1.76	1,16 – 2.65	1.48	0.96 - 2.27
LNG2	6.64			Ref	
COMP	5.96	Ref			

EXPOSURE	Age- and site-adjusted VTE rates and incidence rate ratios for NEW USERS				
		IRR (ref: all comparators)		IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
DRSP	13.67	1.62	1.23 – 2.12	1.48	1.07, 2.05
NGMN	12.29	1.27	0.86 - 1.87	1.09	0.70, 1.69
ETON	11.35	1.23	0.62 – 2.40	1.08	0.53, 2.18
LNG2	9.21			Ref	
COMP	8.21	Ref			

VTE

Table 10c. Age-specific incidence rates and age-adjusted rates for study CHCs for CVD Mortality

EXPOSURE		Age-specific incidence rates					
		NEW USERS			ALL USERS		
		Person-years	Events	Rate (per 10K)	Person-years	Events	Rate (Per 10K)
DRSP	Age (yrs)						
	10-24	39452	1	0.25	79590	2	0.25
	25-34	27362	0	0.00	72346	0	0.00
	35-44	10672	0	0.00	29968	1	0.33
	45-55	2684	0	0.00	7306	0	0.00
		80171	1		189210	3	
NGMN	Age (yrs)						
	10-24	17680	0	0.00	37602	0	0.00
	25-34	9424	0	0.00	22781	1	0.44
	35-44	2651	0	0.00	6515	0	0.00
	45-55	397	0	0.00	967	0	0.00
		30152	0		67865	1	
ETON	Age (yrs)						
	10-24	3913	0	0.00	10901	0	0.00
	25-34	3497	0	0.00	9601	0	0.00
	35-44	1073	0	0.00	2782	0	0.00
	45-55	301	0	0.00	626	1	15.97
		8784	0		23910	1	
LNG2	Age (yrs)						
	10-24	39977	1	0.25	80454	1	0.12
	25-34	33843	4	1.18	89057	4	0.45
	35-44	17544	3	1.71	54546	9	1.65
	45-55	5896	0	0.00	20550	0	0.00
		97260	8		244607	14	
COMP	Age (yrs)						
	10-24	103683	2	0.19	218616	5	0.23
	25-34	77191	8	1.04	207964	12	0.58
	35-44	42631	4	0.94	121685	14	1.15
	45-55	24526	1	0.41	69000	5	0.72
		248031	15		617265	36	

*COMP includes all 4 comparators (NETA, NGM, LNG1, LNG2)

EXPOSURE	Age- and site- adjusted CVD mortality rates and incidence rate ratios for ALL USERS				
		IRR (ref: all comparators)		IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
DRSP	0.13	0.38	0.12 – 1.25	0.36	0.10 – 1.25
NGMN	0.07	0.18	0.02 – 1.37	0.17	0.02 – 1.36
ETON	0.58	0.62	0.08 – 4.57	0.58	0.07 – 4.50
LNG2	0.48			Ref	
COMP	0.60	Ref			

CVD

EXPOSURE	Age- and site-adjusted CVD mortality rates and incidence rate ratios for NEW USERS				
		IRR (ref: all comparators)		IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
DRSP	0.09	0.26	0.03 – 1.95	0.17	0.02 – 1.35
NGMN	0	0	0.00	0	0.00
ETON	0	0	0.00	0	0.00
LNG2	0.76			Ref	
COMP	0.68	Ref			

CVD

Table 10d. Age-specific incidence rates and age-adjusted rates for study CHCs for Total Mortality

EXPOSURE		Age-specific incidence rates					
		NEW USERS			ALL USERS		
		Person-years	Events	Rate (per 10K)	Person-years	Events	Rate (Per 10K)
DRSP	Age (yrs)						
	10-24	39452	5	1.27	79590	15	1.88
	25-34	27362	7	2.56	72346	14	1.94
	35-44	10672	4	3.75	29968	7	2.34
	45-55	2684	1	3.73	7306	1	1.37
		80171	17		189210	37	
NGMN	Age (yrs)						
	10-24	17680	11	6.22	37602	17	4.52
	25-34	9424	1	1.06	22781	6	2.63
	35-44	2651	0	0.00	6515	1	1.53
	45-55	397	1	25.20	967	1	10.34
		30152	13		67865	25	
ETON	Age (yrs)						
	10-24	3913	1	2.56	10901	6	5.50
	25-34	3497	1	2.86	9601	4	4.17
	35-44	1073	0	0.00	2782	0	0.00
	45-55	301	1	33.25	626	2	31.95
		8784	3		23910	12	
LNG2	Age (yrs)						
	10-24	39977	16	4.00	80454	23	2.86
	25-34	33843	13	3.84	89057	27	3.03
	35-44	17544	7	3.99	54546	25	4.58
	45-55	5896	4	6.78	20550	7	3.41
		97260	40		244607	82	
COMP	Age (yrs)						
	10-24	103683	30	2.89	218616	63	2.88
	25-34	77191	27	3.50	207964	63	3.03
	35-44	42631	13	3.05	121685	45	3.70
	45-55	24526	8	3.26	69000	22	3.19
		248031	78		617265	193	

*COMP includes all 4 comparators (NETA, NGM, LNG1, LNG2)

EXPOSURE	Age- and site- adjusted total mortality rates and incidence rate ratios for ALL USERS				
		IRR (ref: all comparators)		IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
DRSP	2.40	0.79	0.55 – 1.13	0.67	0.46 – 1.00
NGMN	3.66	0.74	0.48 – 1.14	0.63	0.39 – 1.02
ETON	4.33	1.27	0.70 – 2.30	1.09	0.58 – 2.02
LNG2	4.53			Ref	
COMP	3.52	Ref			

EXPOSURE	Age- and site-adjusted total mortality rates and Incidence rate ratios for NEW USERS				
		IRR (ref: all comparators)		IRR (ref: LNG2)	
	Age- and site-adjusted rate	Incidence Rate Ratio	95% CI	Incidence Rate Ratio	95% CI
DRSP	2.60	0.84	0.49 – 1.43	0.57	0.32 – 1.01
NGMN	6.33	0.98	0.53 – 1.81	0.67	0.34 – 1.33
ETON	3.70	0.99	0.31 – 3.17	0.68	0.21 – 2.22
LNG2	5.36			Ref	
COMP	3.47	Ref			

Total Mortality

Table 11a.   **Incidence rates for CHC exposures of interest and incident rate ratios relative to comparator CHCs duration for all ATEs in new users***

Exposure	Person-years	Events	Rate (per 10K)	IRR* (ref: all comp)	95% CI	IRR* (ref: LNG2)	95% CI
DSRP							
Duration (months)							
0-3	23529	5	2.13	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
4-6	15480	4	2.58	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
7-12	18326	1	0.55	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
>12	22836	4	1.75	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
NGMN							
Duration (months)							
0-3	12942	1	0.77	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
4-6	6403	1	1.56	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
7-12	6320	1	1.58	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
>12	4487	1	2.23	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
ETON							
Age (months)							
0-3	3932	0	0	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
4-6	1997	1	5.01	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
7-12	1793	0	0	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
>12	1061	1	9.42	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
LNG2							
Duration (months)							
0-3	29780	10	3.36	xxxxxxxx	xxxxxxxx	ref	ref
4-6	18900	1	0.53	xxxxxxxx	xxxxxxxx	ref	ref
7-12	21140	2	0.95	xxxxxxxx	xxxxxxxx	ref	ref
>12	27440	4	1.46	xxxxxxxx	xxxxxxxx	ref	ref
Comparators							
Duration (months)							
0-3	82412	20	2.43	ref	ref	xxxxxxxx	xxxxxxxx
4-6	50937	9	1.77	ref	ref	xxxxxxxx	xxxxxxxx
7-12	54620	6	1.10	ref	ref	xxxxxxxx	xxxxxxxx
>12	60062	10	1.66	ref	ref	xxxxxxxx	xxxxxxxx

*Poisson model did not converge to produce estimate of incidence rate ratio.

Table 11b. **Incidence rates for CHC exposures of interest and incident rate ratios relative to comparator CHCs duration for all VTEs in new users***

Exposure	Person-years	Events	Rate (per 10K)	IRR* (ref: all comp)	95% CI	IRR* (ref: LNG2)	95% CI
DSRP							
Duration (months)							
0-3	23529	30	12.75	**1.93**	**1.26 – 2.95**	1.60	0.96 – 2.68
4-6	15480	13	8.40	1.13	0.62 – 2.08	1.15	0.56 – 2.38
7-12	18326	18	9.82	**2.90**	**1.59 – 5.28**	**2.11**	**1.02 – 4.38**
>12	22836	13	5.69	1.17	0.63 – 2.18	1.26	0.61 – 2.62
NGMN							
Duration (months)							
0-3	12942	20	15.45	1.54	0.93 – 2.57	1.22	0.67 – 2.21
4-6	6403	5	7.81	0.71	0.28 – 1.81	0.70	0.25 – 1.91
7-12	6320	2	3.16	0.61	0.14 – 2.59	0.42	0.09 – 1.90
>12	4487	6	13.37	1.87	0.79 – 4.43	1.90	0.73 – 4.93
ETON							
Age (months)							
0-3	3932	4	10.17	1.02	0.37 – 2.79	0.82	0.28 – 2.34
4-6	1997	1	5.01	0.46	0.06 – 3.32	0.45	0.06 – 3.43
7-12	1793	2	11.15	2.20	0.52 – 9.26	1.56	0.35 – 6.97
>12	1061	2	18.84	2.49	0.60 – 10.27	2.60	0.60 – 11.34
LNG2							
Duration (months)							
0-3	29780	29	9.74	xxxxxxxx	xxxxxxxx	ref	ref
4-6	18900	17	8.99	xxxxxxxx	xxxxxxxx	ref	ref
7-12	21140	12	5.68	xxxxxxxx	xxxxxxxx	ref	ref
>12	27440	16	5.83	xxxxxxxx	xxxxxxxx	ref	ref
Comparators							
Duration (months)							
0-3	82412	77	9.34	ref	ref	xxxxxxxx	xxxxxxxx
4-6	50937	54	10.60	ref	ref	xxxxxxxx	xxxxxxxx
7-12	54620	27	4.94	ref	ref	xxxxxxxx	xxxxxxxx
>12	60062	47	7.83	ref	ref	xxxxxxxx	xxxxxxxx

*Incidence rate ratio, adjusted for age and site.

Table 11c. **Incidence rates for CHC exposures of interest and incident rate ratios relative to comparator CHCs duration for total mortality in new users***

Exposure	Person-years	Events	Rate (per 10K)	IRR* (ref: all comp)	95% CI	IRR* (ref: LNG2)	95% CI
DSRP							
Duration (months)							
0-3	23529	8	3.40	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
4-6	15480	5	3.23	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
7-12	18326	2	1.09	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
>12	22836	2	0.88	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
NGMN							
Duration (months)							
0-3	12942	5	3.86	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
4-6	6403	4	6.25	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
7-12	6320	4	6.33	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
>12	4487	0	0	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
ETON							
Age (months)							
0-3	3932	2	5.09	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
4-6	1997	1	5.01	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
7-12	1793	0	0	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
>12	1061	0	0	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx
LNG2							
Duration (months)							
0-3	29780	13	4.37	xxxxxxxx	xxxxxxxx	ref	ref
4-6	18900	5	2.65	xxxxxxxx	xxxxxxxx	ref	ref
7-12	21140	12	5.68	xxxxxxxx	xxxxxxxx	ref	ref
>12	27440	10	3.64	xxxxxxxx	xxxxxxxx	ref	ref
Comparators							
Duration (months)							
0-3	82412	30	3.64	ref	ref	xxxxxxxx	xxxxxxxx
4-6	50937	13	2.55	ref	ref	xxxxxxxx	xxxxxxxx
7-12	54620	16	2.93	ref	ref	xxxxxxxx	xxxxxxxx
>12	60062	19	3.16	ref	ref	xxxxxxxx	xxxxxxxx

*Poisson model did not converge to produce estimate of incidence rate ratio.

Table 12a. Relative hazard of study endpoints associated with study exposure CHCs relative to the combined comparator CHCs group

	ATE	VTE	VTE hospitalized	CVD mortality	Total mortality
All users					
DRSP	0.99 (0.58, 1.69)	**1.74 (1.42, 2.14)**	**1.78 (1.37, 2.31**	0.37 (0.11, 1.25)	0.85 (0.59, 1.23)
NGMN	1.31 (0.63, 2.74)	**1.55 (1.17, 2.07)**	**1.69 (1.19, 2.42)**	0.20 (0.03, 1.56)	0.80 (0.51, 1.26)
ETON	1.72 (0.61, 4.83)	**1.56 (1.02, 2.37)**	1.63 (0.97, 2.76)	0.62 (0.08, 4.72)	1.31 (0.71, 2.40)
New users					
DRSP	**2.01 (1.06, 3.81)**	**1.77 (1.33, 2.35)**	**2.08 (1.46, 2.98)**	0.25 (0.03, 1.95)	0.88 (0.52, 1.53)
NGMN	1.07 (0.36, 3.23)	1.35 (0.90, 2.02)	1.43 (0.84, 2.41)	-----------------------	1.07 (0.56, 2.05)
ETON	1.65 (0.38, 7.12)	1.09 (0.55, 2.16)	0.89 (0.33, 2.47)	-----------------------	0.96 (0.29, 3.14)

Estimates from Cox proportional hazards models. All models adjusted for age, site, year of entry into study.
ATE and CVD mortality models are further adjusted for hypertension, hyperlipidemia, and diabetes.

Table 12b. Relative hazard of study endpoints associated with study exposure CHCs relative to LNG2

	ATE	VTE	VTE hospitalized	CVD mortality	Total mortality
All users					
DRSP	0.81 (0.45, 1.44)	**1.45 (1.15, 1.83)**	**1.49 (1.11, 2.01)**	0.33 (0.09, 1.18)	0.66 (0.45, 0.99)
NGMN	1.14 (0.52, 24.8)	1.34 (0.97, 1.83)	1.35 (0.92, 1.99)	0.21 (0.03, 1.67)	0.73 (0.45, 1.19)
ETON	1.43 (0.50, 4.12)	1.28 (0.83, 1.99)	1.33 (0.77, 2.30)	0.58 (0.07, 4.67)	1.08 (0.58, 2.04)
New users					
DRSP	1.64 (0.79, 3.40)	**1.57 (1.13, 2.18)**	**1.72 (1.14, 2.59)**	0.57 (0.05, 6.35)	0.57 (0.32, 1.02)
NGMN	0.90 (0.28, 2.91)	1.19 (0.75, 1.87)	1.12 (0.63, 2.00)	0	0.84 (0.41, 1.71)
ETON	1.34 (0.30, 6.05)	0.96 (0.47, 1.95)	0.72 (0.25, 2.03)	0	0.67 (0.20, 2.23)

Estimates from Cox proportional hazards models. All models adjusted for age, site, year of entry into study.
ATE and CVD mortality models are further adjusted for hypertension, hyperlipidemia, and diabetes.

Table 13a1. Relative hazard of all ATEs associated with study exposure CHCs relative to the combined comparator CHCs group by duration of use in new users*

	<3	3-6	6-12	>12
DRSP	1.66 (0.60, 4.65)	2.58 (0.74, 8.98)	0.66 (0.07, 6.01)	2.76 (0.79, 9.68)
NGMN	0.53 (0.07, 4.24)	0.78 (0.09, 7.14)	2.38 (0.21, 27.38)	3.53 (0.36, 35.11)
ETON	0	3.29 (0.26, 20.26)	0	**13.38 (1.45, 123.61)**

Table 13a2. Relative hazard of all ATEs associated with study exposure CHCs relative to LNG2 by duration of use in new users*

	<3	3-6	6-12	>12
DRSP	1.19 (0.39, 3.61)	6.04 (0.66, 54.96)	0.71 (0.06, 8.16)	2.31 (0.54, 10.00)
NGMN	0.57 (0.07, 4.69)	3.96 (0.23, 68.02)	3.23 (0.25, 41.62)	3.65 (0.35, 38.34)
ETON	0	8.62 (0.52, 144.07)	0	**11.97 (1.18, 121.87)**

Table 13b1. Relative hazard of all VTEs associated with study exposure CHCs relative to the combined comparator CHCs group by duration of use in new users†

	<3	3-6	6-12	>12
DRSP	**1.93 (1.24, 3.00)**	1.14 (0.59, 2.21)	**2.80 (1.48, 5.29)**	1.32 (0.68, 2.56)
NGMN	1.58 (0.91, 2.77)	0.89 (0.33, 2.41)	0.39 (0.09, 1.72)	**3.05 (1.23, 7.53)**
ETON	0.92 (0.33, 2.58)	0.45 (0.06, 3.35)	1.79 (0.41, 7.83)	2.54 (0.59, 10.95)

Table 13b2. Relative hazard of all VTEs associated with study exposure CHCs relative to LNG2 by duration of use in new users†

	<3	3-6	6-12	>12
DRSP	1.59 (0.94, 2.67)	1.21 (0.58, 2.53)	2.01 (0.95, 4.24)	1.30 (0.61, 2.78)
NGMN	**2.48 (1.36, 4.52)**	1.61 (0.57, 4.54)	0.57 (0.12, 2.60)	**4.12 (1.54, 11.06)**
ETON	1.20 (0.42, 3.47)	0.62 (0.08, 4.73)	2.07 (0.45, 9.46)	3.37 (0.75, 15.18)

Table 13c1. Relative hazard of all total mortality associated with study exposure CHCs relative to the combined comparator CHCs group by duration of use in new users†

	<3	3-6	6-12	>12
DRSP	1.15 (0.51, 2.60)	2.06 (0.65, 6.56)	0.37 (0.08, 1.68)	0.44 (0.10, 1.97)
NGMN	1.32 (0.47, 3.70)	1.61 (0.44, 5.91)	2.01 (0.57, 7.13)	0
ETON	1.28 (0.29, 5.61)	2.38 (0.28, 20.38)	0	0

Table 13c2. Relative hazard of all total mortality associated with study exposure CHCs relative to LNG2 by duration of use in new users†

	<3	3-6	6-12	>12
DRSP	0.88 (0.36, 2.18)	1.62 (0.44, 6.01)	0.20 (0.04, 0.89)	0.29 (0.06, 1.34)
NGMN	1.07 (0.34, 3.33)	1.25 (0.29, 5.43)	0.83 (0.21, 3.31)	0
ETON	1.00 (0.22, 4.69)	1.85 (0.20, 17.48)	0	0

*adjusted for age, site, year of entry into study, hypertension, hyperlipidemia, and diabetes
†adjusted for age, site, year of entry into study

Table 14a. Relative hazard of study endpoints associated with study exposure CHCs relative to the combined comparator CHCs group stratified by site and age in all users ‡

	ATE	VTE	Total mortality
KPNC/KPSC			
DRSP	1.09 (0.62, 1.94)	**1.84 (1.46, 2.31)**	0.88 (0.58, 1.33)
NGMN	1.34 (0.41, 4.38)	**2.08 (1.35, 3.20)**	0.87 (0.35, 2.17)
ETON	1.66 (0.40, 6.97)	**1.96 (1.13, 3.40)**	0.28 (0.04, 2.04)
Vanderbilt/Washington			
DRSP	0.30 (0.04, 2.28)	1.58 (0.98, 2.54)	0.62 (0.27, 1.46)
NGMN	1.06 (0.40, 2.79)	1.35 (0.91, 1.98)	0.84 (0.49, 1.41)
ETON	1.61 (0.36, 7.25)	1.32 (0.69, 2.53)	2.12 (1.08, 4.17)
Ages 10-34 years			
DRSP	0.48 (0.18, 1.25)	**1.86 (1.41, 2.46)**	0.79 (0.52, 1.20)
NGMN	1.65 (0.70, 3.88)	**1.61 (1.13, 2.28)**	0.89 (0.56, 1.44)
ETON	0.67 (0.09, 5.10)	**2.12 (1.31, 3.40)**	1.35 (0.70, 2.64)
Ages 35-55 years			
DRSP	1.14 (0.61, 2.15)	1.35 (1.00, 1.82)	0.71 (0.32, 1.59)
NGMN	0.34 (0.05, 2.51)	1.41 (0.85, 2.34)	0.59 (0.14, 2.53)
ETON	2.71 (0.81, 8.95)	0.69 (0.26, 1.88)	1.27 (0.30, 5.37)

Table 14b. Relative hazard of study endpoints associated with study exposure CHCs relative to LGN2 stratified by site and age in all users ‡

	ATE	VTE	Total mortality
KPNC/KPSC			
DRSP	0.92 (0.50, 1.71)	**1.58 (1.22, 2.05)**	0.72 (0.46, 1.13)
NGMN	1.13 (0.34, 3.77)	**1.77 (1.13, 2.78)**	0.72 (0.28, 1.82)
ETON	1.40 (0.33, 5.98)	1.68 (0.96, 2.95)	0.23 (0.03, 1.69)
Vanderbilt/Washington			
DRSP	0.23 (0.03, 1.86)	1.42 ((0.81, 2.47)	0.60 (0.24, 1.52)
NGMN	0.78 (0.26, 2.40)	1.20 (0.74, 1.95)	0.80 (0.42, 1.51)
ETON	1.19 (0.24, 5.92)	1.19 (0.58, 2.42)	2.05 (0.96, 4.40)
Ages 10-34 years			
DRSP	0.45 (0.16, 1.26)	**1.68 (1.20, 2.34)**	0.68 (0.43, 1.06)
NGMN	1.55 (0.59, 4.10)	1.39 (0.92, 2.09)	0.77 (0.45, 1.30)
ETON	0.65 (0.08, 5.13)	**1.86 (1.11, 3.11)**	1.16 (0.58, 2.34)
Ages 35-55 years			
DRSP	1.04 (0.52, 2.07)	1.18 (0.84, 1.65)	0.58 (0.25, 1.36)
NGMN	0.30 (0.04, 2.28)	1.18 (0.69, 2.00)	0.50 (0.11, 2.23)
ETON	2.43 (0.71, 8.31)	0.59 (0.21, 1.62)	1.07 (0.25, 4.65)

‡ Site specific models adjusted for age, year of entry into the study and for hypertension, hyperlipidemia, and diabetes in ATE models.
  Age specific models are adjusted for site, age (5 year age groups), and year of entry into the study

Table 14c. Relative hazard of study endpoints associated with study exposure CHCs relative to the combined comparator CHCs group stratified by site and age in new users ‡

	ATE	VTE	Total mortality
KPNC/KPSC			
DRSP	**2.90 (1.41, 6.00)**	**1.84 (1.33, 2.54)**	0.94 (0.51, 1.73)
NGMN	**4.22 (1.16, 15.30)**	**2.09 (1.15, 3.79)**	1.23 (0.37, 4.12)
ETON	2.27 (0.29, 17.58)	1.07 (0.39, 2.93)	0
Vanderbilt/Washington			
DRSP	0.39 (0.05, 3.05)	1.77 (0.96, 3.28)	0.58 (0.14, 2.52)
NGMN	0.23 (0.03, 1.81)	1.11 (0.64, 1.92)	0.97 (0.44, 2.12)
ETON	1.03 (0.13, 8.33)	1.23 (0.48, 3.18)	1.96 (0.56, 6.84)
Ages 10-34 years			
DRSP	0.64 (0.18, 2.26)	**2.12 (1.43, 3.15)**	0.69 (0.36, 1.31)
NGMN	1.03 (0.27, 4.01)	1.45 (0.86, 2.44)	1.12 (0.57, 2.23)
ETON	0.00 (-------------)	1.73 (0.77, 3.84)	0.84 (0.21, 3.55)
Ages 35-55 years			
DRSP	**2.60 (1.25, 5.41)**	1.20 (0.78, 1.84)	1.49 (0.53, 4.16)
NGMN	0.59 (0.08, 4.54)	1.31 (0.68, 2.52)	0.77 (0.10, 6.19)
ETON	3.08 (0.69, 13.69)	0.56 (0.14, 2.30)	1.68 (0.21, 13.18)

Table 14d. Relative hazard of study endpoints associated with study exposure CHCs relative to LNG2 stratified by site and age in new users‡

	ATE	VTE	Total mortality
KPNC/KPSC			
DRSP	**2.32 (1.01, 5.33)**	**1.64 (1.14, 2.38)**	1.14 (0.28, 4.59)
NGMN	3.35 (0.87 (12.90)	**1.87 (1.00, 2.47)**	2.56 (0.26, 25.36)
ETON	1.81 (0.22, 14.52)	0.95 (0.34, 2.64)	0
Vanderbilt/Washington			
DRSP	0.28 (0.03, 2.50)	1.74 (0.81, 3.73)	3.99 (0.34, 47.51)
NGMN	0.16 (0.02, 1.45)	1.02 (0.50, 2.09)	3.20 (0.33, 31.22)
ETON	0.74 (0.08, 6.61)	1.22 (0.42, 3.49)	3.64 (0.20, 64.85)
Ages 10-34 years			
DRSP	0.53 (0.13, 2.11)	**2.16 (1.32, 3.54)**	1.32 (0.40, 4.36)
NGMN	0.78 (0.17, 3.66)	1.40 (0.75, 2.61)	2.85 (0.71, 11.41)
ETON	0.00 (-------)	1.71 (0.72, 4.07)	1.36 (0.15, 12.27)
Ages 35-55 years			
DRSP	**2.42 (1.01, 5.82)**	1.05 (0.65, 1.70)	0.62 (--------)
NGMN	0.55 (0.07, 4.52)	1.02 (0.50, 2.10)	0.67 (--------)
ETON	2.86 (0.60, 13.74)	0.49 (0.12, 2.02)	0.23 (--------)

‡ Site specific models adjusted for age, year of entry into the study and for hypertension, hyperlipidemia, and diabetes in ATE model.
 Age-specific models are adjusted for site, age (5 year age groups), and year of entry into the study.

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