Clinical Drug Interaction Studies with Combined Oral Contraceptives (COCs)

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Why Are Evaluations of Drug Interactions with COCs Important?

- **Combined Oral Contraceptives (COCs):** a progestin and an estrogen
  - widely used in females of reproductive potential in the United States
    - 22% used oral contraceptives among all contraception users in 2016
- **COCs are likely to be used concomitantly with other drugs**
  - ~45% of women use >1 prescription drug
  - ~12% of women use ≥3 prescription drugs
- **Interacting with other drugs may lead to serious consequence**
  - decreased exposure → unplanned pregnancy
  - increased exposure → venous thromboembolism (VTE)
- **Evaluation of drug-drug interactions (DDIs) with COCs is important when developing drugs intended to be used in females of reproductive potential**

Guttmacher Institute (July 2018) Contraception in the United States; Akbar M. et al. J Clin Pharmacol. 2018, 58(12):1655-65; Kavanaugh ML and Pliskin E (2020) F S Rep 1:83-93; National Center for Health Statistics. Health, United States, 2019.

Challenges for Evaluations of DDI with COCs Before A Guidance Was Available

- **Unclear whether a clinical COC DDI study should be conducted**
- **What is considered clinically meaningful COC DDI for exposure-based endpoints?**
- **Is it appropriate to extrapolate DDI results from one COC to another?**
- **No standardized labeling languages and format for**
  - content and location of including COC DDI information
  - results description and interpretation
  - risk mitigation strategies

History of Guidance Development

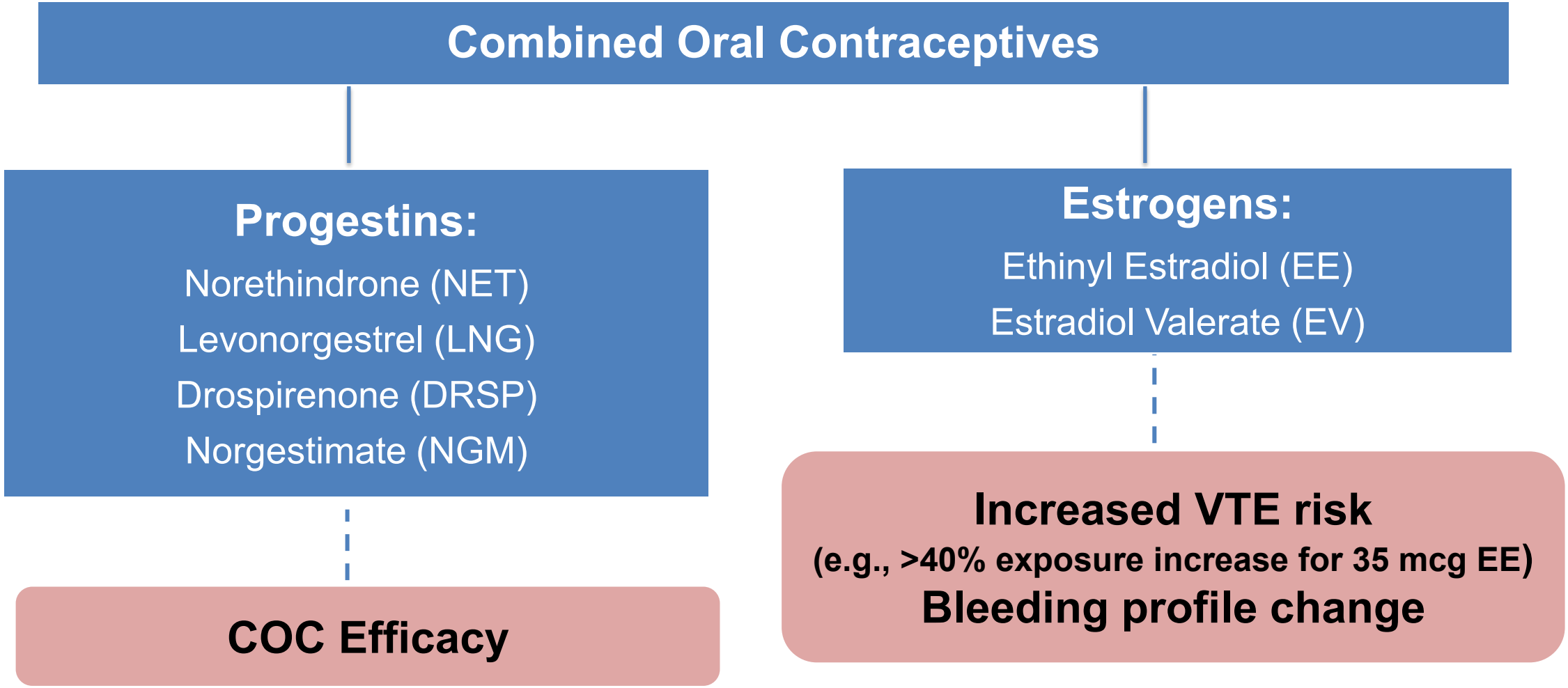
- FDA draft guidance on drug interactions (2012): study the effects of teratogens on contraceptives
- FDA public meeting "Drug Interactions with Hormonal Contraceptives: Public Health and Drug Development Implications" (2015)
- Publications:
  - Teratogenic drugs and their interactions with hormonal contraceptives (Clin Pharmacol Ther., 2016)
  - Role of CYP3A4 in oral contraceptives clearance (Clin Transl Sci., 2018)
  - Combined oral contraceptives as victims of drug interactions (Drug Metab Dispos. 2023)
- Standalone guidance *"Clinical Drug Interaction Studies With Combined Oral Contraceptives"*
  - Draft Guidance (2020)
  - **Final Guidance (2023)**

Final vs. Draft Guidance Changes

- ❑ More explanations/scenarios when a DDI study with COCs may or may not be recommended
- ❑ Adding recommendations for non-teratogenic drugs that are intended to be used as a combination therapy with teratogenic drugs
- ❑ Addition of alternative options for choosing COCs
- ❑ Adding more examples of pharmacodynamic parameters for clinical DDI studies with COCs

Table of Contents of the Guidance

Commonly Used Estrogens and Progestins



Metabolic Pathways of EE and Progestins

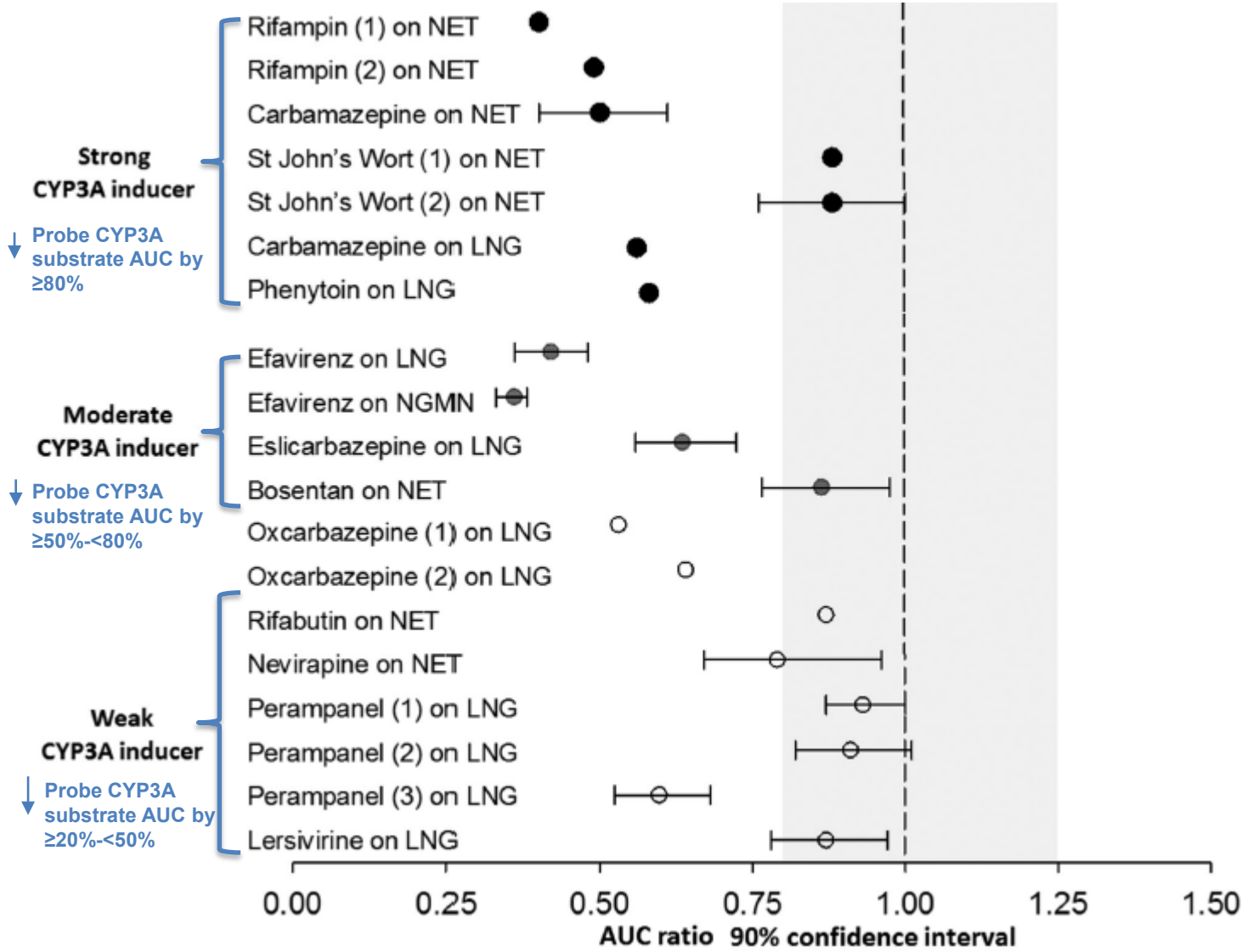
- ❑ CYP3A is involved in the metabolism of EE and commonly used progestins
- ❑ Other enzymes (e.g., SULT and UGT) may also contribute to the clearance of EE and certain progestins

Compound	Phase 1 Metabolism	Phase 2 Metabolism*
EE	CYP3A4 (major), CYP2C9 (minor)	SULT1E1, UGT1A1
NET	CYP3A4 (major), CYP2C19 (minor), Reduction	-
LNG	CYP3A4, Reduction,	SULT, UGT
DRSP	CYP3A4, Reduction	-
NGMN (active metabolite of NGM)	CYP3A4	-

CYP: cytochrome P450; NGMN: norelgestromin; SULT: sulfotransferases; UGT: UDP-glucuronosyltransferases
*Phase 2 enzymes involved in the biotransformation of metabolites of these hormones are not shown.

Li L, et al. Combined Oral Contraceptives As Victims of Drug Interactions. Drug Metab Dispos. 2023, 51(6):718-32.

CYP3A Inducers May Reduce Exposure of Progestins

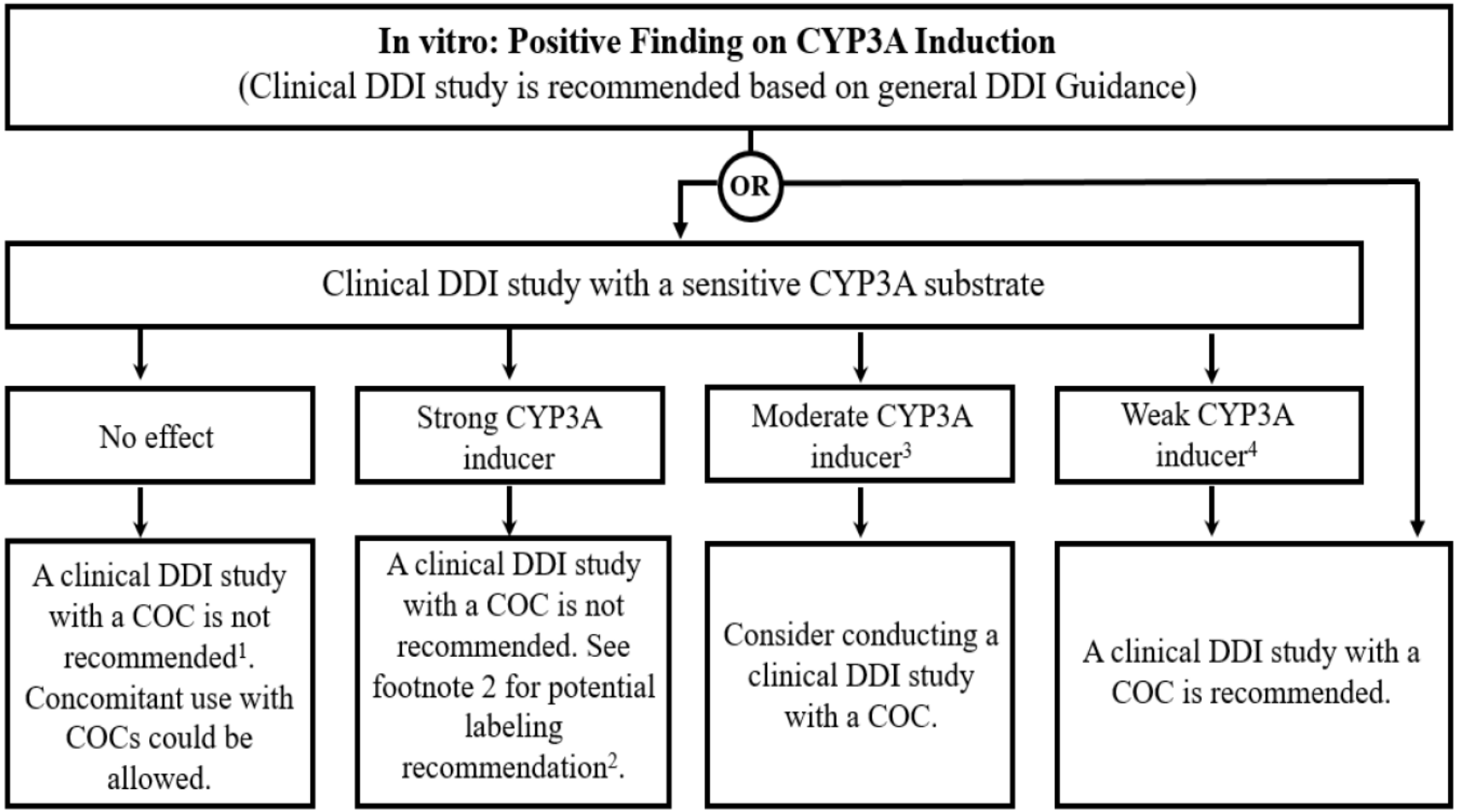


- Progestin exposure reduced significantly by
  - strong CYP3A inducers
  - some moderate CYP3A inducers

- Weak CYP3A inducers may have less effects than moderate inducers depending on
  - CYP3A induction potency
  - Sensitivity of progestin

Figure adapted from Zhang N, et al. Role of CYP3A in Oral Contraceptives Clearance. Clin Transl Sci. 2018, 11(3):251-60.

DDI Study Decision Tree: CYP3A Induction



[4] For weak CYP3A inducers, if sponsors do not intend to conduct a COC DDI study, adequate justification should be provided.
Some factors that should be taken into consideration include: (1) the projected magnitude of the interaction based on the study with a sensitive CYP3A substrate and other scientific evidence such as a lack of concurrent CYP3A inhibition; and (2) whether the investigational drug shows any nonclinical reproductive and developmental toxicity. Sponsors are encouraged to consult the relevant review division in such case.

Effect of CYP3A Inhibition on EE

Strong/moderate CYP3A inhibitors that also inhibit other enzyme(s) involved in the metabolism of EE significantly increased EE exposure

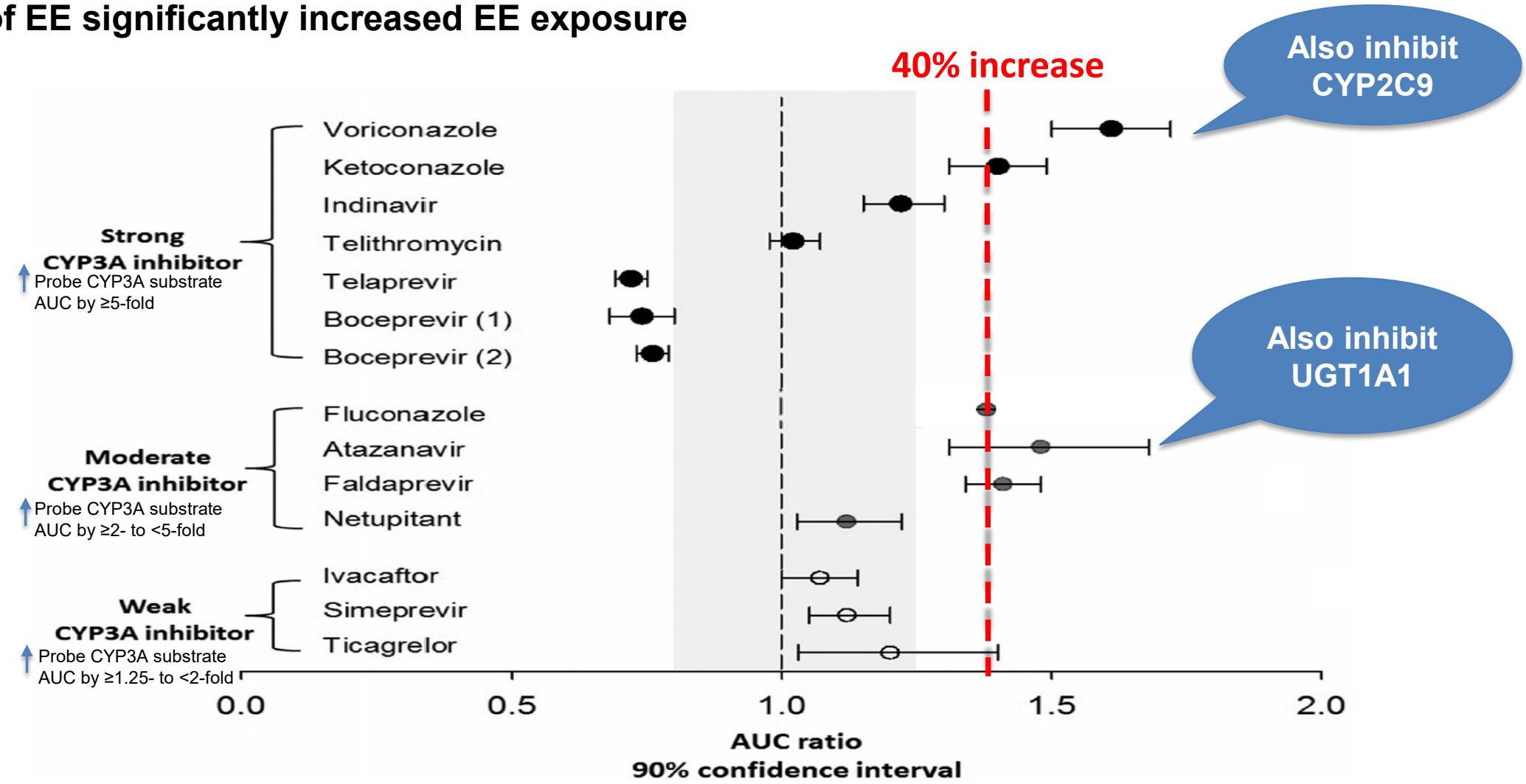
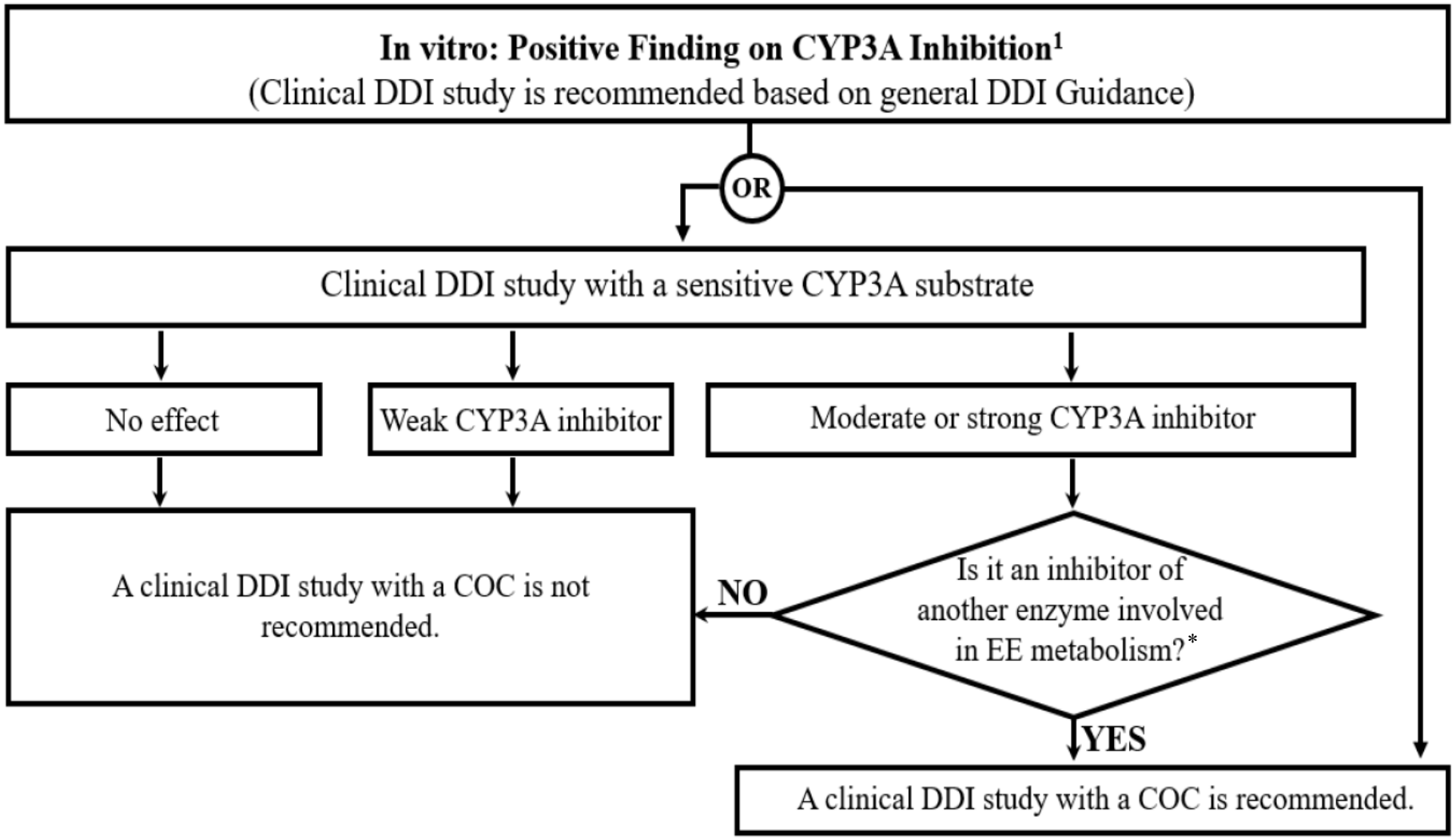


Figure adapted from Zhang N, et al. Role of CYP3A in Oral Contraceptives Clearance. Clin Transl Sci. 2018, 11(3):251-60.

Potent SULT1E1 Inhibitors Can Significantly Increase EE Exposure

- **Sulfate conjugation plays a major role in the first-pass metabolism of EE**
  - SULT1E1 is the primary isoform in EE sulfation
- **Clinical DDI study of EE/DRSP with ziritaxestat (SULT1E1 inhibitor)**
  - EE: Cmax ↑2.8-fold; AUC ↑2.4-fold
  - Significant Inhibition on CYP3A or UGT1A1 is not expected
- **Clinical DDI study of EE/NET with etoricoxib (SULT1E1 inhibitor)**
  - EE: Cmax ↑80%; AUC ↑ 50% - 60%
  - EE-sulfate: AUC ↓~40%

DDI Study Decision Tree: CYP3A Inhibition



* Inhibition of SULT1E1 alone can lead to a significant increase in EE exposures. For drugs that inhibit SULT1E1, regardless of its inhibitory effect on CYP3A, a clinical DDI study with COCs should be considered or appropriate mitigation strategies should be proposed in labeling.

Investigational Drugs That Are Teratogenic[1]

- **High risk of birth defects and development disorders**
- **A clinical DDI study with a COC should be conducted**
  - If the investigational drug is intended for use in women of childbearing potential
  - Regardless of in vitro or in vivo evidence

[1] For drugs that do not have teratogenic potential but are intended to be used with teratogenic drugs as a combination therapy, the sponsor should address the interaction potential with COCs as for teratogenic drugs.

COC DDI Study Design

Consistent with the general DDI Guidance

- **Study Subjects**: healthy premenopausal or postmenopausal women
- **Dosing Regimen**
  - Perpetrator (investigational drug):
    - Highest proposed therapeutic dose
    - Multiple-dose
  - Victim (COC):
    - PK assessment: Single-dose or multiple-dose
    - PD assessment: multiple-dose

COC DDI Study Design

- **Choice of COC**:
  - Commonly used COCs: NET, LNG, DRSP, NGM combined with EE
  - Sensitive progestin (e.g., DRSP) to CYP3A induction
    - A negative DDI result can be extrapolated to COCs containing progestins that are less sensitive to CYP3A induction (e.g., NET and LNG)
  - Less sensitive progestin (e.g., NET and LNG) to CYP3A induction
    - Increase the chances of confirming the lack of impact of a drug as an inducer on a specific COC

Results Interpretation & Labeling

- **Results Interpretation:**
  - 90% CIs for the geometric mean ratio of AUC and C_{max} are within 80-125%: no significant DDI
  - Outside of 80-125%: the totality of evidence (e.g., safety and efficacy of the COC) should be considered when determining the clinical impact of the DDI on the COC
- **Labeling Recommendation:**
  - Decreased exposures that may reduce effectiveness of the COC, use
    - an alternative contraceptive not affected by enzyme inducers (e.g., intrauterine system); or
    - an additional nonhormonal contraception (e.g., condom)
  - Increased EE exposures exceeding those observed at an EE dose of 50 mcg, avoid use with COCs
    - containing EE; or
    - exceeding a specific dose for EE

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❑ **Stakeholders who provided valuable comments to the draft guidance**

Knowledge Check

For a new drug intended for use by women of childbearing potential, which of the following can help determine if a clinical DDI study with COCs needs to be conducted:

a) In vitro studies indicate the drug has potential to alter the metabolism of hormones in COCs

b) Clinical DDI study indicates the drug is an inhibitor or inducer of Cytochrome P450 (CYP) 3A enzyme

c) Drug has teratogenic potential

d) All the above