

## SUPPLEMENTAL APPENDIX

### Data Sources and Search Strategies

A comprehensive search of several databases from each database's inception to February 19, 2020, English language, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of CYP2C19 and clopidogrel, ticagrelor, or prasugrel in human adults. The actual strategy listing all search terms used and how they are combined is available in the Appendix.

#### Ovid

Database(s): PsycINFO 1806 to February Week 2 2020, EBM Reviews - Cochrane Central Register of Controlled Trials January 2020, Embase 1974 to 2020 February 18, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 18, 2020

Search Strategy:

<u>#</u>	<u>Searches</u>	<u>Results</u>
1	exp Cytochrome P-450 CYP2C19/ (CYP2C19 or CYPIIC19 or "cytochrome p-450 cyp2c19" or "cytochrome P450 CYP2C19" or "cytochrome p-450 cypIIC19" or "cytochrome P450 CYPIIC19" or	10419
2	"cytochrome P450CYP2C19" or "cytochrome P450CYPIIC19" or "s-mephenytoin 4-hydroxylase").ti,ab,hw,kw.	13387
3	1 or 2	16691
4	exp Clopidogrel/ (clopidogrel or clopilet or grepid or iscover or "pcr 4099" or pcr4099 or "pcr-4099"	67267
5	or plavix or "sc 25989c" or "sc 25990c" or "sr 25989" or "sr 25990c" or sr25989 or sr25990c or zopya or zylagren or zyllt).ti,ab,hw,kw.	80598
6	exp Prasugrel Hydrochloride/ (34k66tbt99 or "389574-19-0" or "cs 747" or cs747 or "cs-747" or effient or efient	9521
7	or g89jq59i13 or "ly 640315" or ly640315 or "ly-640315" or prasugrel).ti,ab,hw,kw.	12089
8	exp Ticagrelor/ ("azd 6140" or azd6140 or "azd-6140" or brilinta or brilique or glh0314rvc or	9863
9	possia or ticagrelor).ti,ab,hw,kw.	13193
10	or/4-9	85557
11	3 and 10	3980
12	(exp animals/ or exp nonhuman/) not exp humans/	10961741

	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanzee or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.	9811857
14	11 not (12 or 13) limit 14 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in PsycINFO,CCTR,Embase; records were retained]	3961
15	limit 15 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in PsycINFO,CCTR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	3395
16	limit 14 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in PsycINFO,CCTR,Embase; records were retained]	1622
17	limit 17 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in PsycINFO,CCTR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	2926
18	18 not 16	302
19	20 14 not 19	4
20	21 review.pt.	3957
21		5150715

22	20 not 21	3295
23	limit 22 to (conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in PsycINFO,CCTR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	911
24	22 not 23	2384
25	remove duplicates from 24	1533

### Scopus

- 1 TITLE-ABS-KEY(CYP2C19 OR CYPIIC19 OR "cytochrome p-450 cyp2c19" OR "cytochrome P450 CYP2C19" OR "cytochrome p-450 cypIIC19" OR "cytochrome P450 CYPIIC19" OR "cytochrome P450CYP2C19" OR "cytochrome P450CYPIIC19" OR "s-mephenytoin 4-hydroxylase")
- 2 TITLE-ABS-KEY(clopidogrel OR clopilet OR grepid OR iscover OR "pcr 4099" OR pcr4099 OR "pcr-4099" OR plavix OR "sc 25989c" OR "sc 25990c" OR "sr 25989" OR "sr 25990c" OR sr25989 OR sr25990c OR zopya OR zylagren OR zyllt)
- 3 TITLE-ABS-KEY(34k66bt99 OR "389574-19-0" OR "cs 747" OR cs747 OR "cs-747" OR effient OR efient OR g89jq59i13 OR "ly 640315" OR ly640315 OR "ly-640315" OR prasugrel)
- 4 TITLE-ABS-KEY("azd 6140" OR azd6140 OR "azd-6140" OR brilinta OR briliq OR glh0314rvc OR possia OR ticagrelor)
- 5 LANGUAGE(english)
- 6 1 and (2 or 3 or 4) and 5
- 7 TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR

- monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))
- 8 6 and not 7
- 9 TITLE-ABS-KEY(newborn\* or neonat\* or infant\* or toddler\* or child\* or adolescent\* or paediatric\* or pediatric\* or girl or girls or boy or boys or teen or teens or teenager\* or preschooler\* or "pre-schooler\*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric\* OR "old people" OR "old person\*" OR "older people" OR "older person\*" OR "very old")
- 10 8 and not 9
- 11 TITLE(review)
- 12 10 and not 11
- 13 DOCTYPE(ab) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 14 12 and not 13
- 15 INDEX(embase) OR INDEX(medline) OR PMID(0\* OR 1\* OR 2\* OR 3\* OR 4\* OR 5\* OR 6\* OR 7\* OR 8\* OR 9\*)
- 16 14 and not 15

**Supplemental Table 1. Definitions of risk of bias indicators as implemented in this systematic review**

Randomization sequence: Sequence based on a computerized randomization or tables or random numbers.

Allocation concealment: the person enrolling patients and assigning them to a study arm is unaware of the assignment of the next patient. This is typically done with remote centralized assignment or sealed numbered opaque envelopes.

Blinding of patients, caregivers, outcome assessors and data analysts is achieved when these stakeholders perform their part of the trial without knowing the treatment assignment. Thereby deviations from intended intervention are not influenced by trial-specific recruitment and engagement activities.

Loss to follow up: if the proportion of patients on whom a trial does not have outcome data exceeds an arbitrary cutoff 10%, the loss to follow up was considered to increase the risk of attrition bias.

Selection of exposed and nonexposed cohort: selection is considered adequate when the study enrolls all eligible patients such as in consecutive patient enrollment and the enrollment methods do not suggest selective enrollment.

Ascertainment of exposure and outcome: ascertainment is considered adequate when data about exposure or outcome were derived from secured medical records or trial registries. Inadequate data would be derived from self-report or selective entry of data in a registry or database.

Comparability of study cohorts is judged adequate when important prognostic factors were similar between the two groups. This can also be achieved with adjustment for these factors. Factors considered critical in this systematic review were age and gender.

Adequate length of follow up: We considered studies that had a follow up of 6 months or more to have adequate follow up length.