Supplemental Material

Table S1. Details of Data Extraction and Discrepancy Observed between Approval label and Trial Publication.

Drug	Data Extraction Source*	Discrepancy between approval label and trial publication (yes/no)	Additional comments regarding extraction/discrepancy
Regadenoson	Trial publication	No	NA
Clevidipine	Trial publication	No	Approval label did not state percentage race for ESCAPE-1 and ESCAPE-2 trials and baseline characteristics for VELOCITY and ECLIPSE trial
Dronedarone	Trial publication	No	NA
Prasugel	Trial publication	No	NA
Saxagliptin	Trial publication	No	NA
Pitavastatin	Trial publication	NA	Approval label did not state baseline characteristics of study population.
Liraglutide	Approval label	No	Approval label reported overall baseline characteristics of all pivotal trials. Since there was no discrepancy between individual trial publications and data listed in approval label, approval label was preferred to extract data since it listed overall percentage participation of sex and race.
Dabigatran	Approval label	No	Trial publication did not report percentage race.
Azilsartan	Approval label	NA	Trial publication was not found. All data was available in the approval label
Linagliptin	Approval label	No	Approval label reported overall baseline characteristics of all pivotal trials. Since there was no discrepancy between individual trial publications and data listed in approval label, approval label was preferred to extract data since it listed overall percentage participation of sex and race.
Rivaroxaban	Trial publication	Yes	Discrepancy recorded between total number of participants in Record 1 and

			Record 2 studies. Approval label states 6579 receiving study drug while trial publication states 6890 participants receiving study drug. No discrepancy in Record 3 study or percentage participation by sex or race was recorded
Ticagrelor	Trial publication	No	Approval label only listed percentage White/Caucasian when compared to trial publication which listed percentage participation of other under-represented minorities as well (Black/African American and Asian).
Lomitapide Mesylate	Approval label	NA	Trial publication was not found. All data was available in the approval label
Apixaban	Trial publication	No	Race was not included in baseline characteristics for ARISTOTLE study publication. Data for race obtained from approval label.
Alogliptin Benzoate	Trial publication	No	NA
Mipomersen	Approval label	No	Trial publication did not report percentage race
Canagliflozin	Trial publication	No	NA
Riociguat	Trial publication	NA	Approval label did not state baseline characteristics of study population.
Macitentan	Trial publication	No	NA
Dapagliflozin	Trial publication	NA	Approval label did not state baseline characteristics of study population.
Vorapaxar Sulfate	Trial publication	Yes	Mild discrepancy between sex and race was recorded. Approval label states 22% females and 89% White/Caucasian while trial publication lists 24% females and 87% White/Caucasian
Empagliflozin	Trial publication	NA	Approval label did not state baseline characteristics of study population.
Edoxaban	Trial publication	No	Race was not included in baseline characteristics for both publications. Data for

			race was obtained from approval label.
Ivabradine Hydrochloride	Trial publication	No	Approval label did not state baseline characteristics (sex and race) of study population.
Cangrelor	Trial publication	NA	Approval label did not state baseline characteristics of study population.
Sacubitril; Valsartan	Trial publication	No	NA
Insulin Degludec	Approval label	NA	Trial publication was not found. All data was available in the approval label
Selexipag	Approval label	No	Trial publication did not report percentage race
Alirocumab	Trial publication	No	NA
Evolocumab	Trial publication	No	For study 1 and study 2, approval label reports baseline characteristics for patients with atherosclerotic CVD only, not the total population.
Lixisenatide	Approval label	NA	Trial publication was not found. All data was available in the approval label
Betrixaban	Trial publication	No	NA
Semaglutide	Trial publication	No	NA
Ertugliflozin	Trial publication	NA	Approval label did not state baseline characteristics of study population.
Angiotensin II Acetate	Approval label	No	Trial publication did not report percentage race.

*****Extraction details for total population, sex and race
NA = Not Applicable

Table S2. Estimation of Percentage of Women in Disease Populations.

Disease	Men	Women	% women in disease population	Source
Acute Coronary Syndrome	785,000 (unique hospitalisations)*	554,000 (unique hospitalisations)*	41	Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)*. 2016;388(10053):1659-1724
Coronary Heart Disease ~	68,287,106 (prevalence) ǂ	57,705,137 (prevalence) ǂ	46	GBD Compare | IHME Viz Hub. Vizhub.healthdata.org. https://vizhub.healthdata.org/gbd-compare/. [Accessed January 9, 2020.]
Heart Failure	60% (distribution) ^	40% (distribution) ^	40	Lee DS, Gona P, Vasan RS, et al. Relation of Disease Pathogenesis and Risk Factors to Heart Failure with Preserved or Reduced Ejection Fraction. Circulation 2009; 119:3070-3077
Atrial Fibrillation	19,721,283 (prevalence) ǂ	17,703,069 (prevalence) ǂ	47	GBD Compare | IHME Viz Hub. Vizhub.healthdata.org. https://vizhub.healthdata.org/gbd-compare/. [Accessed January 9, 2020.]
Hypertension	694,000,000 (prevalence) !	694,000,000 (prevalence) !	50	Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a system- atic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–450. doi: 10.1161/CIRCULATIONAHA.115.018912.
Pulmonary Arterial Hypertension	110 per 100,000 (hospitalization) §	147 per 100,000 (hospitalizations) §	57	George MG, Schieb LJ, Ayala C, et al. Pulmonary Hypertension Surveillance United States, 2001 to 2010. Chest 2014; 146(2):476-495, p. 484

Disease	Men	Women	% women in disease population	Source
Diabetes Mellitus	244,463,507 (prevalence) ǂ	229,640,671 (prevalence) ǂ	48	GBD Compare | IHME Viz Hub. Vizhub.healthdata.org. https://vizhub.healthdata.org/gbd-compare/. [Accessed January 9, 2020.]
Hyper-cholesterolemia	42,300,000 (prevalence) #	52,300,000 (prevalence) #	55	Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018; 137:e67-e492.

***** Based on first and secondary discharge post hospitalization from National Hospital Discharge Survey, NHLBI in 2014
ǂ GBD global prevalence for all ages
~ Data for Ischemic Heart Disease was utilized from the GBD database.
§ Hospitalization rates in 2009/2010
! Estimated adults aged ≥ 20 years
#Prevalence of TC ≥ 200 mg/dl, 2011-2014: Age ≥ 20 years
^ Patients with reduced ejection fraction in the Framingham HF study

Table S3. Participation of Women across Disease Indication.

Disease Indication	Number of Drugs	Number of Trials	Overall Enrollment, N	Women Enrollment, n	Percentage of Women Participants, %	Percentage of Women Among Disease Population, %	Participation to Prevalence Ratio (PPR)
Acute Coronary Syndrome	3	3	43174	11878	28	41	0.68
Coronary Heart Disease	1	1	26449	6326	24	46	0.52
Heart Failure	2	4	44923	10500	23	40	0.58
Atrial Fibrillation	6	13	94624	39152	41	42	0.98
Hypertension	2	13	7788	3434	44	50	0.88
Pulmonary Arterial Hypertension	3	4	2602	2016	77	57	1.35
Diabetes Mellitus	11	86	64282	29352	46	48	0.96
Hypercholesterolemia	5	16	10129	4691	46	55	0.84

Table S4. Summary of Efficacy* and Safety# Results by Sex for Diabetes Drugs.

Drug	Primary efficacy endpoint	Efficacy of Drug by sex	Drug related adverse events by sex	Source‡
Saxagliptin Hydrochloride		Monotherapy study yielded a "statistically significant interaction for sex with a p-value of 0.01; a larger effect is seen for males than females. This subgroup difference was not observed in other studies."	NR	Clinical/Statistical Review
Liraglutide		Efficacy was not affected by sex	NR	Clinical/Statistical Review
Linagliptin		Efficacy was not affected by sex	NR	Clinical/Statistical Review
Alogliptin Benzoate		Efficacy was not affected by sex	NR	Approval Label
Canagliflozin		Efficacy was not affected by sex	Increased risk genital mycotic infections in both males and females. However Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections.	Clinical/Statistical Review
Dapagliflozin		Efficacy was not affected by sex	"Genital mycotic infections were more frequently reported in females than in males."	Clinical/Statistical Review
Empagliflozin	Changes from baseline in	"For comparison between	"Genital mycotic	Clinical/Statistical Review

	hemoglobin HbA1C	empagliflozin 25mg and placebo, the subgroup analysis by sex shows a greater treatment effect in males (mean= -0.76, SE=0.05) than in females (mean=-0.58, SE=0.06). The p value for the treatment-by-sex interaction term is 0.03. However, for the comparison between empagliflozin 10mg and placebo, no heterogeneity of treatment effect is detected in males vs. females (P=0.18)."	infections occurred more frequently in female than male patients."	
Insulin Degludec		Efficacy was not affected by sex	NR	Clinical/Statistical Review
Lixisenatide		Efficacy was not affected by sex	NR	Clinical/Statistical Review
Semaglutide		"In trial 3625 (SUSTAIN 4), a slightly higher effect was seen in females compared to males with the 0.5 mg dose (-0.45 versus -0.11, nominal p-value = 0.03), but there was no difference with the 1.0 mg dose."	NR	Clinical/Statistical Review
Ertugliflozin		Efficacy was not affected by sex	Female genital mycotic infections were more common than male genital mycotic infections.	Clinical/Statistical Review

***** We evaluated sex difference in efficacy results by reviewing the product labeling first. If the information is not available in labeling, we then obtained efficacy results by sex from FDA clinical and statistical reviews.

Safety results were obtained by reviewing product labelling. Only clinically meaningful differences in safety by sex are described in labelling. If these differences are not identified then they are often not reported. Product labelling that did not report any statement regarding clinically meaningful effect between drug related adverse effects is reported as NR.

NR = Not Reported

‡ Refers to the source from where efficacy results were obtained.

Table S5. HRs and 95% CI for Primary Efficacy Endpoints by sex.

Drug/Sex	Number of patients	Hazard Ratio [95% CI][‡]
Dronedarone		
Male	2,459	0.74 [0.64, 0.85]
Female	2,169	0.77 [0.67, 0.89]
Dabigatran		
Male	11,514	0.72 [0.54, 0.95]
Female	6,598	0.58 [0.40, 0.79]
Apixaban		
Male	11,785	0.82 [0.65,1.04]
Female	6,416	0.74 [0.56, 1.00]
Edoxaban		
Male	8,761	0.87 [0.71, 1.07]
Female	5,310	0.87 [0.69, 1.11]
Prasugrel		
Male	10,085	0.79 [0.70, 0.90]
Female	3,523	0.88 [0.73, 1.07]
Ticagrelor		
Male	13,336	0.85 [0.76, 0.95]
Female	5,288	0.83 [0.71, 0.97]
Cangrelor		
Male	7,889	0.84 [0.69, 1.03]
Female	3,050	0.67 [0.50, 0.92]
Macitentan		
Male	113	0.49 [0.27, 0.89]
Female	379	0.57 [0.41, 0.80]
Selexipag		
Male	233	0.56 [0.31, 1.02][*]
Female	923	0.61 [0.46, 0.82][*]
Ivabradine Hydrochloride		
Male	4, 970	0.84 [0.76, 0.94]
Female	1, 535	0.74 [0.60, 0.91]
Sacubitril; Valsartan		
Male	6,595	0.80 [0.73, 0.89]
Female	1, 847	0.77 [0.62, 0.94]
Vorapaxar Sulfate		
Male	15,801	0.82 [0.74, 0.91]
Female	4,369	0.84 [0.70, 1.00]
Angiotensin II Acetate		
Male	195	9.3 [4.9, 17.9][#]
Female	126	5.9 [2.7, 13.1][#]

[‡] Includes results for primary efficacy endpoint for each drug by sex. Results do not take into account any comparisons or adjustments for any other factor.

[*] Represents 99% Confidence Interval

[#] Odds ratio was reported

Table S6. Summary of Efficacy* and Safety Results# by Sex for Cardiovascular Drugs.

Cardiovascular Area/Drug	Primary efficacy endpoint	Efficacy of Drug by sex	Drug related adverse events by sex	Source‡
Atrial Fibrillation				
Dronedarone	Hospitalization for cardiovascular reasons or death from any cause.	Efficacy was not affected by sex	Adverse events were not affected by sex	Approval Label
Dabigatran	Stroke and systemic embolism	Efficacy was not affected by sex	Adverse events were not affected by sex	Approval Label
Rivaroxaban	Incidences of DVT, non-fatal PE or all-cause death	Efficacy was not affected by sex	NR	Clinical/Statistical Review
Apixaban	Ischemic stroke, hemorrhagic stroke or systemic embolism	Efficacy was not affected by sex	Adverse events were not affected by sex	Clinical/Statistical Review
Edoxaban	Occurrence of stroke or a systemic emboli	Efficacy was not affected by sex	Adverse events were not affected by sex	Approval Label
Betrixaban	Asymptomatic proximal DVT, Symptomatic DVT, Non-fatal PE or VTE related death	Efficacy was not affected by sex	NR	Clinical/Statistical Review
Acute Coronary Syndrome				
Prasugrel	cardiovascular death, nonfatal MI, or nonfatal stroke	Efficacy was not affected by sex	NR	Approval Label
Ticagrelor				
Cangrelor	all-cause death, MI, ischemia-driven revascularization, and stent thrombosis	Efficacy was not affected by sex	Adverse events were not affected by sex	Approval Label
Hypertension				
Clevidipine	Changes from baseline in systolic blood pressure (mmHg)	Efficacy was not affected by sex	NR	Clinical/Statistical Review
Azilsartan			Adverse events were not affected by sex	Approval Label
Pulmonary Arterial Hypertension				
Riociguat	changes from baseline in the 6-	Efficacy was not affected by sex	NR	Clinical/Statistical Review

	minute walk distance (m)			
Macitentan	time to the first occurrence of death, Changes from baseline in the 6-minute walk distance (m)	Efficacy was not affected by sex	NR	Approval Label
Selexipag	Death, hospitalization for PAH, changes from baseline in the 6-minute walk distance (m)	Efficacy was not affected by sex	NR	Approval Label
Heart Failure				
Ivabradine Hydrochloride	Cardiovascular death, hospitalization for worsening heart failure	Efficacy was not affected by sex	NR	Approval Label
Sacubitril; Valsartan		Efficacy was not affected by sex	NR	Approval Label
Coronary Heart Disease				
Vorapaxar Sulfate	Cardiovascular death, MI, stroke	Efficacy was not affected by sex	Adverse events were not affected by sex	Approval Label
Hypercholesterolemia				
Pitavastatin	Percentage decrease from baseline to study end point in LDL-C	"In study NK-104305 females experienced greater LDL-C lowering than did males on Livalo compared to controls."	NR	Clinical/Statistical Review
Lomitapide Mesylate		Efficacy was not affected by sex	NR	Clinical/Statistical Review
Mipomersen		"the treatment effect in females was larger than that seen in males" *	NR	Clinical/Statistical Review
Alirocumab		"There is an indication that the effect for Praluent on the percent change in LDL-C at week 24 is larger in males than females; however, it is unclear whether this difference between sexes in the effect on a surrogate endpoint will	NR	Clinical/Statistical Review

		translate into an important difference between sexes in the clinical cardiovascular outcome."		
Evolocumab		Efficacy was not affected by sex	NR	Clinical/Statistical Review
Other				
Regadenoson	Presence/absence of reversible perfusion defects	Efficacy was not affected by sex	NR	Clinical/Statistical Review
Angiotensin II Acetate	Clinical response of LJPC-501 infusion on MAP	Efficacy was not affected by sex	NR	Clinical/Statistical Review

***** We evaluated sex difference in efficacy results by reviewing the product labeling first. If the information is not available in labeling, we then obtained efficacy results by sex from FDA clinical and statistical reviews.

Safety results were obtained by reviewing product labelling. Only clinically meaningful differences in safety by sex are described in labelling. If these differences are not identified then they are often not reported. Product labelling that did not report any statement regarding no clinically meaningful effect between drug related adverse effects is reported as NR.

‡ Refers to the source from where efficacy results were obtained.

DVT= deep vein thrombosis. PE= pulmonary embolism. VTE= venous thromboembolism. MI= myocardial infarction. MAP= mean arterial pressure. NR = Not Reported

Table S7. Number of Pivotal Drug trials reporting data of ethnic/racial minorities.

Race	No. of Trials reporting data	Overall Population in trials reporting data, N	Participation of Race, n (%)
White/Caucasian	122	269,176	218,054 (81.0)
Black/African American	104	175,487	6,325 (3.6)
Asian	76	178,004	22,076 (12.4)
Ethnicity			
Hispanic/Latino	51	56,235	6,333 (11.3)