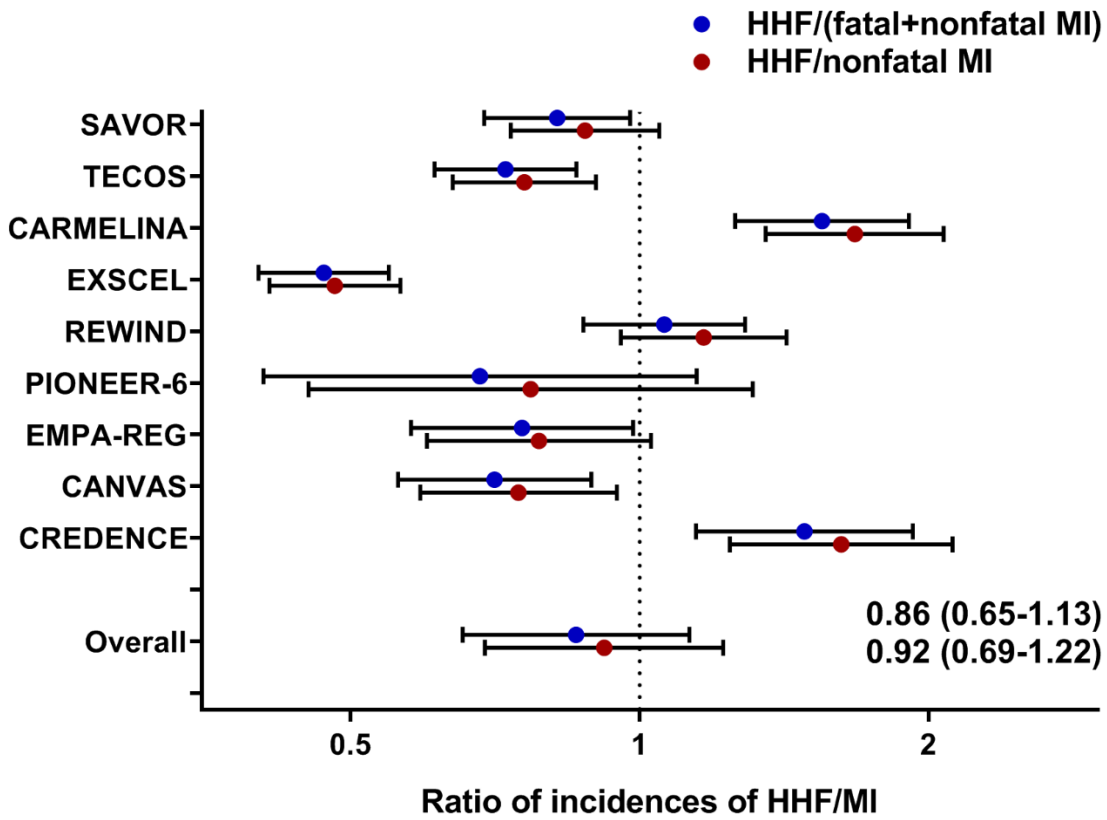
Online-Only Supplemental Material

Supplemental Material

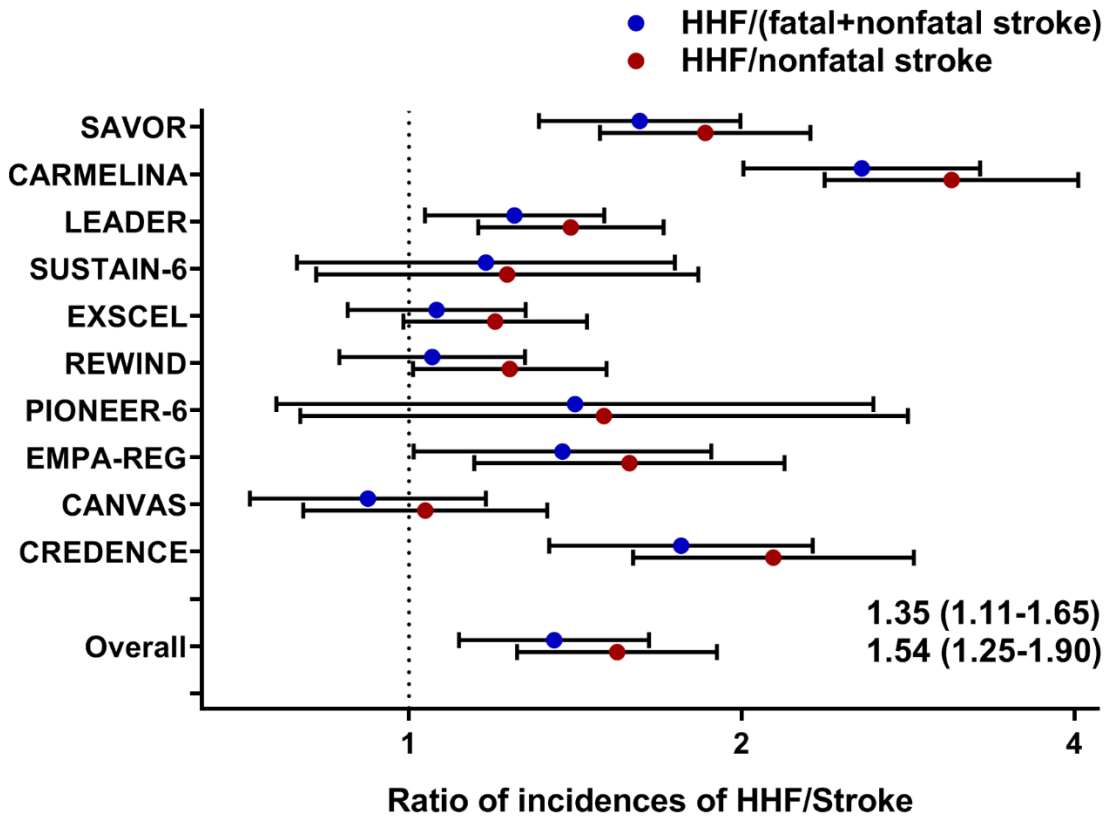
Incidence of MI. Trials varied in two key aspects regarding adjudicated MI events: 1) in- vs. exclusion of silent MIs; and 2) reporting of nonfatal and/or 'fatal + nonfatal' events. Given only 6 trials reported on silent MIs (LEADER, SUSTAIN-6, PIONEER-6, REWIND, OMNEON, and EMPA-REG), incidence rates exclusive of these events were sought for these trials to maximise unity with all others (n.b. this extended to seeking incidence rates of MACE excluding silent MIs). For OMNEON and REWIND, these data were provided directly by the investigators; otherwise, relevant data were available from either trial publications, the clinical study report, or regulatory agency documents (except for SUSTAIN-6 and PIONEER-6, for which MACE excluding silent MI could not be derived).

Incidence of nonfatal MI was preferred for calculation of the HHF/MI ratio; however, rates excluding fatal events were unavailable for ELIXA, LEADER, HARMONY, OMNEON and DECLARE. After comparing ratios of HHF/(nonfatal MI) and HHF/(fatal + nonfatal MI) in nine other trials that reported the breakdown of nonfatal and fatal MIs (Online Figure S1 below), it was determined that inclusion of fatal events had minimal impact on the incidence rate ratio. Thus, HHF/MI data for ELIXA, LEADER, HARMONY, OMNEON and DECLARE – where HHF/MI reflected fatal+nonfatal MI – were retained in analyses.



Supplemental Figure S1. Comparison of incidence rate ratios of HHF/MI, according to inclusion vs. exclusion of fatal MI events.
HHF, hospitalization for heart failure; MI, myocardial infarction.

Incidence of Stroke. Similarly to MI, the ELIXA, HARMONY, TECOS, OMNEON and DECLARE trials only reported on the incidence of stroke inclusive of both fatal and nonfatal events. HHF/stroke data for these trials – where HHF/stroke reflected fatal+nonfatal stroke – were again retained in our analyses nonetheless. This was based on there being no significant underestimation of the incidence rate ratio across 10 other trials that reported on both nonfatal and fatal stroke incidence separately (Online Figure S2 below).



Supplemental Figure S2. Comparison of incidence rate ratios of HHF/Stroke, according to inclusion vs. exclusion of fatal stroke events.
HHF, hospitalization for heart failure.

Incidence of stroke in SAVOR and DECLARE. In both the SAVOR (1) and DECLARE trials (2), rates of stroke were based on ischemic events only and – unlike other trials – excluded hemorrhagic and unknown/undefined stroke types. Since the incidence of stroke inclusive of all stroke types in DECLARE was reported in a subsequent meta-analysis (3), this rate was used in the current study for concordance with all other trials. Although corresponding data for SAVOR were unavailable, reported rates on the incidence of ischemic stroke were still used given DECLARE showed a large majority of its stroke events to be of ischemic origin (90%).

Additional notes regarding specific trials

REWIND. Incidence rates of all CV events in the REWIND trial were not derived from the primary publication (4), but were provided by the REWIND investigators specifically for the current analyses. This was to ensure that: 1) the incidence of HHF was consistent with other trials (REWIND having employed a broader definition that included urgent outpatient visits for heart failure); and 2) the denominator for all CVD vs. MRF comparisons noted in Table 1 (i.e. n=4682) did not include anyone for whom a history of CVD was unknown or missing (as indicated in Figure 3 in the primary publication).

EMPA-REG. The definition of the composite endpoint 'CV death or HHF' in EMPA-REG excluded fatal stroke – unlike other trials. Nevertheless, we retained the reported rate in our analyses given that the rate of fatal stroke in the placebo group was only 0.5% and the number of 'CV death or HHF' events (n=198) would have increased by only a small number – i.e. between zero and 11 events (where zero would apply if all participants who died of stroke also experienced a preceding in-trial HHF event; 11 if none had such an event) (5).

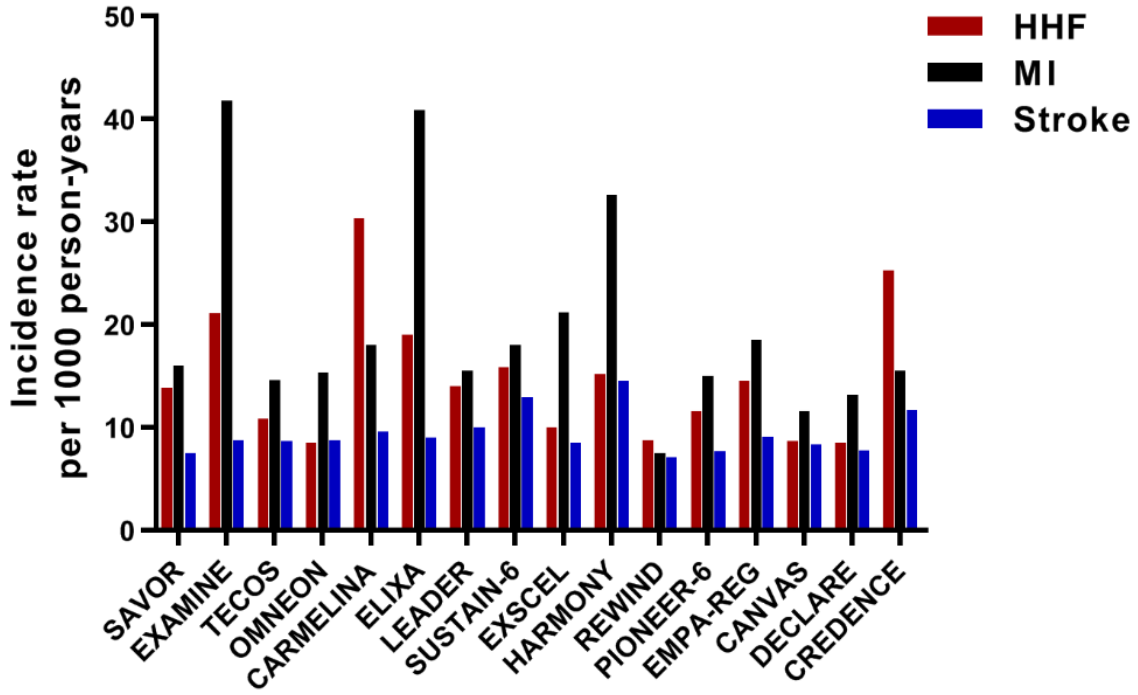
Supplemental Table S1. Eligibility criteria for CVD and MRF subgroups

Trial	CVD group	MRF group
LEADER (6,7)	History of any of the following: - MI - Stroke or TIA - ≥50% coronary artery stenosis - PCI or CABG - Angina with a positive stress imaging test and/or asymptomatic ischemia - ≥50% intracranial or carotid artery stenosis - ≥50% peripheral artery stenosis by imaging or ABI <0.9	≥1 of the following: - CKD (microalbuminuria, proteinuria, or eGFR <60 $ml \cdot min^{-1} \cdot 1.73m^{-2}$) - Hypertension with LV hypertrophy - NYHA class II or III heart failure - LV systolic or diastolic dysfunction
SUSTAIN-6 (8,9)	History of any of the following: - MI - Stroke or TIA - Peripheral artery disease - ≥50% arterial stenosis (any) - PCI, CABG or peripheral revascularization - NYHA class II or III heart failure	≥1 of the following: - Hypertension with LV hypertrophy - LV systolic or diastolic dysfunction - CKD (microalbuminuria, proteinuria, or eGFR <60 $ml \cdot min^{-1} \cdot 1.73m^{-2}$)
EXSCEL (10,11)	History of any of the following: - MI - Ischemic stroke - ≥50% coronary artery stenosis - PCI, CABG or peripheral revascularization - ≥50% carotid artery stenosis - Amputation due to vascular disease or intermittent claudication with ABI or toe-brachial index <0.9	None
REWIND (4)	History of any of the following: - MI - Unstable angina - Ischemic stroke - Need for PCI or hospitalization for unstable angina with ECG changes - Myocardial ischemia by stress test or with cardiac imaging	≥1 indicator of subclinical vascular disease: - >50% arterial stenosis (coronary, carotid, or lower extremity) - LV hypertrophy - CKD (albuminuria or eGFR <60 $ml \cdot min^{-1} \cdot 1.73m^{-2}$) **OR** ≥2 of the following: - Current tobacco use - Dyslipidemia - Hypertension - Abdominal obesity

Trial	CVD group	MRF group
CANVAS (12,13)	History of any of the following: - MI - Stroke - Hospitalized unstable angina - PCI, CABG or peripheral revascularization - Amputation due to vascular disease or symptomatic carotid or peripheral vascular disease	≥2 of the following: - Diabetes duration 10+ years - Systolic BP >140 mmHg on ≥1 antihypertensive medication - Current smoking - Micro- or macro-albuminuria - HDL cholesterol <1 mmol/L
DECLARE (2)	History of any of the following: - Ischemic heart disease (MI, PCI, CABG, or ≥50% coronary artery stenosis) - Cerebrovascular disease (ischemic stroke or carotid revascularization) - Peripheral artery disease (peripheral revascularization, amputation due to vascular disease, or intermittent claudication with ABI <0.9)	≥1 of the following: - LDL cholesterol >3.36 mmol/l - Hypertension (>140 mmHg and >90 mmHg, or on antihypertensive medication) - Current smoking
CREDENCE (14,15) (concurrent CKD was a requirement for both the CVD and MRF groups)	History of coronary, cerebrovascular, or peripheral vascular disease.	None

ABI, ankle-brachial index; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left-ventricular; MI, myocardial infarction; MRF, multiple risk factors; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplemental Results



Supplemental Figure S3. Incidence of CV events in the 16 analyzed trials
Rates of HHF, MI and stroke in the placebo arms of the 16 cardiovascular outcomes trials. For MI and stroke, incidence rates exclusive of silent MIs and fatal events were prioritized. HHF, hospitalization for heart failure; MI, myocardial infarction.

Supplemental Table S2. Baseline characteristics of the CVD and MRF subgroups

Trial	N	Age (years)	Male (%)	BMI (kg/m^2)	Diabetes duration (years)	HbA1c (%)	Insulin therapy (%)	Prior HF (%)	eGFR <60 ml min^{-1} $1.73m^{-2}$ (%)
LEADER									
CVD	3372	64.0	67.8	32.1	12.9	8.7	45.9	18.7	20.3
MRF	1300	65.5	54.4	33.3	13.2	8.7	44.8	15.5	27.6
SUSTAIN-6									
CVD	1271	64.2	63.6	33.0	13.3	8.7	NR	31.2	NR
MRF	378	66.0	47.9	32.3	14.6	8.7	NR	0	NR
EXSCEL									
CVD	5388	63.9	66.8	31.4	12	8.0	51.6	19.1	21.1
MRF	2008	59.4	49.0	33.0	10	8.0	31.7	8.1	11.9
REWIND									
CVD	1554	65.7	69.9	31.9	10.7	7.3	23.6	16.5	24
MRF	3128	66.3	47.2	32.5	10.5	7.4	24.5	5.1	22
CANVAS									
CVD	2900	63.8	67.8	31.7	13.4	8.2	51.3	17.8	22.8
MRF	1447	62.8	54.3	32.5	14.2	8.3	49.6	9.8	18.5
DECLARE									
CVD	3500	62.5	72.1	32.1	10.1	8.4	44.2	16.3	10.9
MRF	5078	64.7	56.1	32.0	9.9	8.3	36.4	5.5	7.9
CREDENCE									
CVD	1107	64.6	69.5	31.6	16.5	8.3	67.8	23.9	61.5
MRF	1092	61.7	63.9	31.0	15.5	8.3	62.4	5.3	58.9

Data are mean/median or %, except where indicated.

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; MRF, multiple risk factors; NR, not reported.

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