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Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

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Abbreviations and acronyms

ABI	Ankle–brachial index
ABPM	Ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACNAT	Acyl-CoA N-acyltransferase
ACS	Acute coronary syndrome
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AF	Atrial fibrillation
ARR	Absolute risk reduction
ART	Arterial Revascularization Trial
ASA	Acetylsalicylic acid
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASCVD	Atherosclerotic cardiovascular disease
ATLAS-ACS TIMI 51	Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 51
BARC	Bleeding Academic Research Consortium
BCRP	Breast cancer resistance protein
b.i.d.	Twice a day (*bis in die*)
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
Cana	Canagliflozin
CANVAS	Canagliflozin Cardiovascular Assessment Study
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus
CAROLINA	Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients With Type 2 Diabetes
CE	Carboxylesterase
CI	Confidence interval
CKD	Chronic kidney disease
CMD	Coronary microvascular dysfunction
COVADIS	Coronary Vasomotion Disorders International Study
COX	Cyclo-oxygenase
CREDENCE	Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P
Dapa	Dapagliflozin
DAPA-CKD	Dapagliflozin and prevention of adverse outcomes in chronic kidney disease
DAPT	Dual antiplatelet therapy
DAT	Dual antithrombotic therapy
DBP	Diastolic blood pressure
DDI	Drug–drug interaction
DECLARE- TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58 trial
DELIVER	Dapagliflozin in Heart Failure with Mildly Preserved or Preserved Ejection Fraction
DES	Drug-eluting stent
DM	Diabetes mellitus

DPP-4	Dipeptidyl peptidase-4
E-ZES	Endeavor zotarolimus-eluting stent
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
EES	Everolimus-eluting stent
eGFR	Estimated glomerular filtration rate
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
Empa	Empagliflozin
EMPA-KIDNEY	The study of heart and kidney protection with empagliflozin
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose
Ertu	Ertugliflozin
ESC	European Society of Cardiology
EXAMINE	Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care
EXCEL	Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
FAME	Fractional Flow Reserve vs. Angiography for Multivessel Evaluation
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
GAD	Glutamic acid decarboxylase
GI	Gastrointestinal
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HARMONY Outcomes	Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease
Hb	Haemoglobin
HbA1c	Glycated haemoglobin
HBPM	Home blood pressure monitoring
HDL-C	High-density lipoprotein-cholesterol
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HfrEF	Heart failure with reduced ejection fraction
HHF	Hospitalization for heart failure
HOT	Hypertension Optimal Treatment trial
HR	Hazard ratio
IA-2	Tyrosine phosphatase islet antigen-2
ICH	Intracerebral haemorrhage
IPD	Individual patient data
IQR	Interquartile range
INOCA	Ischaemia with no obstructive coronary artery disease
INR	International Normalized Ratio
ISTH	International Society on Thrombosis and Haemostasis
LAD	Left anterior descending coronary artery
LD	Loading dose
LDL-C	Low-density lipoprotein-cholesterol
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardio-cerebral event
MACE	Major adverse cardiovascular events
MAIN-COMPARE	Revascularization for Unprotected Left Main Coronary Artery Stenosis
MD	Maintaining dose
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
NA	Not applicable
NACCE	Net adverse clinical and cerebral events
NNH	Number needed to harm
NNT	Number needed to treat
NOAC	Non-Vitamin K Antagonist Oral Anticoagulant
NR	Not reported
NS	Not significant
o.d.	Once a day (*omni die*)
OAC	Oral anticoagulant
OATP	Organic anion-transporting polypeptides
OGTT	Oral glucose tolerance test
PCI	Percutaneous coronary intervention
P-gp	P-glycoprotein
PIONEER 6	A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes
PK	Pharmacokinetics
Pla	Placebo
PTCA	Percutaneous transluminal coronary angioplasty
PVD	Peripheral vascular disease
PY	Patient-years
RAAS	Renin-angiotensin-aldosterone system
RBC	Red blood cell
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
REVIVED-BCIS2	Revascularization for Ischemic Ventricular Dysfunction
RR	Relative Risk
SAPT	Single antiplatelet therapy
SAVOR-TIMI 53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis In Myocardial Infarction 53
SBP	Systolic blood pressure
SD	Standard deviation
Ser	Serine
SGLT2	Sodium–glucose co-transporter-2
Sota	Sotagliflozin
ST	Stent thrombosis
STEMI	ST-elevation myocardial infarction
STICH	Surgical Treatment for Ischemic Heart Failure

SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
SYNTAX	Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery
SYNTAXES	SYNTAX Extended survival
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAT	Triple antithrombotic therapy
$TcPO_2$	Transcutaneous oxygen pressure
TIA	Transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TLF	Target-lesion failure
UA	Unstable angina
UACR	Urinary albumin-to-creatinine ratio
UGT	Uridine 5'-diphosphoglucuronosyltransferase
VKA	Vitamin K antagonist
ZnT8	Zinc transporter-8

1. Diagnosis of diabetes

Table S1 Conditions associated with reduced accuracy of glycated haemoglobin for diabetes diagnosis and management of glycaemia

↑ HbA1c	Clinical relevance
Physiological and/or non-modifiable conditions: Age, ethnicity, haemoglobin variants ***Pathological and/or modifiable conditions:*** Iron-deficiency anaemia, folic acid deficiency, chronic alcoholism	• Incorrect diagnosis of diabetes (if only HbA1c is used) • Over-treatment of high HbA1c and precipitation of hypoglycaemia
↓ *HbA1c*	**Clinical relevance**
Physiological and/or non-modifiable conditions: Pregnancy, haemoglobin variants ***Pathological and/or modifiable conditions:*** Haemolytic anaemia or anaemia of chronic disease, acute blood loss (and transfusion), renal failure	• Missing the diagnosis of diabetes (if only HbA1c is used) • Under-treatment of glycaemia, putting individuals at risk of diabetes complications

↑, raised; ↓, low; HbA1c, glycated haemoglobin.
Adapted from American Diabetes Association as well as Krhač and Lovrenčić.[1,2]

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1.1. Classifying diabetes

Table S2 Classification of diabetes

Type of diabetes	Pathogenic mechanisms and clinical presentation	Diagnostic aids
Type 1 diabetes	Autoimmune destruction of pancreatic β-cells. Presentation is usually in the younger age group (although it can occur at any age) with a short history of osmotic symptoms (polyuria, polydipsia) and significant weight loss. Diabetic ketoacidosis may be the first presentation	Positive antibodies (GAD, IA-2, and ZnT8), low C-peptide levels
Type 2 diabetes	Insulin resistance and relative insulin deficiency, with individuals usually overweight or obese. Presentation is in older adults, although children can be affected due to the rising prevalence of childhood obesity. Some individuals have osmotic symptoms but others can be asymptomatic, with diabetes diagnosed when presenting with cardiovascular complications	Diagnosis is usually clinical. Negative antibodies and high normal or raised C-peptide levels aid diagnosis in unclear cases
Monogenic diabetes	Various mutations in genes involved in insulin secretion and glucose metabolism. Can present with osmotic symptoms or can be discovered during routine testing. A family history of diabetes across several generations (autosomal dominant manner) should raise suspicion of this condition	Negative antibodies and detectable C-peptide levels followed by genetic testing starting with the common mutations

Continued

Secondary diabetes	Pancreatic destruction (pancreatitis, cystic fibrosis, pancreatic cancer), endocrine causes (growth hormone and steroid hypersecretion), therapeutic agents (steroid, anti-retroviral, and cancer therapies)	History, physical examination, and review of drug therapies
Stress hyperglycaemia	Hyperglycaemia during hospital admission that normalizes after discharge. Should not be confused with newly diagnosed diabetes	Raised in-hospital glucose and normal HbA1c. Diagnosis is confirmed by repeat glucose testing within weeks of hospital discharge (preferably using OGTT)
Gestational diabetes	Pathophysiology is related to insulin resistance and relative insulin deficiency (individuals are usually overweight or obese). However, it can also occur in lean women with a predominant insulin secretory defect. Hyperglycaemia is diagnosed in the second or third trimester of pregnancy in those without overt diabetes in pregnancy	OGTT at 24–28 weeks of gestation

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GAD, glutamic acid decarboxylase; HbA1c, glycated haemoglobin; IA-2, tyrosine phosphatase islet antigen-2; OGTT, oral glucose tolerance test; ZnT8, zinc transporter-8.

1.1.1. Alternative diabetes classification

Given the large heterogeneity of the diabetes population and the variable risk of developing complications, data-driven cluster analysis using six variables (glutamic acid decarboxylase [GAD] antibodies, age, body mass index [BMI], glycated haemoglobin [HbA1c], and homeostatic model assessment-2 for β-cell function and insulin resistance) provided the basis for classification into five clusters, which predict complication risk.[3]

While these clusters help to improve the taxonomy of diabetes, this approach risks to over-simplify a highly heterogeneous condition. Moreover, the clusters were created according to a set of variables, and key vascular parameters were not included, such as inflammatory markers and lipid profile. Importantly, in the context of cardiovascular (CV) pathology, the five clusters failed to show differences in coronary artery and cerebrovascular disease outcomes, casting doubt on their practical use in predicting vascular disease.[4] Additional work has shown that phenotypic measures outperform clusters to predict specific outcomes and therefore, at present, risk assessment at an individual level has the best clinical utility.[4–6]

2. Cardiovascular risk assessment in patients with type 2 diabetes

The SCORE2-Diabetes algorithm can be accessed in the European Society of Cardiology (ESC) cardiovascular disease (CVD) Risk app (freely available from app stores).[6a] The SCORE2-Diabetes algorithm does not apply to persons with documented atherosclerotic cardiovascular disease (ASCVD) or severe target-organ damage, or other genetic or rare lipid or blood pressure (BP) disorders, chronic kidney disease (CKD), or to pregnant women.

The correct chart should be selected according to the individual's sex and age:

(i) SCORE2-Diabetes risk chart to estimate 10-year CVD risk in men with diabetes and current age between 40 and 54 years (*Section 2.1*)
(ii) SCORE2-Diabetes risk chart to estimate 10-year CVD risk in men with diabetes and current age between 55 and 69 years (*Section 2.2*)
(iii) SCORE2-Diabetes risk chart to estimate 10-year CVD risk in women with diabetes and current age between 40 and 54 years (*Section 2.3*)
(iv) SCORE2-Diabetes risk chart to estimate 10-year CVD risk in women with diabetes and current age between 55 and 69 years (*Section 2.4*)

STEPS i–iv should be followed on the relevant chart. STEP iv requires the risk region for the individual's county of residence to be known (*Table S3*).

Table S3 Four clusters of countries (low, moderate, high, and very high cardiovascular disease risk)

Cluster	Countries
Low risk countries	Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, and the UK
Moderate risk countries	Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, Republic of San Marino, Slovenia, and Sweden
High risk countries	Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey
Very high risk countries	Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, The Former Yugoslav Republic (North Macedonia), Tunisia, Ukraine, and Uzbekistan

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2.1. SCORE2-Diabetes risk chart to estimate 10-year cardiovascular disease risk in men with diabetes and current age between 40 and 54 years

STEP 1: determine current age (years) and select the corresponding column in the *Points Table S4*.

STEP 2: in this column find the correct category for each risk predictor and record the points listed in the column entitled 'Points for current patient'.

STEP 3: add up the points you have recorded in the final column and record the points total in the box at the bottom of the column.
STEP 4: match the points total to the corresponding risk in the *Risk Table S6*, selecting the value for the risk region of the country of residence.

2.2. SCORE2-Diabetes risk chart to estimate 10-year cardiovascular disease risk in men with diabetes and current age between 55 and 69 years

STEP 1: determine current age (years) and select the corresponding column in the *Points Table S4*.

STEP 2: in this column find the correct category for each risk predictor and record the points listed in the column entitled 'Points for current patient'.
STEP 3: add up the points you have recorded in the final column and record the points total in the box at the bottom of the column.
STEP 4: match the points total to the corresponding risk in the *Risk Table S6*, selecting the value for the risk region of the country of residence.

Table S4 Points table for men with diabetes

Points table for men with diabetes and current age 40–69 years									Reported points by age column
Risk predictor	**Risk predictor category**	**Age 40–44**	**Age 45–49**	**Age 50–54**	**Age 55–59**	**Age 60–64**	**Age 65–69**		
Age of diabetes diagnosis (years)	30–34	3	3	3	3	3	3	→	
	35–39	2	2	2	2	2	2		
	40–44	1	1	1	1	1	1		
	45–49	N/A	0	0	0	0	0		
	50–54	N/A	N/A	0	0	0	0		
	55–59	N/A	N/A	N/A	−1	−1	−1		
	60–64	N/A	N/A	N/A	N/A	−2	−2		
	65–69	N/A	N/A	N/A	N/A	N/A	−3		
Smoking status	Non-smoker	−9	−5	0	4	9	13	→	
	Current smoker	−2	2	6	9	13	17		
Systolic blood pressure (mmHg)	100–119	−1	−1	−1	−1	−1	0	→	
	120–139	1	1	1	1	1	0		
	140–159	3	3	3	2	2	1		
	≥160	6	5	4	4	3	2		
Total cholesterol (mmol/L)	3.0–3.9	−4	−4	−3	−3	−3	−2	→	
	4.0–4.9	−3	−2	−2	−2	−2	−1		
	5.0–5.9	−1	−1	−1	−1	−1	0		
	6.0–6.9	1	1	1	1	1	0		
	≥7.0	3	3	2	2	2	1		
HDL cholesterol (mmol/L)	0.5–0.9	2	1	1	1	1	1	→	
	1.0–1.4	0	0	0	0	0	0		
	≥1.5	−1	−1	−1	−1	−1	−1		
HbA1c (mmol/mol)	30–39	1	1	0	0	0	0	→	
	40–49	2	2	2	2	1	1		
	50–59	4	3	3	3	2	2		
	60–69	5	5	4	4	3	3		
	≥70	7	6	5	5	4	4		
eGFR (mL/min/ 1.73 m^2)	30–44	8	7	6	6	5	4	→	
	45–59	4	4	3	3	3	2		
	60–89	1	1	1	1	1	1		
	≥90	−1	−1	−1	0	0	0		
Points total:									

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, High-density lipoprotein; N/A, not applicable.

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2.3. SCORE2-Diabetes risk chart to estimate 10-year cardiovascular disease risk in women with diabetes and current age between 40 and 54 years

STEP 1: determine current age (years) and select the corresponding column in the *Points Table S5*.
STEP 2: in this column find the correct category for each risk predictor and record the points listed in the column titled 'Points for current patient'.
STEP 3: add up the points you have recorded in the final column and record the points total in the box at the bottom of the column.
STEP 4: match the points total to the corresponding risk in the *Risk Table S6*, selecting the value for the risk region of the country of residence.

2.4. SCORE2-Diabetes risk chart to estimate 10-year cardiovascular disease risk in women with diabetes and current age between 55 and 69 years

STEP 1: determine current age (years) and select the corresponding column in the *Points Table S5*.
STEP 2: in this column find the correct category for each risk predictor and record the points listed in the column titled 'Points for current patient'.
STEP 3: add up the points you have recorded in the final column and record the points total in the box at the bottom of the column.
STEP 4: match the points total to the corresponding risk in the *Risk Table S6*, selecting the value for the risk region of the country of residence.

Table S5 Points table for women with diabetes

Points table for women with diabetes and current age 40–69 years									Reported points by age column
Risk predictor	**Risk predictor category**	**Age 40–44**	**Age 45–49**	**Age 50–54**	**Age 55–59**	**Age 60–64**	**Age 65–69**		
Age of diabetes diagnosis (years)	30–34	4	4	4	4	4	4	→	
	35–39	3	3	3	3	3	3		
	40–44	2	2	2	2	2	2		
	45–49	N/A	1	1	1	1	1		
	50–54	N/A	N/A	−1	−1	−1	−1		
	55–59	N/A	N/A	N/A	−2	−2	−2		
	60–64	N/A	N/A	N/A	N/A	−3	−3		
	65–69	N/A	N/A	N/A	N/A	N/A	−4		
Smoking status	Non-smoker	−11	−6	0	5	11	16	→	
	Current smoker	−1	3	8	12	16	21		
Systolic blood pressure (mmHg)	100–119	−1	−1	−1	−1	−1	−1	→	
	120–139	1	1	1	1	1	1		
	140–159	3	3	3	2	2	2		
	≥160	5	5	4	4	3	3		
Total cholesterol (mmol/L)	3.0–3.9	−5	−4	−4	−3	−3	−2	→	
	4.0–4.9	−3	−2	−2	−2	−2	−1		
	5.0–5.9	−1	−1	−1	−1	−1	0		
	6.0–6.9	1	1	1	1	1	0		
	≥7.0	3	3	3	2	2	1		
HDL cholesterol (mmol/L)	0.5–0.9	2	2	2	2	2	1	→	
	1.0–1.4	0	0	0	0	0	0		
	≥1.5	−2	−2	−2	−1	−1	−1		
HbA1c (mmol/mol)	30–39	1	1	1	1	0	0	→	
	40–49	3	2	2	2	2	1		
	50–59	5	4	4	3	3	2		
	60–69	7	6	5	5	4	3		
	≥70	9	8	7	6	5	4		
eGFR (mL/min/1.73 m^2)	30–44	9	8	7	6	5	4	→	
	45–59	5	5	4	3	3	2		
	60–89	2	1	1	1	1	1		
	≥90	−1	−1	−1	0	0	0		
Points total:									

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, High-density lipoprotein; N/A, not applicable.

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Table S6 Risk table for men and women with diabetes

Men with diabetes. Risk Table: 10-year CVD risk estimate corresponding to each total score																																																						
Risk region	Current age between 40 and 54 years																																																					
Points total	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Low-risk region	2	2	2	2	2	2	3	3	3	3	3	4	4	4	5	5	5	6	6	7	7	8	8	9	10	10	11	12	13	14	15	16	17	18	19	20	22	23	25	27	28	30	32	34	36	38								
Moderate-risk region	2	2	2	2	3	3	3	3	4	4	4	5	5	5	6	6	7	7	8	9	9	10	11	12	13	14	15	16	17	18	20	21	22	24	26	28	30	32	34	36	38	41	43	46	49	51								
High-risk region	2	2	2	2	2	3	3	3	3	4	4	5	5	5	6	7	7	8	9	9	10	11	12	13	15	16	17	19	21	22	24	26	28	31	33	36	39	41	44	48	51	54	57	61	64	68								
Very high-risk region	4	4	4	5	5	5	6	6	7	7	8	9	9	10	11	12	13	14	15	16	17	19	20	22	23	25	27	29	31	33	35	38	40	43	45	48	51	54	57	60	63	66	69	72	75	78								
	Current age between 55 and 69 years																																																					
Low-risk region												4	4	4	5	5	5	6	6	7	7	8	8	9	10	10	11	12	13	14	15	16	17	18	19	20	22	23	25	27	28	30	32	34	36	38	41	43	45	48				
Moderate-risk region												5	5	5	6	6	7	7	8	9	9	10	11	12	13	14	15	16	17	18	20	21	22	24	26	28	30	32	34	36	38	41	43	46	49	51	54	57	60	63				
High-risk region												5	5	5	6	7	7	8	9	9	10	11	12	13	15	16	17	19	21	22	24	26	28	31	33	36	39	41	44	48	51	54	57	61	64	68	71	74	78	81				
Very high-risk region												9	9	10	11	12	13	14	15	16	17	19	20	22	23	25	27	29	31	33	35	38	40	43	45	48	51	54	57	60	63	66	69	72	75	78	80	83	85	88				
Women with diabetes. Risk Table: 10-year CVD risk estimate corresponding to each total score																																																					
Risk region Points total	Current age between 40 and 54 years																																																					
	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Low-risk region		1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	4	4	4	4	5	5	5	6	6	7	7	7	8	9	9	10	10	11	12	13	14	15	15	17	18	19	20	21	23	24	26	27						
Moderate-risk region		1	1	2	2	2	2	2	2	2	3	3	3	3	4	4	4	5	5	5	6	6	7	7	8	8	9	9	10	11	12	13	14	15	16	17	18	19	21	22	24	25	27	29	31	33	35	37						
High-risk region		1	1	2	2	2	2	2	3	3	3	3	4	4	5	5	5	6	7	7	8	9	9	10	11	12	13	15	16	17	19	20	22	24	26	28	31	33	36	38	41	44	47	50	54	57	61	64						
Very high-risk region		3	4	4	4	5	5	5	6	6	7	8	8	9	10	10	11	12	13	14	15	16	18	19	21	22	24	26	28	30	32	34	36	39	41	44	47	50	52	55	58	61	65	68	71	74	76	79						
	Current age between 55 and 69 years																																																					
Low-risk region															3	3	4	4	4	4	5	5	5	6	6	7	7	7	8	9	9	10	10	11	12	13	14	15	15	17	18	19	20	21	23	24	26	27	29	31	32	34	36	38
Moderate-risk region															4	4	4	5	5	5	6	6	7	7	8	8	9	9	10	11	12	13	14	15	16	17	18	19	21	22	24	25	27	29	31	33	35	37	39	42	44	47	49	52
High-risk region															5	5	5	6	7	7	8	9	9	10	11	12	13	15	16	17	19	20	22	24	26	28	31	33	36	38	41	44	47	50	54	57	61	64	67	71	74	77	80	83
Very high-risk region															10	10	11	12	13	14	15	16	18	19	21	22	24	26	28	30	32	34	36	39	41	44	47	50	52	55	58	61	65	68	71	74	76	79	82	84	87	89	91	92

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CVD, cardiovascular disease.

Interpretation: the risk given is the percentage of people with the same risk estimation, who will experience a CVD event (heart attack, stroke, or other fatal CVD event) in the next 10 years. This estimate is an approximate/simplified value based on broad risk predictor categories. A more accurate risk estimation for the precise measured risk predictors can be obtained using the full risk equation provided in the online calculator. Estimates may differ by up to 4%.

2.5. Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medications in diabetes

Table S7 Baseline characteristics and main outcomes of cardiovascular outcomes trials with sodium–glucose co-transporter-2 inhibitors in patients with type 2 diabetes

Characteristic	EMPA-REG OUTCOME[7]	CANVAS programme[8]	DECLARE-TIMI 58[9]	CREDENCE[10]	VERTIS CV[11]	SCORED[12]
SGLT inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin	Sotagliflozin
Duration of follow-up (mean), y	3.1	2.4	4.2	2.6	3.0	1.3
N	7020	10 142	17 160	4401	8246	10 584
Age [mean (SD)], y	63.1 (8.6)	63.3 (8.3)	63.9 (6.8)	63.0 (9.2)	64.4 (8.1)	69 (NR)
Male, %	71.5	64.2	62.6	66.1	70.0	55.1
BMI [mean (SD)], kg/m^2	30.6 (5.3)	32.0 (5.9)	32.1 (6.1)	31.3 (6.2)	32.0 (5.5)	31.8 (NR)
HbA1c [mean (SD)], %	8.1 (0.8)	8.2 (0.9)	8.3 (1.2)	8.3 (1.3)	8.2 (1.0)	8.3 (NR)
Diabetes duration [mean (SD)], y	>10 y: 57%	13.5 (7.8)	11.8 (7.8)	15.8 (8.6)	13.0 (8.3)	NR
Established ASCVD, *n* (%)	7020 (100)	6656 (65.6)	6974 (40.6)	2220 (50.4)	8246 (100)	NR
History of HF, *n* (%)	706 (10.1)	1461 (14.4)	1724 (10.0)	652 (14.8)	1958 (23.7)	3283 (31.0)
eGFR [mean (SD) or median (IQR)], mL/min/1.73 m^2	74.2 (21.6)	76.5 (20.5)	85.3 (15.9)	56.2 (18.2)	75.9 (20.9)	44.6 (37.0–51.4)
UACR [median (IQR)], mg/g	NR	12.3 (6.65–42.1)	NR	927 (463–1833)	NR	74.5 (17.5–481.5)
Cardiovascular outcomes						
Primary outcome	3-P MACE	3-P MACE	3-P MACE	Composite kidney disease + MACE	3-P MACE	CV death, HHF, urgent visits HF
Treatment, rate/1000 patient-years	37.4	26.9	22.6	38.7	40.0	56
Placebo, rate/1000 patient-years	43.9	31.5	24.2	48.7	40.3	75
Hazard ratio (95% CI)	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.80 (0.67–0.95)	0.99 (0.88–1.12)	0.74 (0.63–0.88)
Cardiovascular death						
Treatment, rate/1000 patient-years	12.4	11.6	7.0	19.0	17.6	22
Placebo, rate/1000 patient-years	20.2	12.8	7.1	24.4	19.0	24
Hazard ratio (95% CI)	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.92 (0.77–1.10)	0.90 (0.73–1.12)
Fatal or non-fatal stroke						
Treatment, rate/1000 patient-years	11.2	7.1	6.9	NR	8.0	NR
Placebo, rate/1000 patient-years	9.1	8.4	6.8	NR	8.0	NR
Hazard ratio (95% CI)	1.24 (0.92–1.67)	0.90 (0.71–1.15)	1.01 (0.84–1.21)	NR	1.00 (0.76–1.32)	0.66 (0.48–0.91)
Fatal or non-fatal myocardial infarction						
Treatment, rate/1000 patient-years	16.0	9.7	11.7	NR	17.0	NR
Placebo, rate/1000 patient-years	18.5	11.6	13.2	NR	16.0	NR
Hazard ratio (95% CI)	0.87 (0.70–1.09)	0.85 (0.69–1.05)	0.89 (0.77–1.01)	NR	1.04 (0.86–1.27)	0.68 (0.52–0.89)
Hospitalization for heart failure						
Treatment, rate/1000 patient-years	9.4	5.5	6.2	15.7	7.3	35
Placebo, rate/1000 patient-years	14.5	8.7	8.5	25.3	10.5	51
Hazard ratio (95% CI)	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	0.70 (0.54–0.90)	0.67 (0.55–0.82)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalization for heart failure; HF, heart failure; IQR, interquartile range; 3-P MACE, 3-point major adverse cardiovascular events; NR, not reported; SD, standard deviation; SGLT2, sodium–glucose co-transporter-2; UACR, urine albumin-to-creatinine ratio.

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Table S8 Baseline characteristics and cardiovascular outcomes of cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes

Characteristic	ELIXA[13]	LEADER[14]	SUSTAIN-6[15]	EXSCEL[16]	HARMONY outcomes[17]	REWIND[18]	PIONEER 6[19]	AMPLITUDE-O[20]
GLP-1 receptor agonist	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Oral semaglutide	Efpeglenatide
Duration of follow-up (median), y	2.1	3.8	2.1	3.2	1.6	5.4	1.3	1.8
N (% male)	6068 (69)	9340 (64)	3297 (62)	14 752 (62)	9463 (69)	9901 (54)	3183 (68)	4076 (67)
Age, [mean (SD)], y	60.6 (9.6)	64.4 (7.2)	64.6 (7.6)	62.0 (9.0)	64.2 (8.7)	66.2 (6.5)	66.0 (7.0)	65.0 (8.0)
BMI [mean (SD)], kg/m^2	30.1 (5.6)	32.5 (6.3)	32.8 (6.2)	32.7 (6.4)	32.3 (5.9)	32.3 (5.7)	32.3 (6.5)	32.7 (6.2)
HbA1c [mean (SD)], %	7.7 (1.3)	8.7 (1.6)	8.7 (1.5)	8.1 (1.0)	8.7 (1.5)	7.3 (1.1)	8.2 (1.6)	8.9 (1.5)
Diabetes duration [mean (SD)], y	9.2 (8.2)	12.8 (8.0)	13.9 (8.1)	13.1 (8.3)	14.2 (8.8)	10.5 (7.2)	14.9 (8.5)	15.4 (8.8)
Established CVD, *n* (%)	6068 (100)	7598 (81)	2735 (83)	10 782 (73)	9463 (100)	3114 (31)	2695 (85)	3650 (90)
History of HF, *n* (%)	1358 (22)	1667 (18)	777 (24)	2389 (16)	1922 (20)	853 (9)	388 (12)	737 (18)
eGFR [mean (SD) or median (IQR)], mL/min/1.73 m^2	78 (21)	80 (NR)	80 (61–92)	77 (61–92)	79 (26)	77 (23)	74 (21)	72 (22)
UACR [median (IQR)], mg/g	10.3 (6.0–31.6)	NR	NR	NR	NR	1.8 (0.7–7.0)	NR	28.3 (9.7–114.2)
Cardiovascular outcomes								
Primary outcome	3-P MACE	3-P MACE	3-P MACE	3-P MACE	3-P MACE	3-P MACE	3-P MACE	3-P MACE
Treatment, rate/1000 patient-years	63	34	32.4	37	45.7	23.5	29	39
Placebo, rate/1000 patient-years	64	39	44.4	40	58.7	26.6	37	53
Hazard ratio (95% CI)	1.02 (0.89–1.17)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.91 (0.83–1.00)	0.78 (0.68–0.90)	0.88 (0.79–0.99)	0.79 (0.57–1.11)	0.73 (0.58–0.92)
Cardiovascular death								
Treatment, rate/1000 patient-years	24	12	12.9	14	16.1	12.2	7	15
Placebo, rate/1000 patient-years	23	16	13.5	15	17.2	13.4	14	21
Hazard ratio (95% CI)	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.93 (0.73–1.19)	0.91 (0.78–1.06)	0.49 (0.27–0.92)	0.72 (0.50–1.03)
Fatal or non-fatal stroke								
Treatment, rate/1000 patient-years	9	10	8.0	8	12.5	6.1	6	10
Placebo, rate/1000 patient-years	10	11	13.1	9	14.5	8.1	8	13
Hazard ratio (95% CI)	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.86 (0.66–1.14)	0.76 (0.62–0.94)	0.74 (0.35–1.57)	0.74 (0.47–1.17)
Fatal or non-fatal myocardial infarction								
Treatment, rate/1000 patient-years	41	16	14.0	21	24.3	8.7	18	19
Placebo, rate/1000 patient-years	42	19	19.2	21	32.6	9.1	15	24
Hazard ratio (95% CI)	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.75 (0.61–0.90)	0.96 (0.79–1.15)	1.18 (0.73–1.90)	0.75 (0.54–1.05)
Hospitalization for heart failure								
Treatment, rate/1000 patient-years	19	12	14.9	9	NR	8.3	10	8
Placebo, rate/1000 patient-years	18	14	16.1	10	NR	8.9	12	13
Hazard ratio (95% CI)	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.71 (0.53–0.94)	0.93 (0.77–1.12)	0.86 (0.48–1.55)	0.61 (0.38–0.98)

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; IQR, interquartile range; 3-P MACE, 3-point major adverse cardiovascular events; NR, not reported; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

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Table S9 Baseline characteristics and cardiovascular outcomes of cardiovascular outcomes trials with dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes

Characteristic	SAVOR-TIMI 53[21]	EXAMINE[22]	TECOS[23]	CARMELINA[24]	CAROLINA[25]
DPP-4 inhibitor	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin	Linagliptin
Comparator	Placebo	Placebo	Placebo	Placebo	Glimepiride
Duration of follow-up (median), y	2.1	1.5	3.0	2.2	6.3
N (% male)	16 492 (85.9)	5380 (67.9)	14 671 (70.7)	6979 (62.9)	6041 (59.9)
Age, [mean (SD)], y	65.1 (8.6)	61.0 (NR)	65.5 (8.0)	65.9 (9.1)	64.1 (9.5)
BMI [mean (SD)], kg/m^2	31.2 (5.6)	28.7 (NR)	30.2 (5.6)	31.4 (5.4)	30.1 (5.2)
HbA1c [mean (SD)], %	8.0 (1.4)	8.0 (1.1)	7.2 (0.5)	8.0 (1.0)	7.2 (0.6)
Diabetes duration [mean (SD)], y	10.3 (NR)	7.2 (NR)	11.6 (8.1)	14.8 (9.5)	6.3 (NR)
Established CVD, *n* (%)	12 963 (78.6)	5380 (100)	14 671 (100)	3978 (57.0)	2084 (34.5)
History of HF, *n* (%)	2105 (12.8)	1501 (27.9)	2643 (18.0)	1870 (26.8)	NR
eGFR [mean (SD)], mL/min/1.73 m^2	72.6 (22.6)	71.2 (NR)	74.9 (21.1)	54.6 (25.0)	76.8 (19.8)
UACR [median (IQR)], mg/g	1.9 (0.7–7.7)	NR	10.6 (3.5–35.5)	162 (44–725)	9.7 (5.3–31.0)
Cardiovascular outcomes					
Primary outcome	3-P MACE	3-P MACE	4-P MACE	3-P MACE	3-P MACE
Treatment, *n* (%)	613 (7.3)	305 (11.3)	695 (9.6)	434 (12.4)	356 (11.8)
Placebo, *n* (%)	609 (7.2)	316 (11.8)	695 (9.6)	420 (12.1)	362 (12.0)
Hazard ratio (95% CI)	1.00 (0.89–1.12)	0.96 (≤1.16)[a]	0.98 (0.88–1.09)	1.02 (0.89–1.17)	0.98 (0.84–1.14)
Cardiovascular death					
Treatment, *n* (%)	269 (3.2)	89 (3.3)	380 (5.2)	255 (7.3)	169 (5.6)
Placebo, *n* (%)	260 (2.9)	111 (4.1)	366 (5.0)	264 (7.6)	168 (5.6)
Hazard ratio (95% CI)	1.03 (0.87–1.22)	0.79 (0.60–1.04)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
Fatal or non-fatal stroke					
Treatment, *n* (%)	157 (1.9)[b]	29 (1.1)[b]	178 (2.4)	81 (2.3)	104 (3.4)
Placebo, *n* (%)	141 (1.7)[b]	32 (1.2)[b]	183 (2.5)	88 (2.5)	120 (4.0)
Hazard ratio (95% CI)	1.11 (0.88–1.39)[b]	0.91 (0.55–1.50)[b]	0.97 (0.79–1.19)	0.91 (0.67–1.23)	0.86 (0.66–1.12)
Fatal or non-fatal myocardial infarction					
Treatment, *n* (%)	265 (3.2)[b]	187 (6.9)[b]	300 (4.1)	165 (4.7)	153 (5.1)
Placebo, *n* (%)	278 (3.4)[b]	173 (6.5)[b]	316 (4.3)	146 (4.2)	148 (4.9)
Hazard ratio (95% CI)	0.95 (0.80–1.12)[b]	1.08 (0.88–1.33)[b]	0.95 (0.81–1.11)	1.12 (0.90–1.40)	1.03 (0.82–1.29)
Hospitalization for heart failure					
Treatment, *n* (%)	289 (3.5)	NR	228 (3.1)	209 (6.0)	112 (3.7)
Placebo, *n* (%)	228 (2.8)	NR	229 (3.1)	226 (6.5)	92 (3.1)
Hazard ratio (95% CI)	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; IQR, interquartile range; 3/4-P MACE, 3/4-point major adverse cardiovascular events; NR, not reported; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

[a]Upper boundary of one-sided, repeated CI.

[b]Only non-fatal reported.

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2.6. Blood pressure and diabetes

2.6.1. Screening and diagnosis

In patients with diabetes, conventional office BP measurements with validated auscultatory or oscillometric, semi-automatic or automated sphygmomanometers are recommended. Further, unattended, automatic, multiple readings may improve the reproducibility of BP measurements, reducing a possible 'white coat effect'. Out-of-office BP measurements with either home (HBPM) or ambulatory (ABPM) BP monitoring provide more BP values over 24 hours, which may better represent daily life. They may also help to detect 'masked hypertension', which is very common in untreated patients with diabetes (approx. 30%) and has been found to increase the risk of CV and renal events.[26,27] HBPM or ABPM are also recommended in patients at risk of autonomic dysfunction, and to detect non-dipping or even a nocturnal rise of BP.[28]

Table S10 Randomized controlled trials of intensive vs. standard hypertension treatment strategies[a]

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP[29]	4733 participants with T2DM aged 40–79 years with prior evidence of CVD or multiple CV risk factors	SBP target:<120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 133.5/70.5 mmHg	• No benefit in primary endpoint: composite of non-fatal MI, non-fatal stroke, and CV death • Stroke risk reduced 41% with intensive control, not sustained following the active treatment period • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE BP[30]	11 140 participants with T2DM aged ≥55 years with prior evidence of CVD or multiple CV risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite endpoint of major macro- and microvascular events (by 9%), death from any cause (by 14%), and death from CVD (by 18%) • 6-year observational follow-up found reduced risk of death in intervention group attenuated but still significant without evidence of sex differences[31]
HOT[32]	Subpopulation with 1501 participants with diabetes	DBP target: ≤ 80 mmHg	DBP target: ≤ 90 mmHg	• In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CV events

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CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.
[a]Data from this table can also be found in the American Diabetes Association position statement 'Diabetes and Hypertension'.[33]

2.7. Antithrombotic therapy and diabetes

Acetylsalicylic acid (ASA) irreversibly inhibits cyclo-oxygenase 1-dependent thromboxane A_2 from platelets and platelet precursors already at 75–100 mg o.d. and is not bio-transformed by cytochrome P (CYP)450 as shown in *Figure S1*.[34]

$P2Y_{12}$ receptor inhibitors. Clopidogrel is a pro-drug, with <10% systemic bioavailability, which is bio-transformed by multiple CYP450s into an active metabolite that irreversibly inhibits platelets' $P2Y_{12}$ purinergic receptor (*Figure S2A*).[37] Its complex pharmacokinetics (PK) generate clinically relevant drug–drug interactions (DDIs), mainly through the CPY2C19, including DDIs with omeprazole and esomeprazole. Patients with diabetes generate lower active metabolite concentrations than patients without diabetes.[38]

Prasugrel is a pro-drug, which also irreversibly inhibits $P2Y_{12}$ and is characterized by more favourable PK, since there is no involvement of the major CYP450s known to generate clinically relevant DDIs. This also generates higher active metabolite concentrations and bioavailability, as well as less interindividual variability (*Figure S2B*). Thus, as compared with clopidogrel or ticagrelor, prasugrel has no clinically relevant DDIs.[37] The dose should be reduced in patients aged >75 years and weighing <60 kg.

Ticagrelor is an adenosine triphosphate analogue, and a reversible, direct, non-competitive $P2Y_{12}$ inhibitor. It is bio-transformed by the CYP3A4 and P-glycoprotein with less inter-individual variability than clopidogrel (*Supplementary Figure S3*). Ticagrelor can generate clinically relevant DDIs and is contraindicated with strong CYP3A4 inhibitors, due to increased bleeding risk.[37] Mild-to-moderate dyspnoea is a very common side effect (≥1/10 patients).[39]

Vitamin K antagonist (VKA). The complex PK of the racemic *R*- and *S*-warfarin (*Figure S4*) explains its high intra- and interindividual variability and numerous DDIs. These, and its narrow therapeutic window, necessitate monitoring with prothrombin time, expressed as International Normalized Ratio (INR).[40] Warfarin is teratogenic. No dose adjustment is needed with renal impairment.

Direct non-vitamin K antagonist oral anticoagulant (NOACs). The PK of each NOAC is shown in *Figure S5*. Apixaban, edoxaban, and rivaroxaban directly inhibit activated Factor X (FXa). Dabigatran is a pro-drug that directly inhibits thrombin (Factor IIa). NOACs have different PK, bioavailability, and excretion routes.[40] Variable involvement of CYP450s and/or P-glycoprotein generates distinctive drug-drug interactions (DDIs).

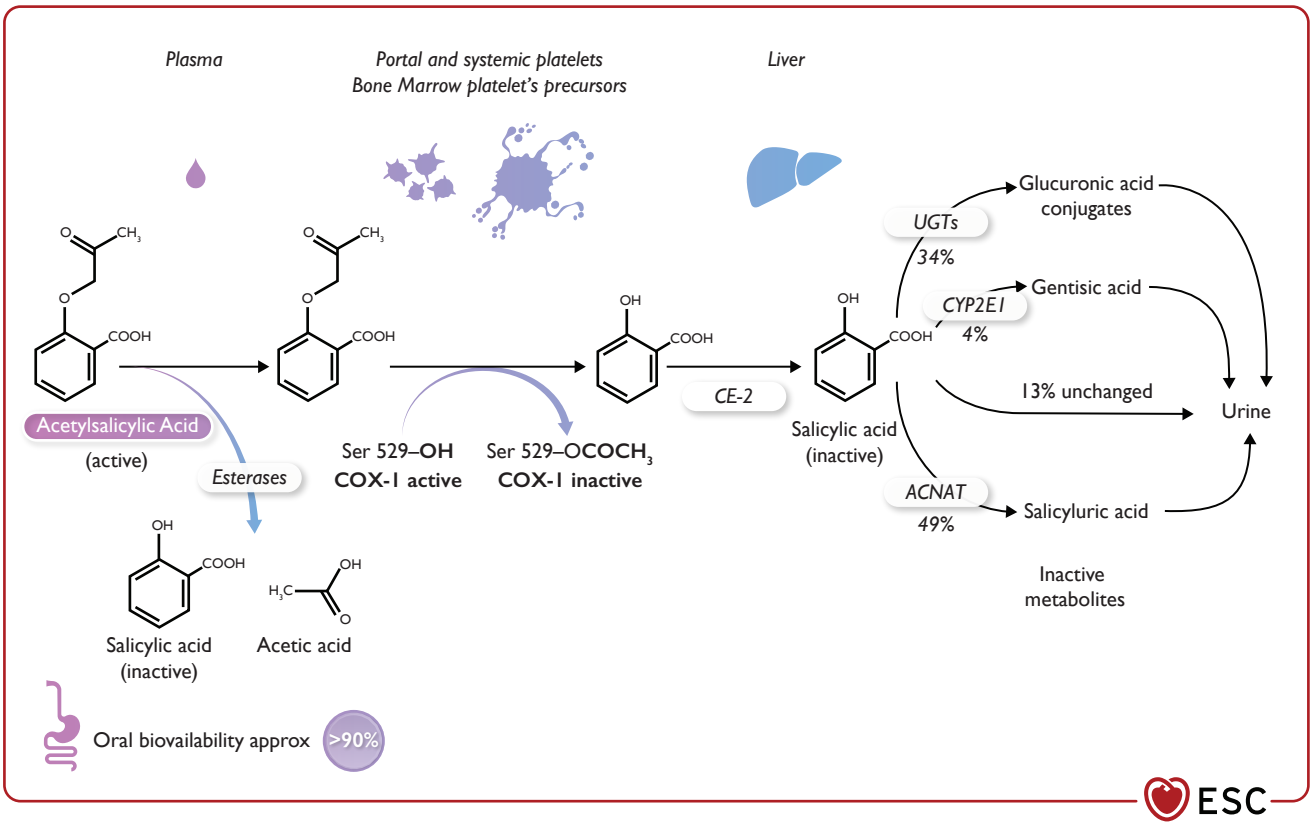

Figure S1 Pharmacodynamics and pharmacokinetics of low dose acetylsalicylic acid. ASA, acetylsalicylic acid; CE, carboxylesterase; COX, cyclo-oxygenase; Ser, serine. Acetylsalicylic acid (ASA) is almost completely absorbed in the stomach and small intestine. It exerts its pharmacodynamic effect through the irreversible acetylation of the serine-529 residue of the platelet enzyme cyclo-oxygenase (COX)-1. This occurs in the portal blood, before the liver first-pass effect, thus inhibiting thromboxane-2-dependent platelet aggregation. Once the serine is acetylated, platelets are inhibited for their remaining lifespan, and after ASA dosing is stopped, platelet aggregation levels will return to baseline as new platelets are formed, typically within 7 to 10 days. ASA is bio-transformed to the inactive compound salicylic acid by carboxylesterases in the intestine, plasma, and liver. Salicylic acid is further bio-transformed in the liver, mainly through phase II enzymes such as acyl-CoA N-acyltransferase (ACNAT) and uridine 5'-diphosphoglucuronosyltransferases (UTGs), while a min-or fraction is excreted without changes, or is bio-transformed by Cytochrome P (CYP)2E1. The average systemic bioavailability is approximately 50% of the orally administered dose after liver first-pass metabolism. Once in the systemic circulation, ASA reaches bone marrow precursors, where it inhibits COX-1 and -2. Data from Rocca *et al.* and Bojić *et al.*[35,36]

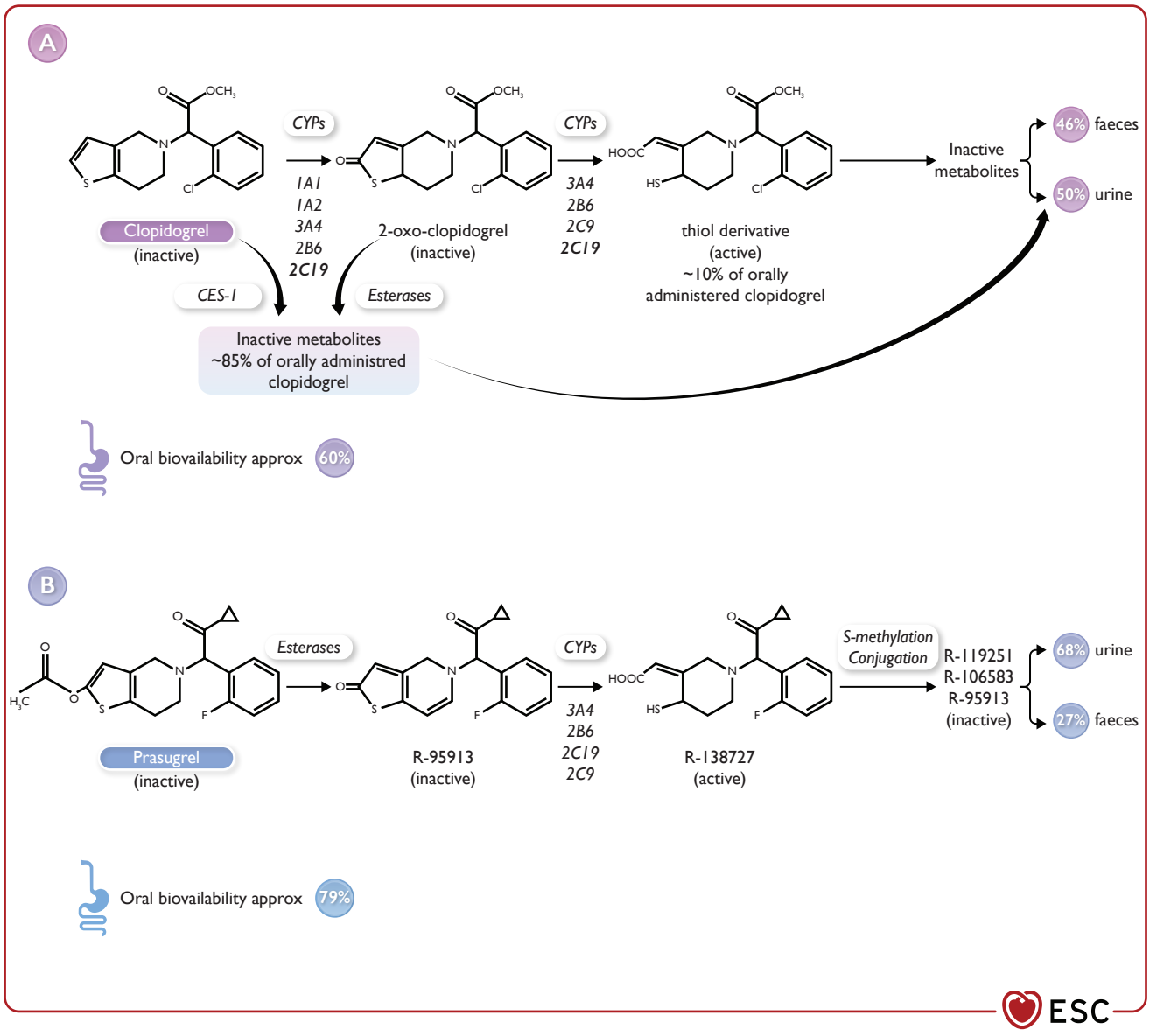

Figure S2 Pharmacokinetics of clopidogrel and prasugrel thienopyridines. CES, carboxylesterases; CYP, Cytochrome P. Clopidogrel and prasugrel are thienopyridine pro-drugs, requiring *in vivo* bio-transformation to form an active metabolite that binds rapidly and irreversibly to the platelet $P2Y_{12}$ receptor, thus inhibiting $P2Y_{12}$-dependent platelet aggregation. Once bound, the $P2Y_{12}$ remains inhibited for the remainder of the platelet's lifespan and once the drug is stopped, platelet function returns to baseline as new platelets are formed, usually after 7 to 10 days. Panel A: clopidogrel, a thienopyridine adenosine diphosphate $P2Y_{12}$ receptor antagonist, is an orally administered pro-drug that forms *in vivo* its active metabolite by approximately 10% of the orally administered dose. Clopidogrel is extensively metabolized by the liver. Esterases hydrolyse it into an inactive carboxylic acid derivative (85% of circulating metabolites). Multiple Cytochrome P (CYP)450 s metabolize clopidogrel into the 2-oxo-clopidogrel intermediate inactive metabolite and subsequent metabolism generates the active thiol derivative. Clopidogrel may generate relevant drug–drug interactions, especially with strong CYP2C19 inhibitors including omeprazole and esomeprazole, fluoxetine, voriconazole, fluconazole, carbamazepine, and efavirenz. Panel B: prasugrel, a thienopyridine $P2Y_{12}$ antagonist, is an oral pro-drug that forms *in vivo* an active metabolite (R-138727). Prasugrel has a distinct chemical structure as compared with clopidogrel, with a more efficient conversion to its active metabolite through rapid hydrolysis by CEs and then by multiple CYP450 enzymes. The R-138727 metabolite is formed very rapidly during first-pass metabolism. No relevant pharmacodynamic and pharmacokinetic clinically relevant drug–drug interactions have been reported for prasugrel.

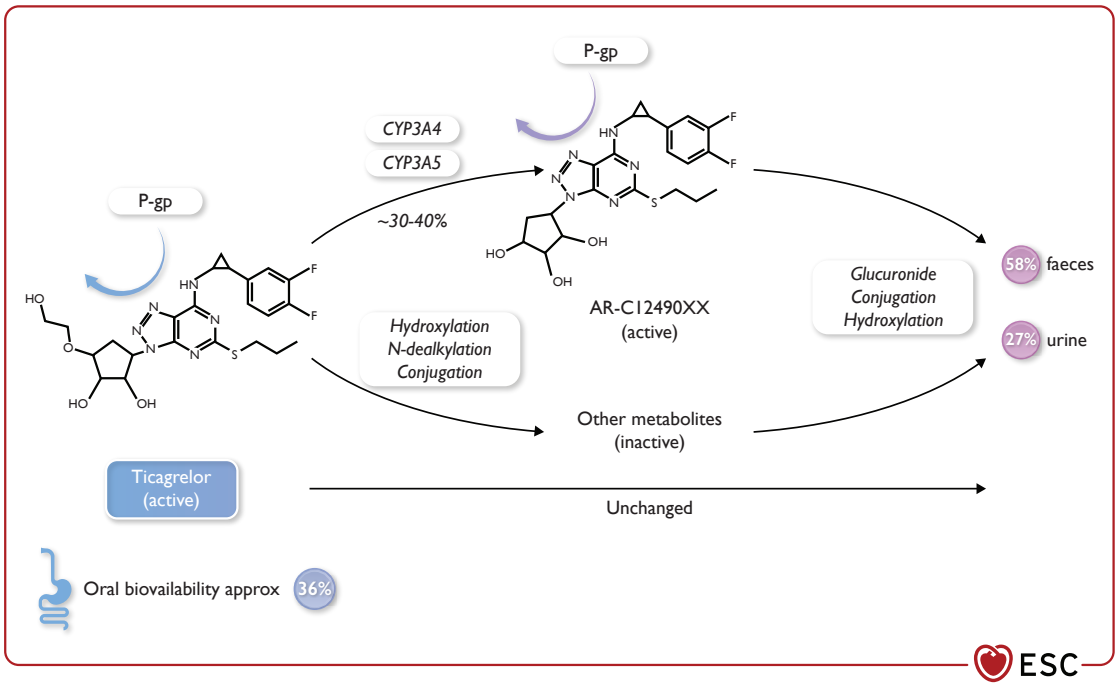

Figure S3 Pharmacokinetics of ticagrelor. CYP, Cytochrome P; DDI, drug–drug interaction; P-gp, P-glycoprotein. Ticagrelor is a complex carbocyclic nucleoside analogue and a reversible and selective $P2Y_{12}$-receptor antagonist. Its bio-transformation leads also to an active metabolite, the AR-C124910XX, by approximately one-third of the absorbed dose. Clinically relevant drug–drug interactions (DDIs) have been reported with strong Cytochrome P (CYP)3A4 inhibitors. Ticagrelor and AR-C124910XX are also P-glycoprotein (P-gp) substrates and inhibitors of the P-gp-mediated transport of digoxin. Co-administration of strong CYP3A4 inhibitors is contraindicated based on clinically relevant DDI.

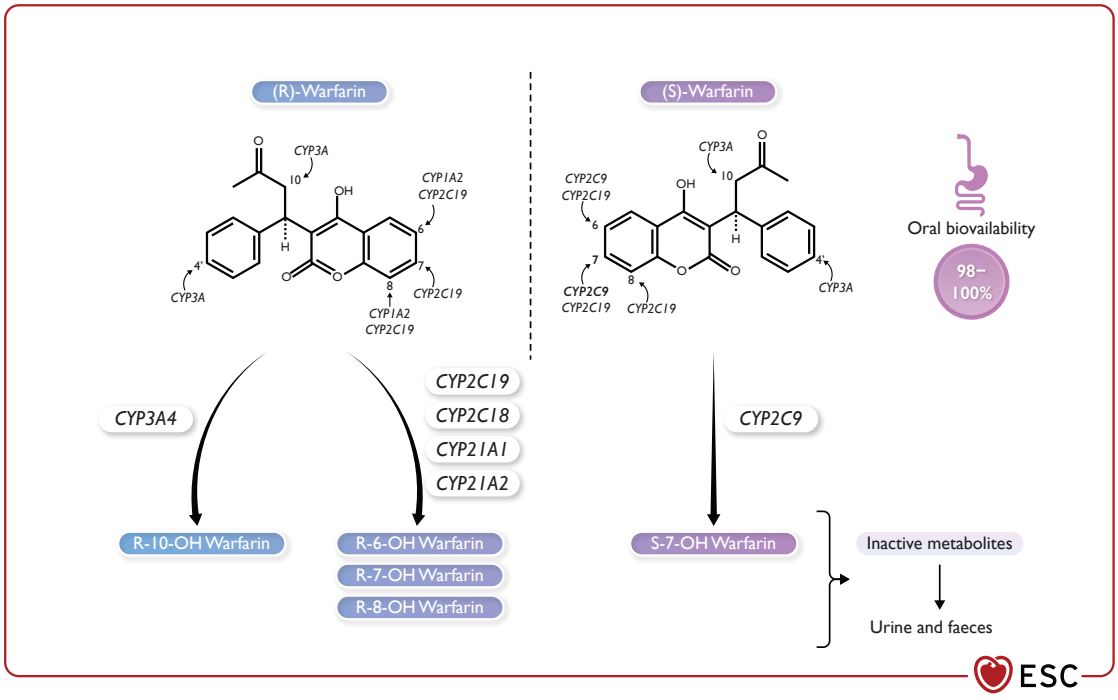

Figure S4 Pharmacokinetics of warfarin. CYP, Cytochrome P. Warfarin is a racemic mixture, which acts as a vitamin K antagonist, thus blocking the carboxylation of factors II, VII, IX, X, and proteins C and S. The S-enantiomer is more potent than the R-enantiomer. The enantiomers undergo different Cytochrome P (CYP)450 bio-inactivation paths. Warfarin is characterized by a high intra- and interindividual variability in response and CYP2C9-mediated drug–drug interactions. Pharmacogenomic variability stems from CYP2C9 alleles and vitamin K epoxide reductase variants. Figure modified from Akamin and Uno.[41]

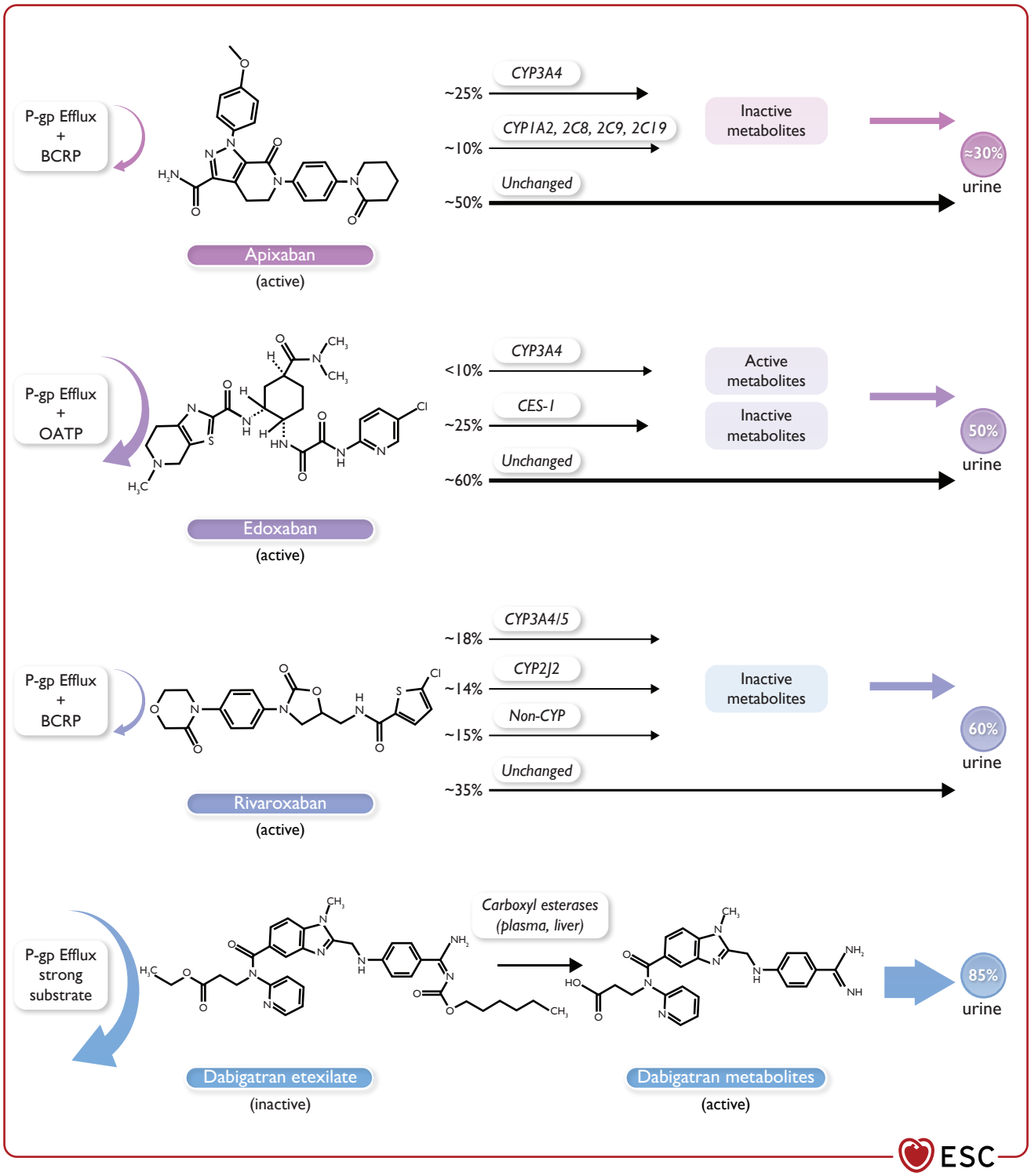

Figure S5 Pharmacokinetic pathways of the direct anti-Xa and IIa oral anticoagulants. BCRP, breast cancer resistance protein; CYP, Cytochrome P; OATP, organic anion-transporting polypeptides; P-gp, P-glycoprotein. Apixaban, edoxaban, and rivaroxaban are orally active, direct, selective inhibitors of the coagulation factor Xa that reversibly bind to the active site of factor Xa. Apixaban is an active compound eliminated by multiple pathways, including bio-transformation, renal, and biliary clearances. Based on its pharmacokinetics, apixaban is not recommended in patients receiving concomitant treatment with strong inhibitors of both Cytochrome P (CYP)3A4 and P-glycoprotein (P-gp). Edoxaban is a substrate for the efflux transporter P-gp. Co-administration of edoxaban with the P-gp inhibitors ciclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction. Rivaroxaban is an active drug also bio-transformed by CYP3A4 and P-gp; its concomitant use with strong inhibitors of both CYP3A4 and P-gp is not recommended. Dabigatran etexilate is an oral pro-drug of the active moiety dabigatran and possesses no anticoagulant activity. Dabigatran is a non-peptide competitive and reversible inhibitor of factor IIa (thrombin). It is a strong substrate of the P-gp protein, and therefore co-administration of P-gp inducers has been shown to generate clinically relevant drug–drug interactions and is discouraged. Strong P-gp inhibitors are contraindicated, including ketoconazole and dronedarone. Kidney function assessment is particularly important for dabigatran given its almost exclusive kidney excretion route. Data are from: Stangier *et al.*[42]; Weinz *et al.*[43]; Raval *et al.*[44]

Table S11 Major trials and individual patient data meta-analyses of acetylsalicylic acid vs. placebo or control in subjects with and without diabetes and with a prior atherosclerotic cardiovascular disease

Study[a]	Sample size, population characteristics, and randomized treatments	Primary efficacy endpoint	Predicted vs. observed primary outcomes (control arm) expected vs. observed proportional benefit	Efficacy outcomes[b]	Safety outcomes[b]
JPAD, 2008[45]	2539 patients with T2DM and without a history of atherosclerotic disease. Low-dose ASA vs. 'non-ASA'	Sudden death; death from coronary, cerebrovascular, and aortic causes; non-fatal acute MI; UA; exertional angina; non-fatal ischaemic and haemorrhagic stroke; TIA; or non-fatal aortic and PVD	Predicted incidence: 5.2%/year Observed incidence: 1.7%/year Predicted relative reduction: 30% Observed relative reduction: 20%	Control: 6.7% (n = 86) ASA: 5.4% (n = 68) HR 0.80 (0.58–1.10) Median follow-up: 4.37 years	Any GI bleeding: Control: n = 4 ASA: n = 12 P = NS
POPADAD, 2008[46]	1276 adults aged ≥40 years with T1DM or T2DM, ABI of ≤0.99, and no symptomatic CVD. Low dose ASA vs. placebo	Death from CAD or stroke, non-fatal MI or stroke, or amputation for critical limb ischaemia	Predicted incidence: 28%/year Observed primary endpoint rate: 2.9%/year Predicted relative reduction: 25%	Control: 18.3% (n = 117) ASA: 18.2% (n = 116) HR 0.98 (0.76–1.26); P = NS Median follow up: 6.7 years	Any GI bleeding: Control: 4.9% (n = 31) ASA: 4.4% (n = 28) HR 0.90 (0.53–1.52); P = NS
ASCEND, 2018[47]	15 480 Patients aged ≥40 years with diabetes, no evident CVD, and substantial uncertainty about whether antiplatelet therapy would confer worthwhile benefit. Low-dose ASA vs. placebo	Non-fatal MI, non-fatal stroke (excluding confirmed ICH), TIA, or death from any vascular cause (excluding confirmed ICH)	Predicted incidence: 1.2–1.3%/year Observed incidence: 1.3%/year Predicted relative reduction: 15% Observed relative reduction: 12%	Control: 9.6% (n = 743) ASA: 8.5% (n = 658) HR 0.88 (0.79–0.97); P = 0.01 Median follow-up: 7.4 years	BARC 2, 3, and 5 bleeding: Control: 3.2% (n = 245) ASA: 4.1% (n = 314) RR 1.29 (1.09–1.52); P = 0.003 No difference in fatal bleeding and ICH
THEMIS, 2019[48]	19 220 patients with diabetes, aged ≥50 years, stable CAD, with no previous MI or stroke. Random: ASA + placebo vs. ASA + ticagrelor 60 mg b.i.d.	Cardiovascular death, MI, or stroke	Predicted incidence: 2.5%/year Predicted relative reduction: 16% Observed relative reduction: 10%	Placebo: 8.5% (n = 818) Ticagrelor: 7.7% (n = 736) HR 0.90 (0.81–0.99); P = 0.04 Median follow-up: 40 months	TIMI major bleeding: Placebo: 1.0% (n = 100) Ticagrelor: 2.2% (n = 206) HR 2.32 (1.82–2.94) ICH: Placebo: 0.5% Ticagrelor: 0.7% HR 1.71 (1.18–2.48) All P < 0.001 High rate of permanent ticagrelor discontinuation: Placebo: 25.4% Ticagrelor: 34.5%

ABI, ankle–brachial index; ASA, acetylsalicylic acid; BARC, Bleeding Academic Research Consortium; b.i.d., twice a day; CAD, coronary artery disease; CVD, cardiovascular disease; GI, gastrointestinal; HR, hazard ratio; ICH, intracerebral haemorrhage; IPD, individual patient data; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RR, rate ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIA, transient ischaemic attack; TIMI, Thrombolysis In Myocardial Infarction; UA, unstable angina.

[a]Studies are listed according to the year of publication.

[b]HRs and RRs are always indicated with (95% confidence interval).

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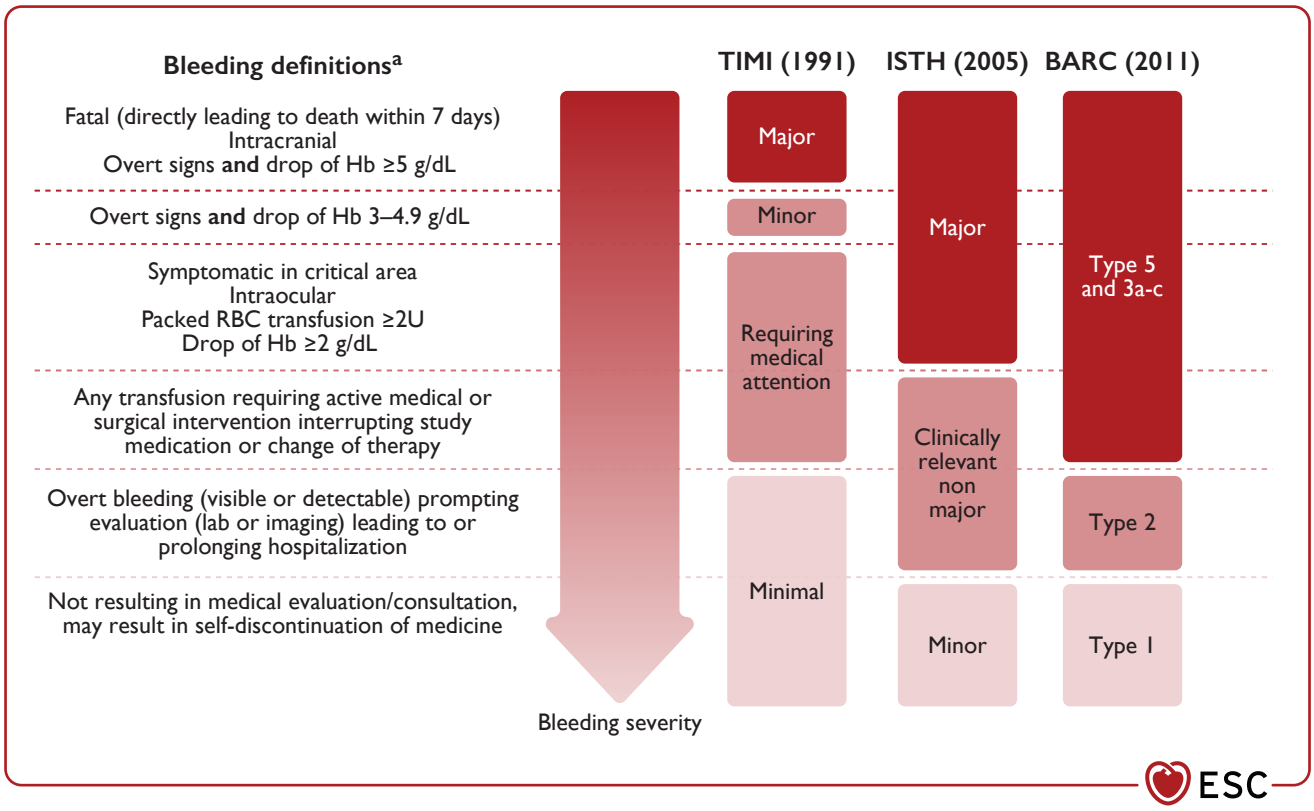

Figure S6 Bleeding definitions in clinical trials. BARC, Bleeding Academic Research Consortium; Hb, haemoglobin; ISTH, International Society on Thrombosis and Haemostasis; RBC, red blood cell; TIMI, Thrombolysis in Myocardial Infarction. The figure depicts a synopsis of the definitions and classifications of non-surgical bleeding, most-commonly used in randomized controlled trials of antithrombotic drugs, according to the TIMI group, the ISTH, and the BARC.[49–51] [a]The severity of bleeding decreases from the top to the bottom of the figure and it is reflected in the decreasing darkness of the red colour.

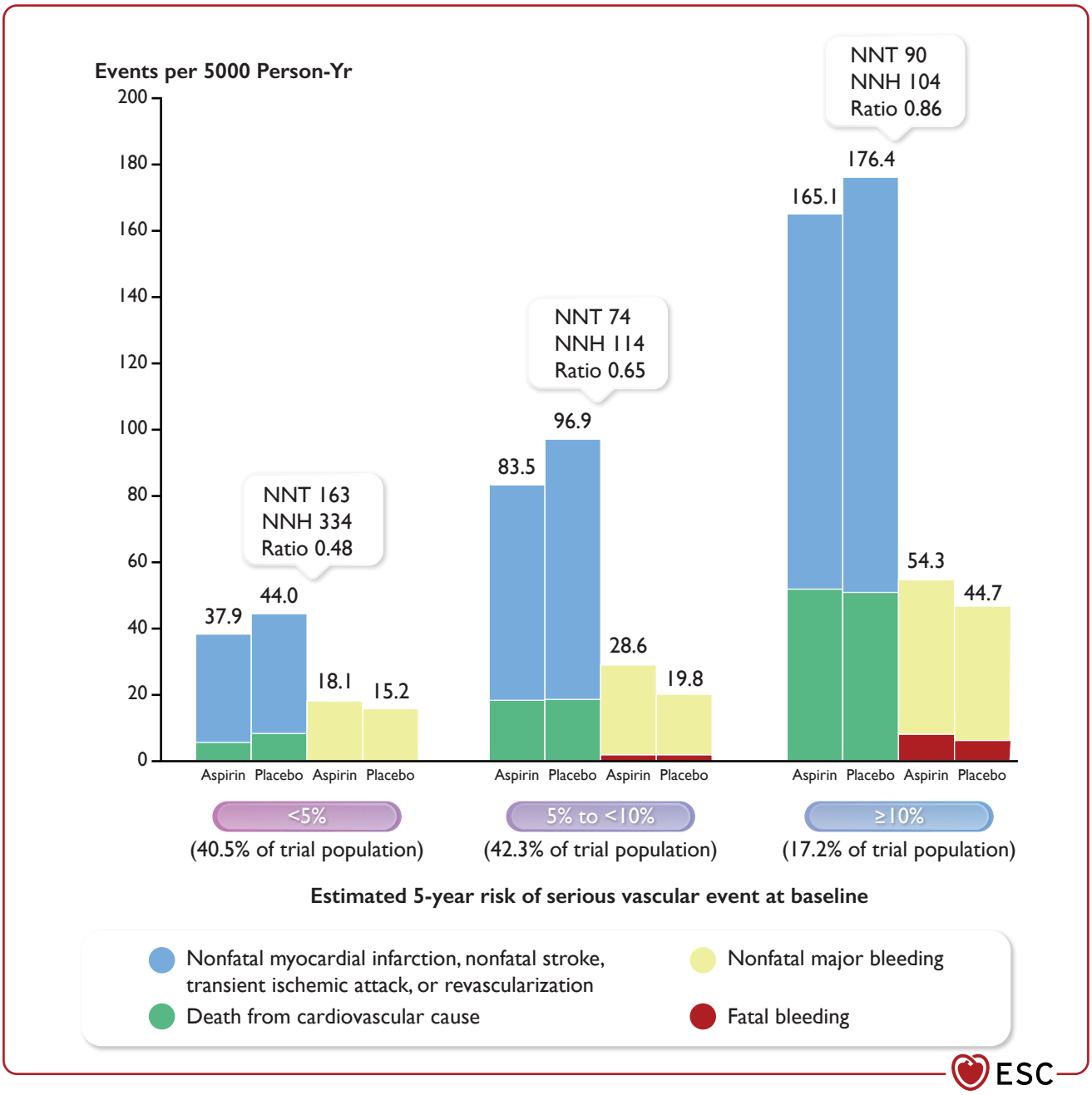

Figure S7 Observed absolute effect in aspirin and placebo groups for serious vascular events, including major bleeding or revascularization. ASCEND, A Study of Cardiovascular Events iN Diabetes; NNH, number needed to harm; NNT, number needed to treat; yr, year. The figure shows the efficacy and safety outcomes in three sub-groups of patients stratified according to the estimated risk of serious vascular events at baseline. The number needed to treat (NNT) and number needed to harm (NNH) are shown in each group, showing no clear difference in the benefit-risk balance according to the baseline risk stratification. The net benefit in each group favours NNT over NNH (ratio NNT:NNH <1). Figure modified from The ASCEND Study Collaborative Group.[47]

Table S12 Randomized phase 3 trials in patients with acute coronary syndrome, overall and in the diabetes mellitus sub-group

Study[a]	Patients	Design	Results[b]	
			Efficacy (primary) endpoints	Safety endpoints
CURE, 2001[52]	12 562 patients within 24 hours of the onset of ACS symptoms 2840 (22%) patients with diabetes Mean follow-up: 9 months	Randomization: ASA + placebo vs. ASA + clopidogrel (300 mg LD, 75 mg o.d. MD) Primary endpoint: MACE Safety endpoint: life-threatening, major bleeding (requiring ≥2 blood units)	Overall population Placebo 11.4%; clopidogrel 9.3% HR 0.80 (0.72–0.90) Sub-group with diabetes Placebo 16.7%; clopidogrel 14.2% Sub-group without diabetes Placebo 9.9%; clopidogrel 7.9%	Overall population Placebo 2.7%; clopidogrel 3.7% HR 1.38 (1.13–1.67) Subgroups with/without diabetes Data not reported No CABG-related excess bleeding (2246 patients underwent CABG/PTCA). *P* for interaction diabetes vs. without diabetes: not significant
TRITON-TIMI-38, 2008[53]	13 608 patients with ACS with scheduled PCI 3146 (17%) patients with diabetes Mean follow-up: 14.5 months	Randomization: Clopidogrel (300 mg LD, 75 mg o.d. MD) + ASA Prasugrel (60 mg LD, 10 mg MD) + ASA Primary endpoint: MACE Safety endpoint: TIMI major bleeding (non-CABG related)	Overall population Clopidogrel 12.1%; prasugrel 9.9% HR 0.81 (0.73–0.90) Sub-group with diabetes Clopidogrel 17.0%; prasugrel 12.2% HR 0.70 (0.58–0.85) Sub-group without diabetes Clopidogrel 10.6%; prasugrel 9.2% HR 0.86 (0.76–0.98)	Overall population Clopidogrel 1.8%; prasugrel 2.4% HR 1.32 (1.03–1.68) Subgroup with diabetes Clopidogrel 2.6%; prasugrel 2.5% HR 1.06 (0.66–1.69) Subgroup without diabetes Clopidogrel 2.4%; prasugrel 1.2% HR 1.43 (1.07–1.91)
PLATO, 2010[54]	18 624 patients with ACS 4662 (25%) patients with diabetes Mean follow-up: 12 months	Randomization: Ticagrelor (180 mg LD, 90 mg b.i.d. MD) + ASA Clopidogrel (300/600 mg LD, 75 mg o.d. MD) + ASA Primary endpoint: MACE Non-CABG-related safety endpoint: fatal, intracranial, or intrapericardial bleeding with cardiac tamponade, hypovolaemic shock or severe hypotension, haemoglobin ≤ 5.0 g/dL, transfusion of ≥4 units	Overall population Clopidogrel 11.7%; ticagrelor 9.8% HR 0.84 (0.77–0.92) Sub-group with diabetes Clopidogrel 16.2%; ticagrelor 14.1% HR 0.88 (0.76–1.03) Sub-group without diabetes Clopidogrel 10.2%; ticagrelor 8.4% HR 0.83 (0.74–0.93)	Overall population Clopidogrel 3.8%; ticagrelor 4.5% HR 1.19 (1.02–1.38) Subgroup with diabetes Clopidogrel 4.9%; ticagrelor 5.5% HR 1.13 (0.86–1.49) Subgroup without diabetes Clopidogrel 3.4%; ticagrelor 4.1% HR 1.22 (1.01–1.46) Dyspnoea (overall population) Clopidogrel 7.8%; ticagrelor 13.8% HR 1.84 (1.68–2.02); $P < 0.001$

Continued

ATLAS-ACS-TIMI-51, 2012[55]	15 526 patients with a recent ACS, randomized within 7 days from hospital admission 4894 (31%) patients with diabetes. Mean follow-up: 13 months	Randomization: DAPT (ASA + clopidogrel) + placebo DAPT + rivaroxaban 2.5 mg b.i.d. DAPT + rivaroxaban 5 mg b.i.d. Primary endpoint: MACE Safety endpoint: non-CABG-related TIMI major bleeding	Overall population Placebo: 10.7% Rivaroxaban 2.5 mg: 9.1% HR 2.5 mg: 0.84 (0.72–0.97) Rivaroxaban 5 mg: 8.8% ARR 1.9%; HR 5 mg: 0.85 (0.73–0.98) Population with diabetes Placebo 7.5%; combined rivaroxaban 7% HR combined rivaroxaban: 0.96 (0.77–1.20) Population without diabetes Placebo 7.2%; combined rivaroxaban 5.6% HR combined rivaroxaban: 0.78 (0.67–0.92)	Overall population Placebo: 0.6%; rivaroxaban 2.5 mg: 1.8% Rivaroxaban 5 mg: 2.4%; ARR: 1.8% HR combined rivaroxaban: 3.96 (2.46–6.38) Population with diabetes Placebo 0.2%; rivaroxaban combined 1.2% HR combined rivaroxaban: 5.09 (1.82–14.24) Population without diabetes Placebo 0.4%; rivaroxaban combined 1.5% HR combined rivaroxaban: 3.66 (2.13–6.28)
ISAR-REACT 5, 2019[56]	4018 patients hospitalized for ACS 892 (23%) patients with diabetes. Mean follow-up: 12 months	Randomization: Ticagrelor 90 mg b.i.d. Prasugrel 10 mg o.d. Primary endpoint: MACE Safety endpoint: BARC type 3–5 bleeding	Overall population Ticagrelor 9.3%; prasugrel 6.9% HR (ticagrelor): 1.36 (1.09–1.70) Population with diabetes Ticagrelor 11.2%; prasugrel 13.0% HR (ticagrelor): 0.84 (0.58–1.24) Population without diabetes Ticagrelor 8.6%; prasugrel 5.2% HR (ticagrelor): 1.70 (1.29–2.24)	Overall population Ticagrelor 5.4%; prasugrel 4.8% HR (ticagrelor): 1.12 (0.83–1.51) Discontinued: Ticagrelor 15.3%; prasugrel 12.5% $P = 0.03$

ACS, acute coronary syndrome; ARR, absolute risk reduction; ASA, acetylsalicylic acid; BARC, Bleeding Academic Research Consortium; b.i.d., twice a day; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; HR, hazard ratio; LD, loading dose; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke); MD, maintaining dose; MI, myocardial infarction; o.d., once a day; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TIMI, Thrombolysis in Myocardial Infarction.

[a]Studies are listed according to the year of publication.

[b]HRs are always indicated with (95% confidence interval).

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Table S13 Major features of trials on shortening dual antiplatelet therapy below 12 months vs. single antiplatelet therapy (acetylsalicylic acid or $P2Y_{12}$ inhibitor) in patients with acute coronary syndrome or post-percutaneous coronary intervention, overall and in the diabetes sub-group

Study[a]	Patient characteristics and sample size	Randomized comparison	Primary endpoints and design	Secondary endpoints	Primary outcomes[b]	Secondary outcomes[b]	Diabetes sub-group
Trials testing SAPT-ASA vs. 12-month DAPT							
RESET, 2012[57]	2117 patients with coronary artery stenosis post-PCI with DES	3-month DAPT (E-ZES) and then ASA alone vs. 12-month DAPT	CV death, MI, ST, target \vessel revascularization, or bleeding. Non-inferiority comparison, absolute margin 4%	Major bleeding	Primary endpoint: 40 (4.7%) patients in E-ZES + 3-month DAPT vs. 41 (4.7%) patients in 12-month DAPT $P <$ 0.001 for non-inferiority	Major bleeding: 2 vs. 4 events	621 patients with diabetes Primary endpoints: 4 vs. 5 events Interaction: $P = 0.7$
EXCELLENT, 2012[58]	1443 patients post-PCI with DES	6-month DAPT and then ASA alone vs. 12-month DAPT (ASA + clopidogrel)	Cardiac death, MI, or ischaemia-driven target-vessel revascularization. Non-inferiority comparison, absolute margin 4%	Death, MI, stroke, ST, or TIMI major bleeding	MACCE: 56 (8.0%) events with 6-month DAPT vs. 60 (8.5%) events with 12-month DAPT HR 0.94 (0.65–1.35); $P = 0.72$	TIMI major bleeding: 2 (0.3%) vs. 4 (0.6%) events HR 0.50 (0.09–2.73); $P = 0.42$	550 patients with diabetes Primary endpoint: 24 (9.1%) vs. 8 (3.0%) events HR 3.16 (1.42–7.03); $P = 0.005$
OPTIMIZE, 2013[59]	3119 patients undergoing PCI with zotarolimus-eluting stents.	3-month DAPT and then ASA alone vs. 12-month DAPT (ASA + clopidogrel)	All-cause death, MI, stroke, or major bleeding. Non-inferiority comparison, absolute margin 2.7%	MACE, emergent coronary artery bypass graft surgery, ST, target-lesion revascularization, or any bleeding	NACCE: 93 (6.0%) patients on short-term vs. 90 (5.8%) patients on long-term DAPT HR 1.03 (0.77–1.38); $P =$ 0.002 for non-inferiority	Any bleeding: 35 (2.3%) vs. 45 (2.9%) events HR 0.77 (0.50–1.20); $P = 0.67$ Major bleeding: 10 (0.6) vs. 14 (0.9) events HR 0.71 (0.32–1.60)	1099 patients with diabetes Primary endpoint: 34 (0.06%) vs. 37 (0.07%) events RR 0.90 (0.58–1.41) Interaction: $P = 0.5$
SECURITY, 2014[60]	1399 patients with stable or unstable angina or documented silent ischaemia undergoing PCI with second-generation DES	6-month DAPT and then ASA alone vs. 12-month DAPT	Cardiac death, MI, stroke, definite or probable ST, or BARC type 3 or 5 bleeding at 12 months. Non-inferiority trial, absolute margin 2%	Cardiac death, MI, stroke, definite or probable ST, or BARC type 2–5 bleeding	Primary endpoint: 31 (4.5%) events with 6-month DAPT vs. 27 (3.7%) events with 12-month DAPT Absolute difference 0.8% (−2.4 to 1.7); $P = 0.469$	BARC type 3–5 bleeding: 4 (0.6%) vs. 8 (1.1%) events Absolute difference −0.5% (−1.4 to 0.4); $P =$ 0.283	429 patients with diabetes. Diabetes independent predictor of the primary endpoint with a borderline significance $P = 0.06$

Continued

ISAR-SAFE, 2015[56]	4000 patients undergoing PCI with DES	6-month DAPT + clopidogrel and then ASA alone vs. 12-month DAPT + clopidogrel	Death, MI, ST, stroke, or TIMI major bleeding at 9 months. Non-inferiority comparison, absolute margin 2%	TIMI major bleeding	Primary endpoint: 29 (1.5%) events with 6-month DAPT vs. 32 (1.6%) events with 12-month DAPT $P < 0.001$ for non-inferiority	TIMI major bleeding: 4 (0.2%) vs. 5 (0.3%) events HR 0.80 (0.21–2.98); $P = 0.74$	979 patients with diabetes Primary endpoint: 9 (1.9%) vs.12 (2.5%) events HR 0.73 (0.31–1.73) Interaction: $P = 0.5$
I-LOVE-IT, 2016[61]	1829 patients undergoing PCI with sirolimus DES	6-month DAPT and then ASA alone vs. 12-month DAPT	Cardiac death, target-vessel MI, or clinically indicated target-lesion revascularization. Non-inferiority comparison, absolute margin <3.7%	All-cause death, all MI, stroke, or BARC bleeding type 3–5	TLF: 61 (6.8%) events with 6-month DAPT vs. 54 (5.9%) events with 12-month DAPT Absolute difference 0.87% (−1.37 to 3.11); $P = 0.006$ for non-inferiority	BARC type 3–5 bleeding: 11 (1.2%) vs. 6 (0.7%) events $P = 0.21$	414 patients with diabetes NACCE: 25 (11.8%) vs. 19 (9.4%) events HR 1.27 (0.72–2.23) Interaction: $P = 0.5$
SMART-DATE, 2018[62]	2712 patients with unstable angina, non-STEMI, or STEMI undergoing PCI	6-month DAPT and then ASA alone vs. 12-month DAPT	All-cause death, MI, or stroke at 18 months. Non-inferiority, absolute margin 2%	Individual components of the primary endpoint; definite or probable ST and BARC type 2–5 bleeding at 18 months	MACCE: 63 (4.7%) patients with 6-month DAPT vs. 56 (4.2%) patients with 12-month DAPT Absolute risk difference 0.5%; $P = 0.03$ for non-inferiority MI: 24 (1.9%) vs. 10 (0.8%) patients HR 2.41 (1.15–5.05); $P = 0.02$	BARC type 2–5 bleeding: 35 (2.7%) vs. 51 (3.9%) patients HR 0.69 (0.45–1.05); $P = 0.09$ Major bleeding: 6 (0.5%) vs. 10 (0.8%) patients HR 0.60 (0.22–1.65); $P = 0.33$	744 patients with diabetes Interaction: $P = 0.4$
Trials testing SAPT-P2Y$_{12}$ vs. 12-month DAPT							
TWILIGHT, 2019[63]	7119 patients post-PCI at high bleeding or ischaemic risk (≥65 years, female sex, troponin-positive, diabetes, CKD) + multivessel CAD, total stent length >30 mm, thrombotic target lesion, bifurcation lesion with two stents, an obstructive left main or proximal LAD lesion, or calcified target lesion treated with atherectomy	3-month DAPT (ticagrelor + ASA). Then randomization: 12-month ASA + ticagrelor or 12-month placebo + ticagrelor	BARC type 2, 3, or 5 bleeding Superiority hypothesis on the safety endpoint	Death from any cause, death for CV causes, non-fatal MI, or non-fatal stroke. Non-inferiority comparison, absolute margin 1.6%	Primary endpoint: 141 (4.0%) events with ticagrelor/placebo vs. 250 (7.1%) events with ticagrelor/ASA HR 0.56 (0.45–0.68); $P < 0.001$ BARC type 3–5 bleeding: 34 (1.0%) vs. 69 (2.0%) events HR 0.49 (0.33–0.74)	MACE: 126 (3.6%) vs. 130 (3.7%) events HR 0.97 (0.76–1.24); $P < 0.001$ for non-inferiority	2620 (37%) patients with diabetes BARC type 2–5 bleeding: 58 (4.6%) vs. 86 (6.6%) events HR 0.65 (0.47–0.91) MACE: 59 (4.6%) vs. 75 (5.9%) events HR 0.77 (0.55–1.09)

Continued

SMART CHOICE, 2019[64]	2993 patients undergoing PCI with DES	3-month DAPT (ASA + a $P2Y_{12}$ inhibitor [77% clopidogrel]). Then randomization: 12-month $P2Y_{12}$ inhibitor (clopidogrel 77%) alone or 12-month DAPT	All-cause death, MI, or stroke. Non-inferiority comparison, absolute margin 1.8%, relative 45% increase in event rate	Composite of primary endpoint + BARC type 2–5 bleeding	MACCE: 42 (2.9%) events with $P2Y_{12}$ inhibitor vs. 36 (2.5%) events with DAPT HR 1.19 (0.76–1.85); $P = 0.007$ non-inferiority MI: 11 (0.8%) vs. 17 (1.2%) events HR 0.66 (0.31–1.40); $P = 0.28$ Stroke: 11 (0.8%) vs. 5 (0.3%) events HR 2.23 (0.78–6.43); $P = 0.14$	BARC type 2–5 bleeding: 28 (2.0%) vs. 49 (3.4%) events HR 0.58 (0.36–0.92); $P = 0.02$ Major bleeding: 12 (0.8%) vs. 14 (1.0%) events HR 0.87 (0.40–1.88); P = NS	1130 patients with diabetes MACCE: 23 (4.1%) vs. 20 (3.8%) events HR 1.13 (0.62–2.05) Interaction: $P = 0.84$
STOP-DAPT, 2019[65]	3045 patients who underwent PCI	1-month DAPT then clopidogrel alone vs. 12-month DAPT with ASA + clopidogrel	CV death, MI, ischaemic or haemorrhagic stroke, definite ST, or TIMI major or minor bleeding. Non-inferiority comparison, relative margin 50%	CV endpoint: CV death, MI, definite ST, or ischaemic or haemorrhagic stroke Bleeding endpoint: TIMI major or minor bleeding	Primary endpoint: 35 (2.4%) events with 1-month DAPT vs. 55 (3.7%) events with 12-month DAPT HR 0.64 (0.42–0.98); $P < 0.01$ for non-inferiority and superiority	CV endpoint: 29 (2.0%) vs. 37 (2.5%) events HR 0.79 (0.49–1.29); $P = 0.34$ Bleeding endpoint: 6 (0.4%) vs. 23 (1.5%) events HR 0.26 (0.11–0.64); $P = 0.004$	1154 patients with diabetes Primary endpoint: 18 (3.1%) vs. 25 (4.5%) events HR 0.70 (0.38–1.29); Interaction: $P = 0.26$

ASA, acetylsalicylic acid; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent; HR, hazard ratio; LAD, left anterior descending coronary artery; MACCE, major adverse cardio-cerebral event; MACE, major arterial cardiovascular events (cardiovascular death, myocardial infarction, stroke); MI, myocardial infarction; NACCE, net adverse clinical and cerebral events; NS, not significant; PCI, percutaneous coronary intervention; RR, relative risk; SAPT, single antiplatelet therapy; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TLF, target-lesion failure.

[a]Studies are listed according to the year of publication.

[b]HRs and absolute differences are always indicated with (95% confidence interval).

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Table S14 Overview of trials and meta-analyses of subjects with atrial fibrillation and acute coronary syndrome or post-percutaneous coronary intervention, overall and in the diabetes mellitus sub-group (if pre-specified)

Study[a]	Characteristics, sample size	Design	Primary endpoints (safety)	Secondary endpoints (efficacy)	Primary outcomes (safety)	Secondary outcomes (efficacy)	DM subgroup
PIONEER-AF-PCI[66]	2124 patients with AF and PCI with stenting	Group 1: Rivaroxaban 15 mg o.d. + $P2Y_{12}$ inhibitor for 12 months Group 2: Rivaroxaban 2.5 mg b.i.d. + DAPT for 1, 6, or 12 months and receiving ASA + rivaroxaban 15 mg for the remainder of the 12 months Group 3: VKA + DAPT for 1, 6, or 12 months and receiving ASA + VKA for the remainder of the 12 months 94% clopidogrel	Major and minor TIMI bleeding or bleeding requiring medical attention. Follow-up: 12 months	Composite of cardiovascular death, MI, or stroke (MACE)	16.8% Group 1 18.0% Group 2 26.7% Group 3 HR Group 1 vs. Group 3 0.59; (95% CI, 0.47–0.76) HR Group 2 vs. Group 3 0.63; (95% CI, 0.50–0.80)	MACE: Group 1: 41 (6.5%) Group 2: 36 (5.6%) Group 3: 36 (6.0%) HR Group 1 vs. Group 3 1.08; (95% CI, 0.69–1.68) HR Group 2 vs. Group 3 0.93; (95% CI, 0.59–1.48)	624 (29%) mostly on 6 or 12 month DAPT
REDUAL PCI[67]	2725 patients with AF and PCI	Randomized to: • VKA + $P2Y_{12}$ inhibitor + ASA (3 months for DES; TAT) then continue with VKA + $P2Y_{12}$ inhibitor • Dabigatran (2 doses) + $P2Y_{12}$ inhibitor (DAT) for 12 months 88% clopidogrel	Major or clinically relevant non-major bleeding (ISTH definition). Non-inferiority comparison. Follow-up: 14 months	Composite of MI, stroke, systemic embolism, death, unplanned revascularization. Non-inferiority comparison	15.4% for 110 mg DAT vs. 26.9% TAT HR 0.52; (95% CI, 0.42–0.63); $P < 0.001$ for non-inferiority and superiority 20.2% for 150 mg DAT vs. 25.7% TAT HR 0.72; (95% CI, 0.58–0.88); $P < 0.001$ for non-inferiority only	239 (13.7%) DAT vs. 131 (13.4%) TAT HR 1.04; (95% CI 0.84–1.29); $P = 0.005$ for non-inferiority Thrombo-embolic events: 168 (9.6%) DAT vs. 83 (8.5%) TAT HR 1.17; (95% CI 0.9–1.53); $P = 0.11$ for non-inferiority	1296 (36%) ~300 patients/arm Higher rate of secondary efficacy outcomes in the DM vs. non-DM population No heterogeneity of outcomes vs. the overall trial population
ENTRUST[68]	1506 patients with AF after PCI for stable CAD or ACS	• Edoxaban (60 mg o.d.) + $P2Y_{12}$ inhibitor for 12 months • VKA + a $P2Y_{12}$ inhibitor + ASA for a minimum of 1 month and maximum of 12 months 93% clopidogrel	Major or clinically relevant non-major bleeding according to the ISTH definition. Follow-up: 12 months	Cardiovascular death, stroke, systemic embolic event, MI, or definite stent thrombosis	128 (17%) DAT-edoxaban vs. 152 (20%) patients on TAT HR 0.83; (95% CI, 0.65–1.05); $P = 0.0010$ for non-inferiority only; P = NS for superiority. Median TAT: 2 months	49 (7%) DAT vs. 46 (6%) TAT HR 1.06; (95% CI, 0.71–1.69)	517 (34%) DM patients, ~250 per arm. Non-pre-specified subgroup

Continued

AUGUSTUS[69]	4614 patients with persistent, permanent, paroxysmal AF and recent ACS or PCI with planned use of $P2Y_{12}$ inhibitor	Two-by-two factorial design: • Apixaban or VKA • ASA 81 mg or placebo All for 6 months On a background of 93% clopidogrel	Major or clinically relevant non-major bleeding (ISTH definition). Non-inferiority and superiority comparisons Follow-up: 6 months	Death, hospitalization, composite of stroke, MI, stent thrombosis (definite or probable), or urgent revascularization	10.5% apixaban vs. 14.7% VKA HR 0.69; (95% CI, 0.58–0.81); $P < 0.001$ for non-inferiority and superiority 16.1% ASA vs. 9.0% placebo HR 1.89; (95% CI, 1.59–2.24); $P < 0.001$	154 patients (6.7%) on apixaban vs. 163 (7.1%) on VKA 149 patients (6.5%) on ASA vs. 168 (7.3%) on placebo $P = NS$	1678 diabetes (36%). Higher rate of both primary and secondary endpoints vs. without diabetes. No heterogeneity of outcomes vs. the overall trial population
Meta-analysis[70]	Patients with AF undergoing PCI from four trials: PIONEER AF-PCI, REDUAL PCI, AUGUSTUS, and ENTRUST 10 234 patients: DAT = 5496 vs. TAT = 4738	DAT vs. TAT	ISTH major or clinically relevant non-major bleeding at longest available follow-up (between 6 and 14 months)	All-cause death, cardiovascular death, trial-defined MACE, MI, stroke, stent thrombosis	13.4% DAT vs. 20.8% TAT RR 0.66; (95% CI, 0.56–0.78); $P < 0.0001$	DAT vs. TAT: • CV death 2.6% vs. 2.4%; RR 1.10; (95% CI, 0.86–1.41) • MACE 8.6% vs. 8.0%; RR 1.08; (95% CI, 0.95–1.23) ; $P = 0.26$ • MI 3.6% vs. 3.0%; RR 1.22; (95% CI, 0.99–1.52); $P = 0.07$ • Stent thrombosis 1.0% vs. 0.6%; RR 1.59; (95% CI, 1.01–2.50); $P = 0.04$. Similar results in ACS and patients with stable CAD	Not available
Meta-analysis[71]	Patients with AF undergoing PCI from three trials: PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS 9463 patients	DAT vs. TAT	Major bleeding ISTH and TIMI-refined, clinically relevant, non-major bleeding	All-cause and cardiovascular death, stroke, MI, stent thrombosis	DAT vs. TAT ISTH-defined major bleeding: OR 0.59; (95% CI, 0.49–0.72); $P < 0.001$	All ischaemic events: 4.1% DAT vs. 3.2% TAT MI: OR 1.2; (95% CI, 0.96–1.5); $P = 0.1$ Stent thrombosis: OR 1.67; (95% CI 1.02–2.73); $P = 0.04$	Not available

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; AF, atrial fibrillation; b.i.d., twice a day; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DAT, dual antithrombotic therapy; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DM, diabetes mellitus; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular events; MI, myocardial infarction; o.d., once a day; NS, not significant; OR, odds ratio; PCI, percutaneous coronary intervention; RR, risk ratio; TAT, triple antithrombotic therapy; TIMI, Thrombolysis In Myocardial Infarction; VKA, vitamin K antagonist.
[a]Studies are indicated according to the year of publication.

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3. Management of coronary artery disease and diabetes

3.1. Chronic coronary syndromes and diabetes

3.1.1. Revascularization

In the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical an Invasive Approaches) trial, in patients with documented stable coronary artery disease (CAD) and moderate or severe ischaemia, a routine invasive strategy, compared with an initial conservative approach, did not significantly reduce the risk of ischaemic CV events or all-cause death over a median of 3.2 years.[72] In the separate analysis of the sub-group with diabetes (around 41% of the total population), despite the higher risk of death or myocardial infarction (MI), the study also showed no significant benefit of routine invasive management.[73] A recently published meta-analysis of 25 trials, including ISCHEMIA, involving 19 806 patients revealed that in patients with stable CAD, elective coronary revascularization plus optimal medical therapy reduced cardiac mortality compared with medical therapy alone.[74] The cardiac survival benefit after revascularization improved with longer follow-up times and was associated with fewer spontaneous MIs. Interestingly, subjects with multivessel disease, a typical feature of type 2 diabetes mellitus (T2DM), derive a highly significant, direct incremental, cardiac mortality benefit of revascularization with increased percentages of multivessel disease ($P = 0.0004$).[74] A smaller meta-analysis did not support the benefit of routine revascularization vs. initial medical therapy in reducing mortality.[75] Another pooled analysis of studies in patients with diabetes also showed a significant reduction in the combined endpoint (death, MI, stroke, and revascularization) with revascularization plus medical therapy compared with medical treatment alone, and that this increased over time.[76] Of note, in the percutaneous coronary intervention (PCI) group, the benefit of revascularization was observed only in patients who achieved a low-density lipoprotein-cholesterol (LDL-C) level < 70 mg/dL. The prolonged observation of patients in the ISCHEMIA trial (median follow-up of 5.7 years) revealed a lower risk of CV mortality with an initial invasive strategy than with an initial conservative strategy, with no difference in all-cause mortality between groups.[77]

The role of revascularization in patients with HF remains an unresolved problem. In the STICH (Surgical Treatment for Ischemic Heart Failure) trial, the incidence of death from any cause at 5 years was similar in the group of patients with an ejection fraction 35% or less (39% had diabetes) assigned to undergo coronary artery bypass grafting (CABG) and the group treated with medical therapy alone. This observation was partly due to the higher early mortality of patients who underwent CABG.[78] However, survival benefits accrued over time, and at 10 years of follow-up, patients who received revascularization were more likely to be alive than those on medical therapy alone.[78] Recently published, the REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction) trial was conducted in a similar population (ejection fraction 35% or less, 41% had diabetes), but patients underwent percutaneous revascularization to avoid an early hazard of CABG. Over a median of 41 months, PCI did not reduce the incidence of death from any cause or hospitalization for heart failure. In addition, the left ventricular ejection fraction was similar in the two groups at 6 and 12 months, although quality-of-life scores favoured the PCI group.[79] It can be presumed that the follow-up time needed to be longer to demonstrate the benefit of revascularization in this group, analogous to the STICH study.

Selecting the optimal myocardial revascularization strategy for patients with diabetes and multivessel CAD requires particular attention due to more extensive and diffuse disease. Thus, PCI in patients with diabetes is often more complex than in those without diabetes. Trials comparing CABG and PCI with old-generation stents in people with diabetes and stable multivessel disease have provided evidence in favour of CABG, with improved outcomes for death, MI, and repeat revascularization, despite an excess of stroke.[80] The FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial compared elective revascularization with CABG or PCI with first-generation drug-eluting stents (DESs) in 1900 patients with diabetes and multivessel disease but without left-main stenosis.[81] The primary endpoint of any-cause death, non-fatal MI, or non-fatal stroke at 5 years occurred in 26.6% in the PCI group vs. 18.7% in the CABG group. The incidences of death (16.3% vs. 10.9%, respectively; $P = 0.049$) and MI (13.9% vs. 6.0%, respectively; $P < 0.001$) were higher in the PCI group, whereas the incidence of stroke was lower (2.4% vs. 5.2%, respectively; $P = 0.03$). The prolonged observation of these patients (median follow-up of 7.5 years) also confirmed the advantage of surgical revascularization in reducing all-cause mortality.[76] In the subset of 452 patients with diabetes and multivessel CAD enrolled in the SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) trial, there were no differences in the composite safety endpoint of all-cause death, stroke, and MI at 5 years. However, repeated revascularization was significantly more frequent in patients with diabetes treated with PCI than CABG.[82] A higher incidence of cardiac death was noted in patients who were insulin-dependent and treated with PCI. In the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial, patients with diabetes (41% of the total population) treated with PCI had a higher rate of the combined primary endpoint of death, MI, or target-vessel revascularization compared with those treated with CABG.[83] A meta-analysis of four randomized controlled trials covering 3052 patients compared PCI with early-generation DES vs. CABG in patients with diabetes and multivessel CAD. The study revealed a higher risk of death and MI with early-generation DES treatment, but a lower risk of stroke.[84] A sensitivity analysis showed that the superiority of CABG was most pronounced among patients with a high SYNTAX score.

Another network meta-analysis suggested that the survival benefit of CABG over PCI in patients with diabetes might be lost when using the new generation of everolimus-eluting stents (EESs) though this was not confirmed in a subsequent meta-analysis that also directly compared EES with CABG.[85,86] In a collaborative, individual patient data, pooled analysis of 11 518 patients with multivessel or left main disease randomized to CABG or PCI with stents, all-cause death was significantly lower after CABG in patients with diabetes, but not in those without.[87] However, no mortality benefit was noted with CABG in patients with left main disease regardless of diabetes status. Consequently, current evidence continues to favour CABG over PCI for revascularization in patients with diabetes, chronic coronary syndrome, and multivessel disease.[88]

Recently, the SYNTAX II study demonstrated that the outcomes after state-of-the-art percutaneous coronary revascularization in patients with *de novo* three-vessel disease (30% with diabetes) were equivalent to those of matched patients who underwent CABG in SYNTAX at 5-year follow-up; still, this study did not differentiate between patients with or without diabetes.[89] However, more contemporary data shows that even modern PCI techniques still do not

match CABG in such patients. The FAME 3 (Fractional Flow Reserve vs. Angiography for Multivessel Evaluation) trial, in which 1500 patients with three-vessel CAD were randomized to physiology-guided PCI with current-generation DES or CABG, failed to demonstrate PCI non-inferiority to surgery in the composite endpoint of death, MI, stroke, or repeat revascularization at 1 year. A similar result was observed in patients with diabetes mellitus, comprising 29% of the total population.[88] This result can be explained, among others, by the significant progress in coronary artery surgery observed in recent years.[90] Finally, the SYNTAXES (SYNTAX Extended Survival) study provided data on all-cause mortality after a 10-year follow-up. Among patients with three-vessel disease, mortality was significantly reduced in the CABG group compared with the PCI group, whereas no CABG advantage was found among patients with left-main CAD. Notably, there was no treatment-by-sub-group interaction with diabetes.[91] In patients with diabetes and a left main or multivessel disease, PCI and CABG had similar mortality after 10 years. Interestingly, landmark analyses revealed that mortality was significantly higher with PCI at 5 years, whereas it was numerically higher with CABG between 5 and 10 years. Patients treated with insulin had a numerically higher mortality at 10 years with PCI, as compared with CABG.[92]

The revascularization approach for left-main obstruction remains unclear. When patients present with comorbidities that increase surgical risk, the choice of revascularization method is best decided by multidisciplinary, individualized risk assessment. However, recent advances in PCI (new DES, intracoronary physiological and imaging tests) may alter current evidence. In a pre-specified sub-group analysis from the EXCEL (Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, the primary composite endpoint of all-cause death, MI, or stroke after 3 years of observation was significantly higher in patients with diabetes than in those without diabetes (20.0% vs. 12.9%, respectively; $P < 0.001$).[93] There was no difference in the primary endpoint in relation to the treatment strategy in the diabetes sub-group (PCI vs. CABG: 20.7% vs. 19.3%, respectively; HR 1.03; [95% CI, 0.71–1.50; $P = 0.87$]). All-cause death at 3 years occurred in 13.6% of PCI patients and 9.0% of CABG patients ($P = 0.046$). A recent meta-analysis of four randomized controlled trials that reported outcomes after PCI vs. CABG in unprotected left main coronary artery stenosis among patients with diabetes found that at long-term follow-up (3–11 years), there was no difference for individual outcomes of all-cause and CV mortality or MI. However, the risk of stroke was reduced, whereas the rate of repeat revascularization was increased with PCI.[94] Ten-year data from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis) registry of 2240 consecutive patients with unprotected left main CAD revealed that the adjusted 10-year mortality or composite outcome was similar between PCI and CABG, irrespective of the presence of diabetes. Nevertheless, the clinical outcomes favoured CABG in the cohort of patients with diabetes treated with bare-metal stents.[95]

3.2. Ischaemia with no obstructive coronary artery disease in diabetes

Although coronary artery stenoses constitute the most common cause of ischaemia and angina, many symptomatic patients with confirmed ischaemia do not have obstructive CAD.[96] This phenomenon may be explained by diffuse disease presenting as mild or moderate lesions on coronary angiography, dynamic stenoses of epicardial vessels, or coronary microvascular dysfunction (CMD).[97] In all these cases, patients may have typical angina symptoms during exercise, and ischaemia on non-invasive functional tests. Details of this phenomenon were described in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.[98] Several mechanisms by which diabetes increases the risk of CMD have been proposed, such as hyperglycaemia-induced oxidative stress, insulin resistance, inflammation and reduced nitric oxide production, and an imbalance between the sympathetic and parasympathetic systems.[99–103] A correlation with albuminuria has also been reported.[104] Finally, T2DM itself may damage endothelial cells and reduce capillary surface area.[99–103,105] (*Figure S8*).

Although some studies show that coronary vessels appear angiographically smaller in patients with diabetes compared with patients without diabetes, a recent analysis showed that T2DM does not influence the dimensions of coronary arteries in the absence of atherosclerosis.[106] T2DM is commonly regarded as a risk factor of obstructive CAD, yet in most patients with diabetes and angina without significant coronary lesions, CMD can be diagnosed.[100] Standardized criteria for diagnosing microvascular angina have recently been proposed by the COVADIS (Coronary Vasomotion Disorders International Study) Group.[107] T2DM, along with dyslipidaemia, obesity, and metabolic syndrome, has been recognized as the main risk factor. Treatment of ischaemia with no obstructive CAD (INOCA), apart from lifestyle modification and proper metabolic control (glucose and lipids), in patients with diabetes should not differ from that in patients without diabetes, and has been published elsewhere.[108] It should be noted that T2DM is a risk factor for worse prognosis among patients with INOCA.[109]

In contrast to INOCA, MI with non-obstructive coronary arteries (MINOCA) is observed less frequently in patients with diabetes than in those without diabetes.[110–112] MINOCA is a complex, non-homogenous condition with underlying cardiac and non-cardiac causes.[113–115] Patients presenting with MINOCA have a lower survival rate than matched healthy individuals.[116,117] T2DM, but also high blood glucose levels, regardless of the presence of diabetes, has been reported as important risk factors of early and late mortality.[113,118,119] The treatment of patients with diabetes diagnosed with MINOCA should not differ from those without diabetes. As in any other patient with acute coronary syndrome, assessing and controlling glucose level early is recommended (*Section 6.2.2.2* of the main text).

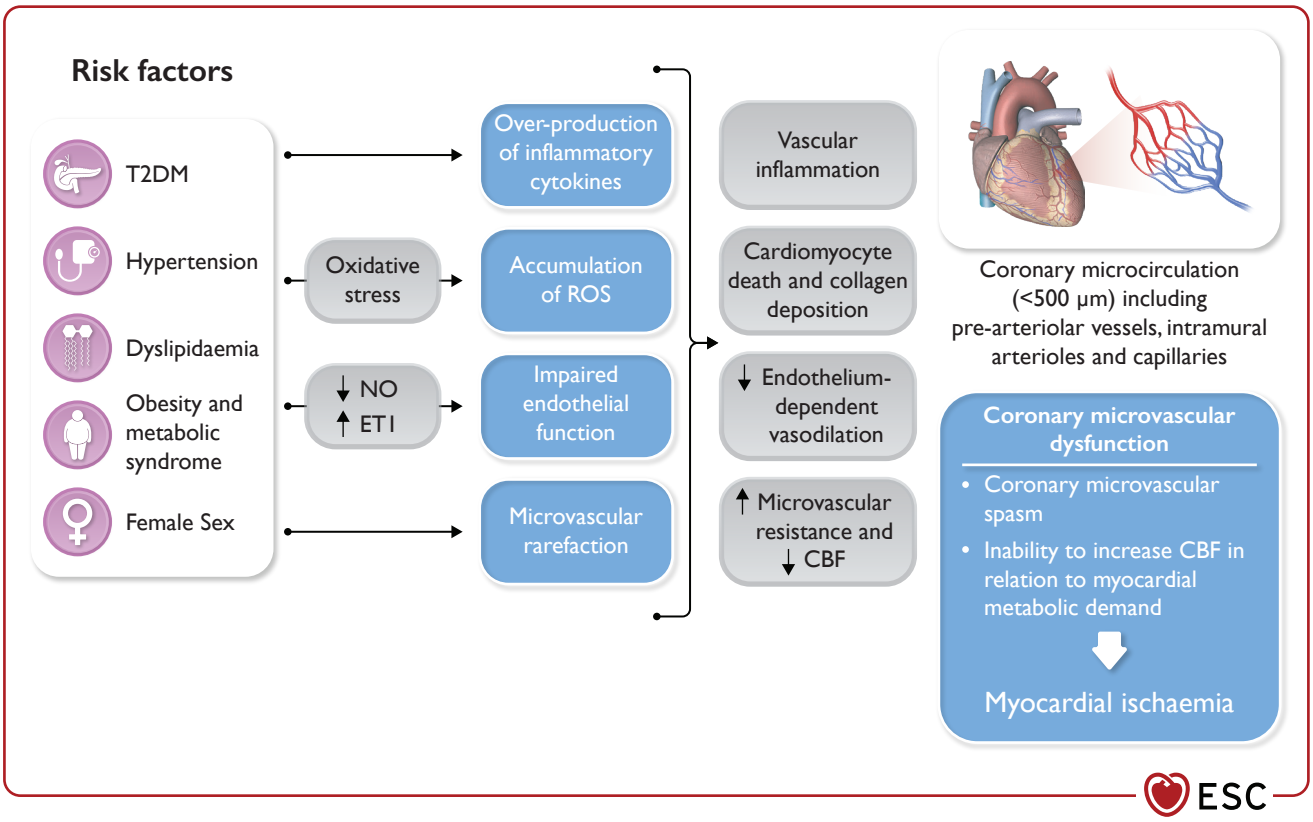

Figure S8 Pathophysiology of coronary microvascular dysfunction. ↑, increased; ↓, decreased; CBF, coronary blood flow; ET1, endothelin-I; NO, nitric oxide; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus. Figure modified from Crea *et al.* 2021.[103]

4. Heart failure and diabetes

Table S15 Overview of baseline characteristics and outcomes of cardiovascular outcomes trials with sodium–glucose co-transporter-2 inhibitors in patients with atherosclerotic cardiovascular disease, high atherosclerotic cardiovascular disease risk, chronic kidney disease, heart failure, and/or diabetes

Trial population	T2DM with ASCVD or at high ASCVD risk								CKD ± diabetes			
Trial	DECLARE-TIMI 58[9,120]		CANVAS[8]		VERTIS CV[11,121]		EMPA-REG OUTCOME[7]		DAPA-CKD[122]		EMPA-KIDNEY[123]	
Drug	Dapa	Pla	Cana	Pla	Ertu	Pla	Empa	Pla	Dapa	Pla	Empa	Pla
N	8582	8578	5795	4347	5499	2747	4687	2333	2152	2152	3304	3305
Age (years); mean ± SD or median (IQR)	63.9 ± 6.8	64.0 ± 6.8	63.0 ± 8.3	63.4 ± 8.2	64.4 ± 8.1	64.4 ± 8.0	63.1 ± 8.6	63.2 ± 8.8	61.8 ± 12.1	61.9 ± 12.1	63.9 ± 13.9	63.8 ± 13.9
Established CVD, *n* (%)	3474 (40.5)	3500 (40.8)	3756 (64.8)	2900 (66.7)	4144 (75.4)	2112 (76.9)	4657 (99.4)	2307 (98.9)	813 (37.8)	797 (37.0)	861 (26.1)	904 (27.4)
HF total, n (%)	852 (9.9)	872 (10.2)	803 (13.9)	658 (15.1)	1286 (23.4)	672 (24.5)	462 (9.9)	244 (10.5)	235 (10.9)	233 (10.8)	N/A	N/A
HFpEF	N/A	N/A	N/A	N/A	680 (13.4)	327 (11.9)	N/A	N/A	N/A	N/A	N/A	N/A
HFrEF	318 (3.7)	353 (4.1)	N/A	N/A	319 (5.8)	159 (5.8)	N/A	N/A	N/A	N/A	N/A	N/A
Diabetes (%)	100	100	100	100	100	100	100	100	67.6	67.4	100	100
eGFR (mL/min/1.73 m^2); mean ± SD or median (IQR)	85.4 ± 15.8	85.1 ± 16.0	76.7 ± 20.3	76.2 ± 20.8	76.1 ± 20.9	75.7 ± 20.8	74.2 ± 21.6	73.8 ± 21.1	43.2 ± 12.3	43.0 ± 12.4	37.4 ± 14.5	37.3 ± 14.4
First HHF/CVD, events, *n*	417	496	N/A	N/A	444	250	265	198	100	138	131	152
Event rate first HHF/CVD (per 1000 PY)	12.2	14.7	16.3	20.8	23	27	19.7	30.1	22	30	20.4	23.7
Outcome first CVD/HHF, HR (95% CI)	0.83 (0.73–0.95)		0.78 (0.67–0.91)		0.88 (0.75–1.03)		0.66 (0.55–0.79)		0.71 (0.55–0.92)		0.84 (0.67–1.07)	
HHF, HR (95% CI)	0.73 (0.61–0.88)		0.67 (0.52–0.87)		0.70 (0.54–0.90)		0.65 (0.50–0.85)		N/A		N/A	
CVD, HR (95% CI)	0.98 (0.82–1.17)		0.87 (0.72–1.06)		0.92 (0.77–1.11)		0.62 (0.49–0.77)		0.81 (0.58–1.12)		0.84 (0.60–1.19)	

Continued

Trial population	CKD + diabetes				LVEF ≥40% ± diabetes				HFrEF ± diabetes				Worsening HF + diabetes	
Trial	CREDENCE[10]		SCORED[12]		EMPEROR-Preserved[124]		DELIVER[125]		DAPA-HF[126]		EMPEROR-Reduced[127]		SOLOIST-WHF[128]	
Drug	Cana	Pla	Sota	Pla	Empa	Pla	Dapa	Pla	Dapa	Pla	Empa	Pla	Sota	Pla
N	2202	2199	5292	5292	2997	2991	3131	3132	2373	2371	1863	1867	608	614
Age (years); mean ± SD or median (IQR)	62.9 ± 9.2	63.2 ± 9.2	69 (63–74)	69 (63–74)	71.8 ± 9.3	71.9 ± 9.6	71.8 ± 9.6	71.5 ± 9.5	66.2 ± 11.0	66.5 ± 10.8	67.2 ± 10.8	66.5 ± 11.2	69 (63–76)	70 (64–76)
Established CVD, *n* (%)	1113 (50.5)	1107 (50.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HF total, n (%)	329 (14.9)	323 (14.7)	1640 (31.0)	1643 (31.0)	2997 (100)	2991 (100)	3131 (100)	3132 (100)	2373 (100)	2371 (100)	1863 (100)	1867 (100)	608 (100)	614 (100)
HFpEF	N/A	N/A	1133 (21.4)	1115 (21.1)	2997 (100)	2991 (100)	3131 (100)	3132 (100)	N/A	N/A	N/A	N/A	127 (20.9)	129 (21.0)
HFrEF	N/A	N/A	505 (9.5)	528 (10.0)	N/A	N/A	N/A	N/A	2373 (100)	2371 (100)	1863 (100)	1867 (100)	481 (79.1)	485 (79.0)
Diabetes (%)	100	100	100	100	48.9	49.2	44.7	44.9	41.8	41.8	49.8	49.8	100	100
eGFR (mL/min/1.73 m^2); mean ± SD or median (IQR)	56.3 ± 18.2	56.0 ± 18.3	44.4 (37.0–51.3)	44.7 (37.0–51.5)	60.6 ± 19.8	60.6 ± 9.9	61 ± 19	61 ± 19	66.0 ± 19.6	65.5 ± 19.3	61.8 ± 21.7	62.2 ± 21.5	49.2 (39.5–61.2)	50.5 (40.5–64.6)
First HHF/CVD, events, *n*	179	253	400	530	415	511	512	610	386	502	361	462	245	355
Event rate first HHF/CVD (per 1000 PY)	31.5	45.4	56	75	69	87	78	96	116	156	158	210	510	763
Outcome first CVD/HHF, HR (95% CI)	0.69 (0.57–0.83)		0.74 (0.63–0.88)		0.79 (0.69–0.90)		0.82 (0.73–0.92)		0.74 (0.65–0.85)		0.75 (0.65–0.86)		0.67 (0.52–0.85)	
HHF, HR (95% CI)	0.61 (0.47–0.80)		0.67 (0.55–0.82)		0.71 (0.60–0.83)		0.79 (0.69–0.91)		0.70 (0.59–0.83)		0.69 (0.59–0.81)		0.64 (0.49–0.83)	
CVD, HR (95% CI)	0.78 (0.61–1.00)		0.90 (0.73–1.12)		0.91 (0.76–1.09)		0.88 (0.74–1.05)		0.82 (0.69–0.98)		0.92 (0.75–1.12)		0.84 (0.58–1.22)	

ASCVD, atherosclerotic cardiovascular disease; Cana, canagliflozin; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; Ertu, ertugliflozin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; IQR, interquartile range; N/A, not applicable; LVEF, left ventricular ejection fraction; Pla, placebo; PY, patient-years; SD, standard deviation; Sota, sotagliflozin; T2DM, type 2 diabetes mellitus.

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5. Arrhythmias: atrial fibrillation, ventricular arrhythmias, sudden cardiac death, and diabetes

Table S16 Presumed benefits and potential risks of atrial fibrillation screening

Presumed benefits	Potential risks
• Preventing thrombo-embolic events and stroke by OAC treatment • Preventing subsequent onset of symptoms • Preventing and/or reversing electrical/mechanical atrial remodelling • Preventing and/or reversing tachycardiomyopathy and/or haemodynamic derangements • Preventing AF-related morbidity and reducing AF-related hospitalizations and mortality	• Abnormal results may cause anxiety • Misinterpreting ECG results may lead to over-diagnosis and over-treatment • ECG may detect abnormalities (either true- or false-positive results) that may lead to invasive testing and treatments that have the potential for harm (e.g. angiography and revascularization associated with bleeding, contrast-induced nephropathy, and allergic reactions to contrast)

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AF, atrial fibrillation; ECG, electrocardiogram; OAC, oral anticoagulant.

6. Aortic and peripheral arterial diseases and diabetes

Table S17 Assessing the risk of amputation: the Wound, Ischaemia, foot Infection classification

	Wound	Ischaemia			Foot Infection
Score		**ABI**	**Ankle pressure (mmHg)**	**Toe pressure or $TcPO_2$ (mmHg)**	
0	No ulcer (ischaemic rest pain)	≥0.80	>100	≥60	No symptoms/signs of infection
1	Small, shallow ulcer (distal leg or foot); no gangrene	0.60–0.79	70–100	40–59	Local infection involving only skin and subcutaneous tissue
2	Deep ulcer (exposed bone, joint, or tendon) ± gangrenous changes limited to toes	0.40–0.59	50–70	30–39	Local infection involving deeper than skin/subcutaneous tissue
3	Extensive deep ulcer, full-thickness heel ulcer ± extensive gangrene	<0.40	<50	<30	Systemic inflammatory response syndrome

One-year amputation risk

	Ischaemia–0				Ischaemia–1				Ischaemia–2				Ischaemia–3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

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ABI, ankle–brachial index; fI, foot Infection; H, high risk; L, low risk; M, moderate risk; $TcPO_2$, transcutaneous oxygen pressure; VL, very low risk; W, wound.
Wound, Ischaemia, Foot and Infection defined from 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery.[129]
Table adapted from Cosentino *et al.* 2020.[130]

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