Supplementary materials

Table 1. Brief summary of all studies performed on sST2 in relation to CVD.

References	Study features	Results
Aleksova A, Paldino A, Beltrami AP, Padoan L, Iacoviello M, Sinagra G, Emdin M, Maisel AS. J Clin Med 2019;8:270. [22]	sST2 levels and patient outcomes: cardiac emergency	SST2, with NPs, troponins, and clinical variables, enhances ED patient risk assessment.
Kim H-L, Lee JP, Wong N, Lim WH, Seo JB, Zo JH, Kim MA, Kim SH. Scientific Reports 2021;11:15203 [42]	388 patients, coronary angiography for suspect CAD	Elevated baseline sST2 linked to higher risk and independent predictor of MACE in stable CAD patients.
Sun Y, Pavey H, Wilkinson I, Fisk M. PLoS ONE 2021;16:e0259026. [25]	77 studies included for meta-analysis and systematic review: 62075 participants with CVD	Soluble ST2 shows a stronger association with all-cause mortality risk in ACS than in HF.
Rezar R, Paar V, Seelmaier C, Pretsch I, Schwaiger P, Kopp K, Kaufmann R, Felder TK, Prinz E, Gemes G, Pistulli R, Hoppe UC, Wernly B, Lichtenauer M. Sci Rep 2021;11:21756 [33]	106 patients after cardiopulmonary resuscitation	Elevated sST2 is associated with increased risk for combined endpoint at 6 months.
Ip C, Luk KS , Yuen VLC, Chiang L, Chan CK, Ho K, Gong M, Lee TTL, Leung KSK, Roever L, Bazoukis G, Lampropoulos K, Li KHC, Tse G, Liu T. IJC Heart & Vasculature 2021;37:100887 [29]	14 studies were included in the meta-analysis: 1050 patients with AHF, 7126 patients with CHF,	SST2 levels in acute heart failure tended to indicate higher mortality risk. In chronic heart failure, higher SST2 levels in non-survivors were associated with increased mortality risk. Stable coronary artery disease exhibited higher SST2 levels in non-survivors, significantly correlating with elevated mortality risk.

References	Study features	Results
	2799 patients with CAD	
Luo G, Qian Y, Sheng X, Sun J, Wu Z, Liao F, Feng Q, Yin Y, Ding S, Pu J. Front Cardiovasc Med 2021;8:688522. [39]	120 patients with non-ST-elevation ACS: 167 lesions	SST2 levels correlate with coronary plaque components in non-ST-elevation ACS patients.
Van den Berg VJ, Vroegindewey MM, Umans VA, Van der Harst P, Asselbergs FW, Akkerhuis KM, Kardys I, Boersma E. Biomarkers 2022;27:264-9.[40]	A multicentre: 18 hospitals in the Netherlands-prospective study.	Asymptomatic post-ACS patients with persistently higher sST2 levels are at increased risk of recurrent ACS or cardiac death.
Liu R, Liu L, Wei C, Li D. Front Cardiovasc Med 2022;9:990007. [23]	Review and meta-analysis: seven case-control studies met included a total of 10686 cases and 10775 healthy subjects	IL-33/ST2 axis links to CAD risk.
Liu L, Li S, Ding X, Wang D, Li W, Li H. Pol Arch Intern Med 2022;132:16317. [24]	A prospective cohort study: a total of 350 patients with ST-segment elevation myocardial infarction	Elevated plasma sST2 post pPCI predicts 1-year MACEs. The change in the sST2 level from admission to 24 hours post pPCI (Δ1 sST2) was significantly higher in the MACE group. After multivariable adjustment, Δ1 sST2 was an independent risk factor for MACEs, with an area under the curve of 0.621 (95% CI, 0.547–0.695). Patients with a greater Δ1 sST2 had a

References	Study features	Results
		significantly higher incidence of composite MACEs, coronary revascularization, and cardiac rehospitalization.
Zhang J, Chen Z, Ma M, He Y. Front. Cardiovasc Med 2022;9:924461. [30]	Review	sST2 utility in coronary artery disease: gauging plaque burden, predicting noreflow events, prognostic indication, reflecting left ventricular remodeling, and guiding myocardial infarction patient management.
Berezin AE, Berezin AA. Ann Lab Med 2023;43:225-36. [36]	Narrative review	sST2 offers high precision, repeatability and cost-effectiveness in clinical practice.
Chen D, Untaru R, Stavropoulou G, Assadi-Khansari B, Kelly C, Croft AJ, Sugito S, Collins NJ, Sverdlov AL, Ngo DTM. J Clin Med 2023;12:2790. [43]	Longitudinal cohort study: 250 patients, confirmed cardiovascular diagnosis	sST2 levels robustly predict hospital readmission for MACE within 1 year. High sST2 levels and diabetes remained as risk predictors of any MACE occurrence; an sST2 level in the highest quartile (Q4: >28.4 ng/mL) was independently associated with older age, use of beta-blockers, and number of MACE events within a 1 year period.
Clemente G, Soldano JS, Tuttolomondo A. Rev. Cardiovasc Med 2023;24:310.[31]	Review	These biomarkers could offer valuable insights into the clinical risk of heart failure patients.
Katsioupa M, Kourampi I , Oikonomou E, Tsigkou V, Theofilis P, Charalambous G, Marinos G, Gialamas I, Zisimos K, Anastasiou A, Katsianos E, Kalogeras K,	Review	Research delves into various biomarkers highlights the need for ongoing research in establishing biomarkers with enhanced prognostic or diagnostic value in ACS settings.

References	Study features	Results
Katsarou O, Vavuranakis M, Siasos G, Tousoulis D. Life 2023;13:1992. [63]		

NPs, Natriuretic Peptides; ED, Emergency Department; MACE, Major Adverse Cardiovascular Events; CAD, Coronary Artery Disease; T2DM, Type 2 Diabetes Mellitus; CVD, Cardiovascular Disease; IL-33, Interleukin-33; SNPs, Single Nucleotide Polymorphisms; IL1RL1, Interleukin 1 Receptor-Like 1; IL1RAcP, Interleukin 1 Receptor Accessory Protein; pPCI, Primary Percutaneous Coronary Intervention; HF, Heart Failure; ACS, Acute Coronary Syndrome; IHD, Ischemic Heart Disease; CK-MB, Creatine Kinase-MB; BMI, Body Mass Index; MI, Myocardial Infarction; CHF, Congestive Heart Failure; LVEF, Left Ventricular Ejection Fraction.

Table 2. Brief summary of all studies performed on suPAR in relation to CVD.

References	Study features	Results
Sörensen NA, Nikorowitsch J, Neumann JT, Rübsamen N, Goßling A, Hartikainen TS, Blankenberg S, Westermann D, Zeller T, Karakas M. Clin Res Cardiol 2019;108:1386–93. [51]	suPAR in 1314 suspected AMI in ED.	suPAR levels reliably predicted mortality in patients with suspected AMI.
Al-Badri A, Tahhan AS, Sabbak N, Alkhoder A, Liu C, Ko YA, Vaccarino V, Martini A, Sidoti A, Goodwin C, Ghazzal B, Beshiri A, Murtagh G, Mehta PK, Quyyumi AA. J Am Heart Assoc 2020;9:e015515. [56]	suPAR, hsTnI, in 556 patients, no CAD.	Higher levels of suPAR and hsTnI were independently and additively associated with an increased risk of adverse events.

References	Study features	Results
Hodges G, Lyngbæk S, Selmer C, Ahlehoff O, Theilade S, Sehestedt TB, Abildgaard U, Eugen-Olsen J, Galløe AM, Hansen PR, Jeppesen JL, Bang CN. Scandinavian Cardiovascular J 2020;54:339–45. [58]	Plasma suPAR, 1635 patients, 73% with CAD, underwent angiography.	suPAR independently predicts death/myocardial infarction in coronary artery disease patients.
Chenevier-Gobeaux C, Lemarechal H, Doumenc B, Peschanski N, Claessens YE, Borderie D, Ray P. Clin Biochem 2021;92:19–24. [52]	Plasma suPAR in 198 patients (median age 56 years), chest pain < 6h, 30-day outcome.	suPAR is a promising biomarker for early prediction of events in chest pain emergency patients.
Huet F, Dupuy AM, Duflos C, Reis CA, Kuster N, Aguilhon S, Cristol JP, Roubille F. Future Sci. OA 2021;FSO697. [34]	95 patients were included	The suPAR level of expression was significantly higher in the group of patients who died at one month (7.90 ± 4.35 ng/ml vs 11.94 ± 6.86 ng/ml; $p < 0.05$) or 1 year (7.28 ± 4.27 ng/ml vs 11.81 ± 4.88 ng/ml; $p < 0.01$), but there was no significant difference according to the readmission.
Velissaris D, Zareifopoulos N, Koniari I, Karamouzos V, Bousis D, Gerakaris A, Platanaki C, Kounis N. J Clin Med Res 2021;13:133-42. [54]	Review: 39 studies	suPAR shows potential in assessing acute coronary syndromes, heart failure, and aortic valve disease. Elevated levels correlate with adverse outcomes.
Santeri S, Andersen AP, Nyyssönen K, Eugen-Olsen J, Hyppölä H. BMC Emerg Med 2021;21:149. [53]	1747 acute medical patients in the ED	suPAR levels below 4 ng/ml indicate low risk (99.0% negative predictive value, 94.6% sensitivity), 4-6 ng/ml suggest medium risk (8.4% mortality), and above 6 ng/ml indicate high risk (20.3% mortality, 20.1% positive predictive value, 78.7% specificity) for 30- and 90-day mortality in acute medical patients.

References	Study features	Results
Bengaard AK, Iversen E, Kallemose T, Juul-Larsen HG, Rasmussen LJH, Dalhoff KP, Andersen O, Eugen-Olsen J, Houlind MB. Br J Clin Pharmacol 2022;88:1679–90. [55]	26,291 patients divided into suPAR groups: low (0–3 ng/mL), intermediate (3–6 ng/mL), high (>6 ng/mL). Hyper-polytherapy ≥10 drugs prescribed	Patients with high suPAR or ≥10 drugs show significantly increased risk of 90-day readmission and mortality. Among patients with low suPAR, patients with ≥10 prescribed medications had a hazard ratio of 2.41 (95% confidence interval = 2.09–2.78) for 90-day readmission and 8.46 (95% confidence inter- val = 2.53–28.28) for 90-day mortality compared to patients with 0 medications.
Holstein RM, Seppälä S, Kaartinen J, Hongisto M, Hyppölä H, Castrén M J Clin Med 2022;11:3283. [6]	1858 patients. A prospective cohort study in two Finnish hospital regions: Helsinki and Mikkeli.	High suPAR levels correlate with increased mortality and reduced ED discharge likelihood, predicting 30-day mortality across all ages. The outcomes were assessed in the group of <75 years (=younger) and ≥75 years (=elderly). The elderly had higher median suPAR levels than the younger (5.4 ng/mL vs. 3.7 ng/mL, $p < 0.001$). Increasing suPAR levels were associated with higher probability for 30-day mortality and hospital admission in all age groups.
Velissaris D, Zareifopoulos N, Karamouzos V, Pierrakos C, Karanikolas M. Caspian J Internal Med 2022;13:650-65. [48]	Review	suPAR may be a promising addition to the established biomarkers for the initial assessment of patients in EDs.
Goodchild TT, Li Z, Lefer DJ. J Clin Invest 2022;132:e165868. [46]	Commentary	The causal relationship between suPAR and coronary artery calcification and the data for cumulative incidence of CVD events.
Holstein RM, Mäkinen MT, Castrén	A comparative	Integration of suPAR measurement into

References	Study features	Results
MK, Kaartinen JM. Biomarker Insights 2022;17:1–7. [5]	cross-sectional study in Emergency Medicine and Services Unit of Helsinki University Hospital	routine blood draws and decision making had no impact on emergency department discharge or emergency department/hospital length of stay.
Hindy G, Tyrrell DJ, Vasbinder A, Wei C, Presswalla F, Wang H, Blakely P, Ozel AB, Graham S, Holton GH, Dowsett J, Fahed AC, Amadi KM, Erne GK, Tekmulla A, Ismail A, Launius C, Sotoodehnia N, Pankow JS, Thørner LW, Erikstrup C, Pedersen OB, Banasik K, Brunak S, Ullum H, Eugen-Olsen J, Ostrowski SR,Haas ME, Nielsen JB, Lotta LA,; Engström G, Melander O, Orho-Melander M, Zhao L, Murthy VL, Pinsky DJ, Willer CJ,Heckbert SR, Reiser J, Goldstein DR, Desch KC, Hayek SS. J Clin Invest 2022;132:e158788. [50]	A multicenter observational cohort study: genome-wide association study (GWAS) meta-analysis for suPAR levels in over 24,000 individuals	suPAR levels predict coronary artery calcification and cardiovascular events in 5,406 participants.
Li Y, Ding Y, Zhao Y, Gui Y, Shen Y, Xiang Q. Eur J Clin Invest 2022;52:e13867. [4]	Meta-analysis: 9 studies included	Patients with CAD that exhibited increased suPAR levels had a substantially higher risk of all-cause mortality (HR = 2.24; 95% CI 1.97–2.55) or cardiovascular mortality (HR = 2.02; 95% CI 1.58–2.58), but not of developing other major cardiovascular events (HR = 1.63; 95% CI 0.86–3.11).

References	Study features	Results
Pruc M, Jannasz I, Swieczkowski D, Procyk G, Gasecka A, Rafique Z, Chirico F, Bragazzi NL, Jaguszewski MJ, Wysocki J, Szarpak L. Cardiol J 2023;30:335–36. [47]	5 studies: 1148 patients with ACS and 2269 in the control group.	All 5 studies indicated suPAR differences between ACS and non-ACS (control) patients. Mean suPAR level in ACS: 3.56 ± 1.38 ng/mL, compared to 2.78 ± 0.54 ng/ml in the control group.
Rehan ST, Hussain HU, Ali E, Kumar KA, Tabassum S, Hasanain M, Shaikh A, Ali G, Yousaf Z, Asghar MS. Medicine 2023;102:e35718. [3]	13 studies: 35,178 participants (6004 with high suPAR concentration and 18,582 with low suPAR concentration).	High suPAR linked to increased risk in 30-day and 90-day mortality, 30-day readmission, and hospital stay length. Lower rates of discharge within 24 hours.
Wohlwend NF, Grossmann K, Aeschbacher S, Weideli OC, Telser J, Risch M, Conen D, Risch L. Diagnostics 2023;13:2938. [49]	GAPP study: 1951 participants	Higher suPAR levels in females than males with sex-specific differences in cardiovascular risk factors. In both genders, suPAR inversely correlated with HDL levels, higher in smokers than non-smokers, and positively correlated with cholesterol levels in females. Healthy lifestyle and Framingham scores correlated with suPAR in males, not in females.

suPAR, Soluble Urokinase Plasminogen Activator Receptor; AMI, Acute Myocardial Infarction; HSTNL, High-Sensitivity Troponin; GWAS, Genome-Wide Association Study; PLAUR, Plasminogen Activator, Urokinase Receptor; CAD, Coronary Artery Disease; STADE-HF, Seattle Heart Failure Model; CHD, Coronary Heart Disease; ACS, Acute Coronary Syndrome; HDL, High-Density Lipoprotein.