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The Heart of the Matter

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CONTENTS

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EDITORIAL

Optimizing individual heart failure treatment

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A mineralocorticoid receptor antagonist (MRA) is recommended in patients with chronic heart failure.[1–5] However, the effects of the early initiation of an MRA in patients with acute heart failure (AHF) is less documented. Kitakaze and co-workers from Japan have performed a multicentre, randomized, double-blind, placebo-controlled, parallel-group study in 300 patients with AHF. The patients were randomized to eplerenone or placebo. The primary outcome was a composite of cardiac death or first rehospitalization due to cardiovascular disease within 6 months. No significant difference in primary outcome was found. The authors concluded that early initiation of eplerenone in patients with AHF could safely be utilized.

The PARADIGM-HF study[6] did not analyse the effect of ventricular remodelling on patients with different aetiologies, which may affect clinical treatment outcomes. In a paper from Taiwan, Chang and co-workers aimed to compare left ventricular ejection fraction (LVEF) following sacubitril/valsartan (SAC/VAL) treatment and its association with clinical outcomes in 1576 patients. The authors found that patients with non-ischaemic cardiomyopathy (NICM) had a higher degree of LVEF improvement than those with ischaemic cardiomyopathy (ICM) following SAC/VAL treatment, and significant improvement of LVEF in NICM patients.

Anticancer drugs may be associated with different kinds of heart problems.[7–9] The anti-HER2 agent trastuzumab reduces risk of disease progression or death in breast cancer patients.[9] However, HER2 isoforms are also expressed in cardiomyocytes and may cause increased risk of left ventricular (LV) dysfunction and a five- to sevenfold increased risk of heart failure.[9] Paterson and co-workers from Canada aimed to characterize the cardiac and cardiometabolic phenotype of trastuzumab-mediated toxicity and potential interactions with cardiac pharmacotherapy. The study was an analysis of serial magnetic resonance imaging (MRI) and circulating biomarker data acquired from patients with HER2-positive early stage breast cancer participating in a randomized controlled clinical trial for the pharmacoprevention of trastuzumab-associated cardiotoxicity. The authors report that trastuzumab results in impaired cardiac function and early myocardial inflammation. Trastuzumab was also associated with deleterious changes to the cardiometabolic phenotype, which may contribute to the increased cardiovascular risk in this population.

The beneficial effect of β-blocker on heart failure with reduced ejection fraction (HFrEF) is well established.[1,10] However, its effect on the short-term outcome of heart failure with midrange ejection fraction (HFmrEF) is less clear. Zheng *et al.* from China have analysed the data of 1036 patients with LVEF between 40% and 49% in China The Patient-centred Evaluative Assessment of Cardiac Events Prospective Heart Failure (China, PEACE 5p-HF) study. Two primary outcomes were all-cause death and all-cause hospitalization. The authors concluded that in patients with HFmrEF, β-blocker use was associated with lower risk of all-cause death, but not with lower risk of all-cause hospitalization.

Uncontrolled blood pressure (BP) increases the risk of developing HF.[1] The effect of spironolactone on the BP of patients at risk of developing HF is yet to be determined. Ferreira and co-workers aimed to evaluate the effect of spironolactone on the BP of patients at risk for HF and whether renin can predict spironolactone's effect in a prospective multicentre randomized open-label blinded endpoint (PROBE) trial including 527 patients at risk for developing HF randomly assigned to either spironolactone (25–50 mg/day) or usual care alone for a maximum of 9 months. The authors report that a higher proportion of patients on spironolactone had controlled BP in the spironolactone group and lower baseline renin levels predicted a greater response to spironolactone. The conclusion of the study was that spironolactone should be considered for lowering blood pressure in patients who are at risk of developing HF.

The pandemic caused by the SARS-CoV-2 virus has spread worldwide and many questions about the pathophysiology of the SARS-CoV-2 infection are unanswered. In a study from Spain, Masana and co-workers aimed at assessing the effect of statin therapy at hospital admission for COVID-19 on inhospital mortality. In a retrospective observational study, they report a significantly lower mortality rate in patients on statin therapy than the matched non-statin group and the mortality rate was even lower in patients who maintained their statin treatments during hospitalization compared with the non-statin group. Also, the Cox model suggested that statins were associated with reduced COVID-19-related mortality. The authors

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concluded that a lower SARS-CoV-2 infection-related mortality was observed in patients treated with statin therapy prior to hospitalization. Statin therapy should not be discontinued due to the global concern of the pandemic or in patients hospitalized for COVID-19. Several other observational studies have shown potential beneficial effects of lipid-lowering treatment on the course of COVID-19 with significantly improved prognosis and reduced mortality.[11–13] Findings from ongoing rigorously conducted and adequately powered randomized clinical trials (RCTs) can assess the possible efficacy of lipid-modulating agents in the prevention or treatment of various stages of COVID-19 and may open new horizons for research and clinical practice.[14]

Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEis/ARBs) is thought to affect COVID-19 through modulating levels of angiotensin-converting enzyme 2, the cell entry receptor for SARS-CoV2.[15,16] There are many observational studies on this topic.[17,18] In a meta-analysis, McMurray and co-workers included non-randomized observational COViD-19 studies, comparing ACE inhibitor/ARB treatment. Eighty six studies, including 459 755 patients (103 317 with hypertension), were analysed. In patients with hypertension, ACE inhibitor or ARB treatment was not associated with a greater likelihood of SARS-CoV-2 infection in 60 141 patients, hospitalization or case fatality in 18 735 patients with 2893 deaths. In all patients (irrespective of hypertension), findings were consistent for likelihood of SARS-CoV-2 infection in 363 865 patients. The authors concluded that ACE inhibitors and ARBs appear safe in the context of SARS-CoV-2 infection and should not be discontinued.

The rising prevalence of obesity and its associated comorbidities represents a growing public health issue, as a risk factor for both cardiovascular disease[19,20] and COVID-19. Many randomized controlled trials have demonstrated the clinical utility of orlistat in achieving weight loss when compared with lifestyle measures alone.[21–23] Collins and co-workers aimed to explore long-term cardiovascular outcomes after orlistat therapy in a propensity score matched cohort study of healthcare records of the Clinical Practice Research Datalink. The 36 876 patients with obesity who had completed a course of orlistat were matched with controls who had not taken orlistat. The authors concluded that orlistat was associated with lower rates of overall major adverse cardiovascular events, new onset heart failure, renal failure, and mortality during the median study follow-up of 6 years.

Heart failure patients are usually at high risk of polypharmacy and, consequently, potentially inappropriate prescribing leading to poor clinical outcomes.[24–26] We are pleased to publish a position statement from Coats and co-workers entitled 'Position statement on HFrEF specific inappropriate prescribing'.

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ORIGINAL ARTICLE

ESC/EAS guidelines for the detection, prevention, and treatment of individuals at risk of a first myocardial infarction: effect of 5 years of updates and the new SCORE2

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Aims The European Society of Cardiology (ESC) has released three consecutive guidelines within 5 years addressing cardiovascular prevention, risk scores, and cholesterol treatment. This study aims to evaluate whether the 2021 ESC guidelines improved the eligibility of individuals for primary prevention statin therapy before their first ST-segment elevation myocardial infarction (STEMI), and for intensive lipid-lowering treatments in secondary prevention.

Methods and results The cardiovascular risk category of 2757 consecutive individuals admitted for a first STEMI was evaluated to assess whether they would have been eligible for primary prevention statins according to 2021 vs. 2019 and 2016 ESC guidelines. Eligibility for intensive lipid-lowering therapy in secondary prevention was assessed according to the real-life follow-up low-density lipoprotein cholesterol (LDL-C) and the expected follow-up LDL-C. More individuals would have been eligible for primary prevention statins according to 2021 and 2019 vs. 2016 guidelines (61.8% vs. 38.7% vs. 23.6%, $P < 0.01$), a finding observed in both men (62.3% vs. 35.0% vs. 24.9%, $P < 0.01$) and women (60.2% vs. 50.7% vs. 19.3%, $P = 0.18$). Only 27% of individuals reached the LDL-C objective of 55 mg/L in secondary prevention: using the ESC stepwise approach, 61.7% were eligible for higher doses of statins, 26.2% for ezetimibe, and 12.1% for a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (PCSK9i). Based on expected LDL-C reductions, eligibility for a PCSK9i in secondary prevention was greater with 2021 vs. 2016 guidelines (44.5% vs. 22.5%, $P < 0.01$).

Conclusion The 2021 ESC guidelines improved the detection and treatment of individuals at risk for a first myocardial infarction. In secondary prevention, 70% of patients kept LDL-C levels above 55 mg/dL: increasing the statin dose and adding ezetimibe were the most frequently recommended therapeutic actions.

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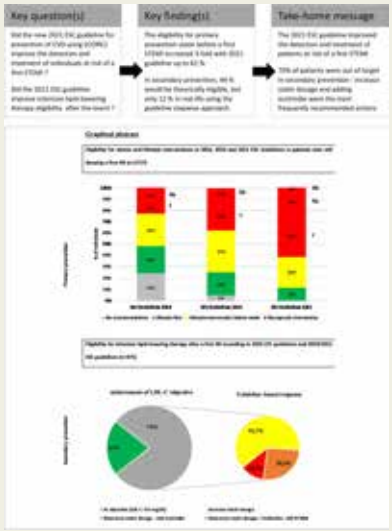
Graphical Abstract



Keywords Cardiovascular risk • Dyslipidaemia • Statin • PCSK9 inhibitor

Introduction

Despite the major advancements in the detection and treatment of cardiovascular risk, cardiovascular disease (CVD) is still the main cause of mortality in Europe with 4 million deaths per year, including 2.2 million deaths of women.[1,2] From 2016 to 2021, the European Society of Cardiology (ESC) provided three consecutive guidelines aiming to prevent cardiovascular disease.[3–5] In 2019, the *ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk* updated the recommendations on the detection and treatment of individuals at risk in primary and secondary prevention with the following major changes: first, the task force implemented risk modifiers to target specific populations at risk, especially sex-related risk factors, in the algorithms; secondly, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) are recommended with a class I for very high risk patients before any symptomatic cardiovascular disease; thirdly, in secondary prevention, PCSK9is are recommended on top of statins and ezetimibe in case of a persistently elevated low-density lipoprotein cholesterol (LDL-C) above 55 mg/dL (1.4 mmol/L). In 2021, the *ESC Guidelines on Cardiovascular Disease (CVD) Prevention in Clinical Practice* (2021 ESC guidelines) implemented the use of Systematic Coronary Risk Estimation 2 (SCORE2) and Systematic Coronary Risk Estimation 2—Older Persons (SCORE2-OP) in place of the Systematic Coronary Risk Estimation (SCORE), which was reported to underestimate the CVD burden because of including only fatal events.[6–8] Population-based studies have demonstrated the limitations of previous ESC guidelines to detect and recommend primary prevention statins in patients at risk of cardiovascular disease. Furthermore, while theoretical estimations of ezetimibe and PCSK9i eligibility in secondary prevention have been based on LDL-C expected reductions, the real-life effect of the stepwise approach in patients after a first ST-segment elevation myocardial infarction (STEMI) is unknown.

Thus, using baseline characteristics of patients admitted for a first STEMI, our primary objective was to assess whether they would have been eligible for primary prevention statins based on 2021, 2019, and 2016 ESC guidelines if they had been seen before this first event. Our second objective was to evaluate the guideline-recommended response for intensive lipid-lowering therapies in secondary prevention overall and according to sex.

Methods

Study design and population

The e-PARIS registry is a prospective registry of all consecutive individuals admitted for an STEMI at the University Hospital of Pitié-Salpêtrière, Paris, France. The design of the e-PARIS registry has been well described before.[9,10] In brief, it includes a pre-specified data set of clinical and biological characteristics, cardiovascular risk factors, angiographic characteristics, and follow-up for major non-fatal cardiovascular events and vital status. For the present study, we included individuals of the e-PARIS registry admitted for a first STEMI between January 2000 and October 2018, free of prior cardiovascular disease, with available cholesterol samples at admission. STEMI was defined as the presence of clinical myocardial ischaemia, associated with new or presumed new ST-segment elevation of 1 mm or more in two or more contiguous leads, bundle-branch block, or true posterior myocardial infarction (MI). The final diagnosis of STEMI was confirmed by the presence of an acute coronary artery occlusion during the coronary angiography. The registry was approved by the local ethical committee of the University Hospital Pitié-Salpêtrière of Paris.

Cardiovascular risk assessment prior to first ST-segment elevation myocardial infarction

Cardiovascular risk prior to first STEMI was estimated using the data collected at admission. The ESC/ European Atherosclerosis Society (EAS)

guidelines classify individuals as 'very high risk', 'high risk', 'moderate risk', and 'low risk', with each category related to goals of LDL-C levels to determine eligibility for primary prevention statins. Following 2019 and 2021 ESC/EAS algorithms (Supplementary material online, *Tables S1 and S2*), individuals were classified based on (1) prior high-risk comorbidities such as diabetes with or without target organ damage, severe or moderate chronic kidney disease, familial hypercholesterolaemia, and severe arterial hypertension; (2) the SCORE (2016 and 2019 ESC guidelines) and SCORE2 (2021 ESC guidelines) charts for low-risk countries for 'apparently healthy individuals' (without previous high-risk comorbidities); and (3) their baseline LDL-C at admission. This risk estimation allowed assessing the number of individuals who would have been recommended for preventive statin treatment before their first STEMI.

Interpretation of 2019 and 2021 ESC guidelines for primary prevention

The updates that occurred from the 2016 to 2019/2021 ESC guidelines are reported in the Supplementary material online, *Table S3*. In brief, the 2019 ESC/EAS guidelines provided several updates compared with the 2016 ESC/EAS guidelines: first, the SCORE model included patients up to 70 years of age, compared with 65 years in prior guidelines; secondly, individuals aged 70 or more were considered eligible for statins (class IIb), while there was no prior recommendation for this age category before; more importantly, low-risk and moderate-risk individuals became eligible for direct intervention with statins in case of LDL-C above the level of 190 mg/dL. The recommendation for primary prevention using statins was updated from class IIa to I for all the high-risk individuals with a baseline LDL-C above 100 mg/dL. PCSK9i therapy was recommended for individuals at very high risk and uncontrolled LDL-C under maximal tolerated dose of statins and ezetimibe, either in a primary prevention setting (class IIb) or in secondary prevention (class I).

In the 2021 ESC guidelines, SCORE was replaced by SCORE2/2OP to stratify the risk of individuals without diabetes and without prior cardiovascular disease. The newness of SCORE2/2OP is that it included individuals from 40 to 89 years old, provides a different risk stratification giving more importance for risk factors other than for age or sex, and evaluates the risk of both non-fatal and fatal events at 10 years. The age extension allows a better risk screening, especially in female individuals who present their coronary events later than male ones.[11] The model was validated using a global population of 12.5 million individuals. Patients already treated with statins at admission were considered as eligible for both guidelines.

Eligibility for intensive lipid-lowering therapy after a first ST-segment elevation myocardial infarction

In secondary prevention, real-life follow-up LDL-C and guideline-based response were also evaluated among a subset of patients with intrahospital follow-up by using consultation reports and hospitalizations records. Medical data were checked for LDL-C levels until a censoring point of death occurrence or the date of 1 January 2021. Persistent active smoking, hypertension (>140/90 mmHg), diabetes control (Hb1ac > 6.5%), and lipid-lowering therapies prescribed were also obtained. Eligibility was assessed using the collected data and each patient's specific follow-up.

In a secondary analysis, the individual LDL-C level expected during follow-up was calculated based on baseline LDL-C, following the ESC guidelines: 50% of baseline LDL-C reduction in individuals discharged with high-intensity statins, 65% of baseline LDL-C reduction in individuals discharged with high-intensity statins plus ezetimibe, and 85% reduction of baseline LDL-C with high-intensity statins with ezetimibe plus PCSK9i. Thus, using the expected LDL-C follow-up and considering a maximal dosage of statin at discharge with full adherence, we also tried to assess the theoretical eligibility for either ezetimibe or PCSK9i.

Similarly, major adverse cardiovascular events (MACEs) defined by death, recurrence of acute coronary syndrome (ACS), or stroke were collected.

Endpoints

The first objective was to compare the 2016, 2019, and 2021 ESC/EAS guidelines' efficiency to detect and treat patients who will develop a first STEMI, and then in men vs. women. Thus, eligibility for statins prior to a first STEMI was defined as a class I, IIa, or IIb recommendation. Secondly, we compared the proportion of men and women with hospital follow-up eligible for an intensive lipid-lowering therapy with PCSK9i and ezetimibe, based on real-life LDL-C. A similar analysis was performed according to expected reductions of LDL-C as described in ESC/EAS guidelines.

Statistical analysis

Continuous variables are presented as median and interquartile ranges and compared across sex categories using *P*-values for trends: Cochrane–Armitage Trend test for binary variables, Cochran–Mantel–Haenszel test for categorical variables, and Spearman correlation test for continuous variables. Descriptive summaries of the cohort and risk factors are based on available data with missing values excluded from calculations. The performance of the 2016 and 2021/2019 ESC/EAS guidelines were compared using a Welch/Student's *t*-test or the Mann–Whitney U test, as appropriate. No adjustment was made for multiple comparisons. A two-sided *P*-value <0.05 was considered significant. Statistical analysis was performed using GraphPad Prism version 6.04 for Windows, GraphPad Software, La Jolla, CA, USA.

Results

Baseline characteristics

Between February 2000 and October 2018, 2757 patients were admitted for a first STEMI, including 648 women (23.5%). Baseline characteristics are displayed in *Table 1*. Risk modifiers were more frequent in women than men, especially chronic inflammatory diseases. The median LDL-C level at admission for acute MI was 115 mg/dL (2.9 mmol/L) in women [interquartile range (IQR) 92–151] and 121 mg/dL (3.1 mmol/L) in men (IQR 92–151) ($P = 0.52$).

According to 2019 ESC guidelines, 17.2% of individuals with a first STEMI would have been considered at very high risk for a MACE (*Table 2*). Following the updates provided by the 2021 ESC/EAS guidelines, using SCORE2, 40.9% of individuals were considered at very high risk for a first major cardiovascular (*Table 2*). The SCORE and SCORE2 of individuals aged at least 40 years old without diabetes or chronic kidney disease are displayed in the Supplementary material online, *Table S4*.

At discharge, the maximal dosage of statin was administered to 72.4% of patients, with women being less likely to be discharged on the maximal dose of statin (69.8% vs. 73.1%, $P < 0.001$). Atorvastatine was the most prescribed drug.

Table I Baseline characteristics according to sex

	Overall, $n = 2757$	Men, $n = 2109$	Women, $n = 648$	*P*-value
Age	56.8 (45.8–68.94)	54.5 (44.9–64.7)	67.3 (54.1–81.1)	<0.001
BMI	20.6 (16.9–25.4)	25.5 (23.7–28.4)	24.4 (21.7–27.7)	<0.001
Obese (BMI >30 kg/m^2)	346/2443 (14.1%)	255/1877 (13.6%)	90/566 (15.9%)	
Smoking status				
Never	947 (34.4%)	581 (27.6%)	366 (56.5%)	<0.001
Active	1395 (50.6%)	1192 (56.5%)	203 (31.2%)	—
Prior	415 (15.0%)	336 (15.9%)	79 (12.1%)	—
Familial history of CAD	735 (26.6%)	565 (27.8%)	170 (26.2%)	0.78
Hypertension	1066 (38.7%)	720 (34.1%)	346 (53.4%)	<0.001
Diabetes	518 (18.8%)	390 (18.5%)	128 (19.7%)	0.47
GFR < 30 mL/min/1.73 m^2	79 (2.9%)	32 (1.5%)	47 (7.2%)	<0.001
GFR median (mL/min/1.73 m^2)	95.3 (67.11–122.1)	102 (78.5–126.3)	67 (45.6–94.14)	<0.001
Risk modifiers				
At least one risk modifier	859/2567 (33.4%)	656/2031 (32.3%)	203/536 (37.9%)	0.015
Atrial fibrillation	104 (4.0%)	73 (3.6%)	31 (5.8%)	0.022
Chronic immune-mediated inflammatory disorder	67 (2.6%)	45 (2.2%)	22 (4.1%)	0.015
CKD	145 (5.6%)	108 (5.3%)	37 (6.9%)	0.16
HIV	50 (1.9%)	46 (2.3%)	4 (0.7%)	0.024
LV hypertrophy	213 (8.3%)	167 (8.2%)	47 (8.7%)	0.69
NASH	14 (0.5%)	11 (0.5%)	3 (0.5%)	1
Obstructive sleep syndrome	49 (1.9%)	44 (2.2%)	5 (0.8%)	0.063
Physical inactivity	165 (6.4%)	127 (6.3%)	38 (7%)	0.48
Psychiatric disorder	170 (6.6%)	112 (5.5%)	58 (10.8%)	<0.001
Social deprivation	235 (9.1%)	187 (9.2%)	48 (8.9%)	0.85
Localization of MI				
Anterior	1609 (58.4%)	1250 (59.3%)	359 (55.4%)	
Lateral	209 (7.6%)	159 (7.5%)	50 (7.7%)	
Inferior	921 (33.4%)	688 (32.6%)	233 (35.9%)	
Other	18 (0.6%)	12 (0.6%)	6 (0.9%)	
Angiographic findings				
Single-vessel disease	1759 (63.8%)	1340 (63.5%)	419 (64.7%)	0.45
Two-vessel disease	577 (20.9%)	437 (20.7%)	140 (21.6%)	—
Three-vessel disease	421 (15.3%)	332 (15.7%)	89 (13.7%)	—
Lipid dataStatins prior to admission	266 (9.6%)	216 (10.2%)	50 (7.7%)	0.44
LDL-C > 190 mg/dL	233 (8.4%)	177 (8.3%)	53 (8.2%)	0.84
LDL-C > 160 mg/dL	503 (18.2%)	386 (18.3%)	117 (18.0%)	0.89
LDL-C (mg/dL)	120 (90–151)	121 (92–151)	115 (87–150)	0.52
HDL-C (mg/dL)	43 (34–53)	40 (33–50)	51 (41–63)	<0.001
Total cholesterol (mg/dL)	192 (165–224)	192 (164–221)	195 (165–233)	<0.01
Triglycerides (mg/dL)	120 (87–166)	122 (90–174)	109 (82–150)	<0.001
Other biological data				
Creatinine (μmol/L)	75 (63–89)	77 (66–90)	66 (54–83)	<0.001
Troponin (mg/L)	139 (18.6–3150)	133 (19.8–3111)	150 (13.0–3414)	0.11
NtproBNP (pg/mL)	1015 (250–3146)	806 (220–2504)	2182 (434–4702)	<0.001
Haemoglobin (g/dL)	12.9 (11.6–13.9)	13.2 (12.1–14.1)	11.6 (10.5-12.6)	<0.001
Hb1aC (%)	5.80 (5.50–6.30)	5.80 (5.50–6.30)	5.90 (5.57–6.30)	0.32
CRPus (mg/L)	6.00 (2.00–24.0)	6.00 (2.00–22.0)	7.00 (2.00–31.0)	0.16
Type and dosage of statin at discharge				
Every statin at maximum dosage, *n* (%)	1338/1849 (72.4%)	1058/1448 (73.1%)	280/401 (69.8%)	<0.001
Atorvastatine 80 mg, *n* (%)	1152 (62.3%)	941 (64.9%)	211 (52.6%)	<0.001
Atorvastatine 40 mg or less, *n* (%)	288 (15.6%)	185 (12.8%)	104 (25.9%)	—
Rosuvastatine 20 mg, *n* (%)	154 (8.3%)	134 (9.3%)	20 (5.0%)	—
Rosuvastatine 10 mg or less, *n* (%)	116 (6.3%)	90 (6.2%)	26 (6.5%)	—
Others	80 (4.3%)	56 (3.9%)	24 (6.0%)	—
None	59 (3.2%)	43 (2.9%)	16 (4.0%)	—

BMI, body mass index; CAD, coronary artery disease, GFR, glomerular filtration rate; CKD, chronic kidney disease; HIV, human immunodeficiency virus; LV, left ventricle; NASH, non-alcoholic steatohepatitis.

Table 2 Estimation of cardiovascular risk in primary prevention according to sex

	Overall, *n* = 2757	Men, *n* = 2109	Women, *n* = 648	*P*-value
Risk category—ESC 2019[a]				
Low risk	449 (16.3%)	374 (17.7%)	75 (11.6%)	<0.001
Moderate risk	1033 (37.5%)	855 (40.5%)	178 (27.5%)	—
High risk	692 (25.1%)	444 (21.1%)	248 (38.3%)	—
Very high risk	474 (17.2%)	368 (17.4%)	106 (16.4%)	—
Risk category—ESC 2021[b]				
Low to moderate risk	539 (19.6%)	404 (19.2%)	135 (20.8%)	0.33
High risk	1088 (39.5%)	826 (39.2%)	262 (40.4%)	—
Very high risk	1130 (40.9%)	879 (41.6%)	251 (38.8%)	—
Eligibility for statins (grade I, IIa, IIb)				
2016 ESC guidelines	650 (23.6%)	525 (24.9%)	125 (19.3%)	<0.001
2019 ESC guidelines	1066 (38.7%)	738 (35.0%)	328 (50.6%)	<0.001
2021 ESC guidelines	1704 (61.8%)	1314 (62.3%)	390 (60.2%)	0.18

[a]Based on clinical factors and SCORE.
[b]Based on clinical factors and SCORE2.

Eligibility for primary prevention intervention in men and women

Based on the 2021 ESC guidelines, 61.8% of individuals would have met a class I, IIa, or IIb recommendation for primary prevention statins prior to STEMI, 38.6% according to the 2019 ESC/EAS guidelines, and 24% with the 2016 guidelines ($P < 0.01$) (*Figure 1A*). The increase in detection of individuals at risk from 2016 to 2021 occurred in both women (60.2% vs. 50.7% vs. 19.3%, $P < 0.001$) and men (62.3% vs. 35.0% vs. 24.9%, $P < 0.001$) (*Figure 1B*). Of note, based on the 2016 ESC guidelines, 24% of patients were not given any recommendation—either because of too low CV risk or because of their age being too advanced. The proportion of patients left out of any recommendation dropped to 5% with the 2019 guidelines, and 0% in 2021.

According to the 2019 ESC/EAS guidelines, 368 (17.4%) men and 106 (16.4%) women were considered at very high risk and thus would be potentially eligible for primary prevention PCSK9is in case of uncontrolled LDL-C with statins and ezetimibe. According to the 2021 ESC guidelines, intensive lipid-lowering therapy before a first cardiovascular event in very high risk patients would involve 879 (41.6%) men and 251 (38.8%) women.

Guideline-based intensive lipid-lowering therapy after a first ST-segment elevation myocardial infarction according to real-life low-density lipoprotein cholesterol (*n* = 975 patients)

Using health records linked to the ePARIS registry, the LDL-C levels of 975 patients were collected. After a median follow-up of 33 months [interquartile range: 7–71] after the MI, only 27% of patients reached the LDL-C objective below 55 mg/dL (1.4 mmol/L), and 39% below 70 mg/dL (1.8 mmol/L) (*Figure 2*).

Following the stepwise approach recommended by ESC guidelines, among 711 patients out of the LDL-C objective during follow-up, 439 (61.7%) were eligible for an increase of their statin dosage, 186 (26.2%) were eligible to add ezetimibe, and 86 (12.1%) were eligible to add a PCSK9i because they were already on the maximally tolerated dose of statins and ezetimibe without significant gender differences (*Figure 3A* and *B*). Following its introduction in the 2021 ESC guidelines with a class IIB recommendation, 189 (19.4%) patients were also eligible to add icosapent ethyl due to a triglyceride level >135 mg/dL.

Guideline-based intensive lipid-lowering therapy after a first ST-segment elevation myocardial infarction according to expected low-density lipoprotein cholesterol (*n* = 2757)

Using the ESC estimation of LDL-C reductions at discharge after a first STEMI, 38.7% of the cohort would reach LDL-C ≤55 mg/dL (≤1.4 mmol/L) even under a full dose of statins and total adherence, 16.8% of patients would require ezetimibe, and 44.5% would still have LDL-C above 55 mg/dL (1.4 mmol/L) under statins and ezetimibe and thus be eligible for a PCSK9i without statistical difference between men and women (*Figure 4*). Using the 2016 guidelines, 14.3% of patients would be eligible for ezetimibe and 22.5% for a PCSK9i for LDL-C levels below 70 mg/dL (1.8 mmol/L).

Control of other cardiovascular risk factors and outcomes

The follow-up of cardiovascular risk factors is displayed in *Table 3*. Persistent active smoking was frequent and concerned 35% of men and 14% of women. Among diabetic patients, Hb1aC was above 6.5% in 81 (47%) men and 21 (68%) women. The vast majority of patients had a well-controlled blood pressure (72%). During total

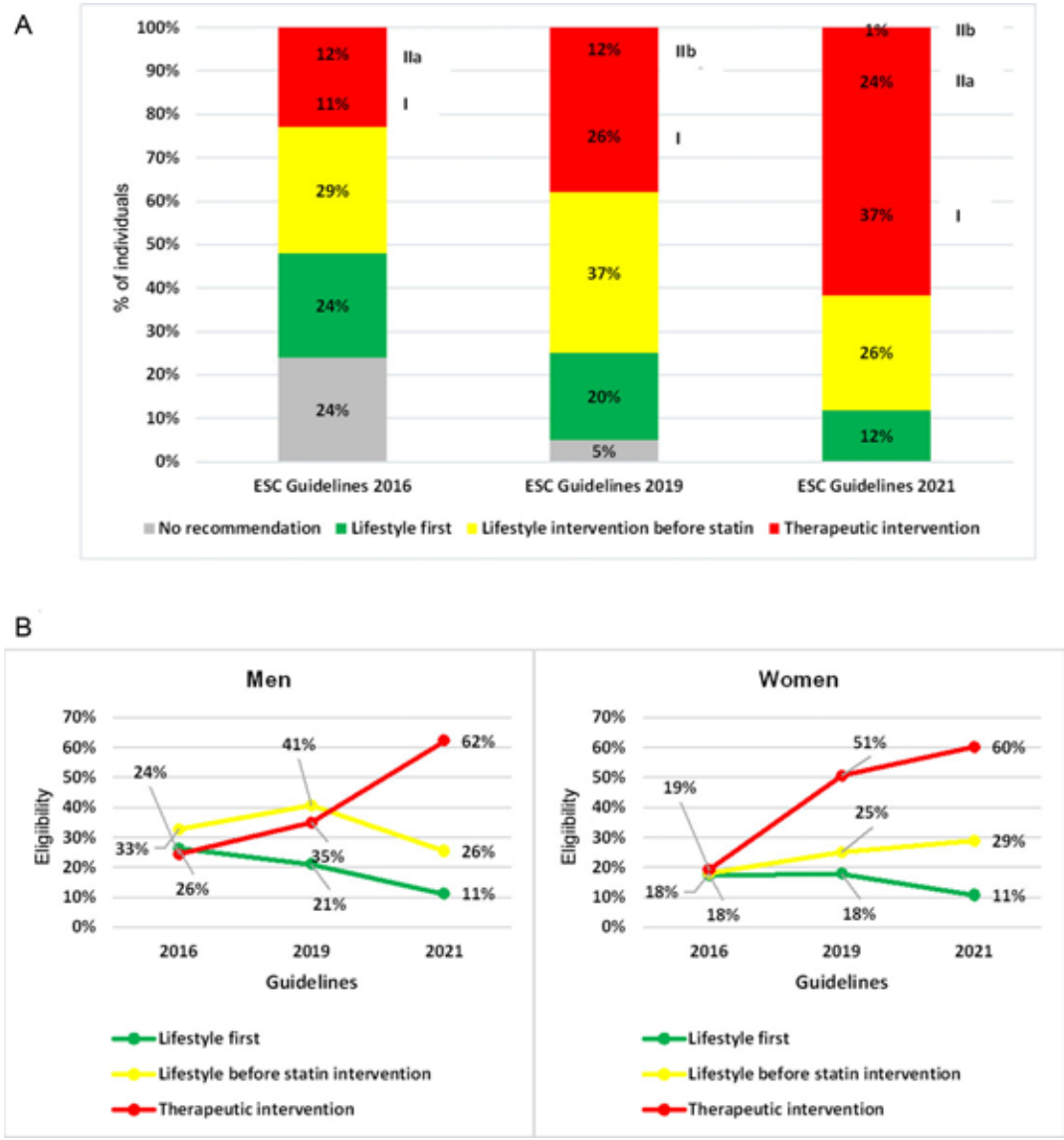


Figure 1 Eligibility for primary prevention statins and lifestyle interventions in 2016, 2019, and 2021 European Society of Cardiology guidelines before a first ST-segment elevation myocardial infarction overall (*A*) and according to sex (*B*).

follow-up, the composite of ACS, stroke, or death occurred at a rate of 5.1 per 1000 patient-years.

Discussion

Within 5 years, the ESC and EAS have implemented a substantial number of updates in the guidelines: the 2019 ESC/EAS guidelines lowered the LDL-C thresholds to start primary prevention therapy, modified the criteria to be considered at very high risk, and implemented novel intensive lipid-lowering therapy such as PCSK9is on top of statins and ezetimibe, with an objective of LDL-C at 55 mg/dL (1.4 mmol/L) or below. The 2021 ESC guidelines on CVD prevention for clinical practice implemented a new SCORE2 to improve risk stratification and provide an estimation of both non-fatal and fatal events at 10 years. Based on a cohort of consecutive individuals admitted for a first STEMI, we observed a significant improvement in the detection of high-risk individuals, with a three-fold increase in the eligibility for primary prevention statins. This improvement was especially observed for women, for whom cardiovascular risk was previously underestimated.[12,13] When analysing the follow-up of risk factors in secondary prevention and a guideline-based stepwise approach, most of the patients were eligible for an increase in statin dosage or for adding ezetimibe, but rarely a PCSK9i despite a vast majority of the patients having persistently high LDL-C levels.

In 2019, the *ESC/EAS Guidelines for the Management of Dyslipidemia* improved the identification of individuals at risk of MI compared with prior guidelines but still failed to assign direct statin therapy to 60%

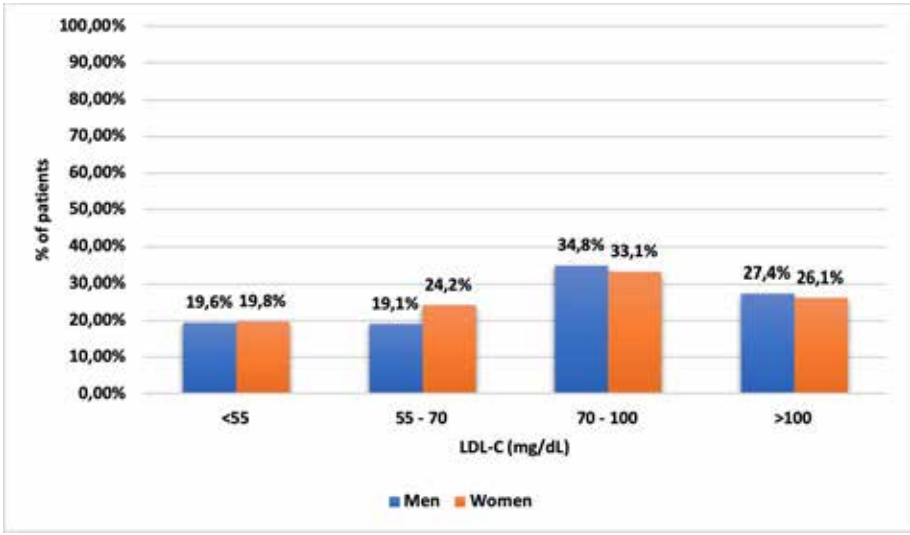


Figure 2 First low-density lipoprotein cholesterol measured during follow-up after a first ST-segment elevation myocardial infarction according to sex.

of these individuals. This improvement in the identification and treatment of adults who developed MI involved both men and women but was mostly seen in the population of women. Similarly to our findings, MB Mortensen *et al.* also showed an increase in eligibility for primary prevention statins from 15% to 32% in the Copenhagen General Population Study with new European guidelines.[14] Of note, this improvement was particularly driven by the increase in age from 65 to 70 years in the recommendation for statins, which particularly involved women. Despite the improvements to identifying and treating individuals at risk, the 2019 ESC guidelines failed to identify 60% of the patients before their first MI. The first explanation involved the SCORE system itself: pivotal in the management of primary prevention, this algorithm has several well-documented limitations, the first being the estimation of the 'last fatal event' rather than the first non-fatal ischaemic event. The second reason is the use of old epidemiological data from 1986 not reflecting the actual CVD burden and underestimating global or individual risk. Eventually, the restricted age range of the previous SCORE (40–70 years old), prevented an efficient detection of women at risk of cardiovascular disease, for whom the average age of MI in Western Europe is 75 years. Thus, using an updated SCORE2 apprehending both non-fatal and fatal events, the new 2021 ESC guidelines greatly improve the identification and treatment of individuals before they have a first MI, with more than one-third of individuals considered at very high risk and two-thirds directly eligible for statin therapy. Such improvement was made possible via the risk model recalibration, which particularly changed the eligibility for statins for women at risk.

Still, the latest ESC guidelines failed to identify and treat more than one-third of individuals before their first MI. A better implementation of risk modifiers in the decisional algorithms is paramount to better detect and treat high-risk subgroups such as women and young individuals despite their many high-risk features.[15,16] While the task force listed important, meaningful, and frequent risk modifiers in the women and young individuals of our cohort, such as social deprivation and chronic immune-mediated inflammatory disorder, none of these criteria were efficiently implemented to guide the decision to prescribe statins. In parallel, improvements in the detection of high-risk patients should be weighted with the necessity to avoid unnecessary exposure to statins, with their potential side effects and health costs. As described by Mortensen *et al.*, the improved sensitivity of the 2019 ESC guidelines compared with 2016 was associated with a reduction in specificity, and thus statin treatment for patients who would have not developed atherosclerotic cardiovascular disease.[14]

Within 3 years after their first STEMI, more than 70% of the patients did not meet the LDL-C target of 55 mg/dL (1.4 mmol/L): these patients were mostly treated with low- to moderate-intensity statins and without ezetimibe. Thus, when following the gradual response recommended by ESC guidelines, 26% of individuals would be eligible for ezetimibe and 12% for a PCSK9i after a first event—because more than 60% would be first eligible for an increase in statins before considering such therapies. A low rate of patients eligible for PCSK9is after a first MI based on the guidelines was also found by a previous study in a UK real-world study.[17] In contrast, when using the ESC algorithm to predict the expected follow-up LDL-C, around 17% of patients could be eligible for ezetimibe and 40% for a PCSK9i.

Questions remain regarding the proportion of patients requiring a PCSK9i on top of statins and ezetimibe directly after an ACS to reduce LDL-C levels below 55 mg/dL as recommended by the ESC/EAS. In the EVACS (Evolocumab in Acute Coronary Syndrome) trial, only 23.8% of the patients treated with statins reached the objective of LDL-C $\leq$ 55 mg/dL ($\leq$1.4 mmol/L) at 30 days, demonstrating that nearly 80% would be eligible for a PCSK9i; in contrast, LDL-C $\leq$ 55 mg/dL was reached for 65.4% and 90% of patients with a PCSK9i at discharge and 30 days, respectively.[18] In the EVOPACS (Evolocumab for Early Reduction of LDL-cholesterol Levels in Patients with Acute Coronary Syndromes) trial, only 37%

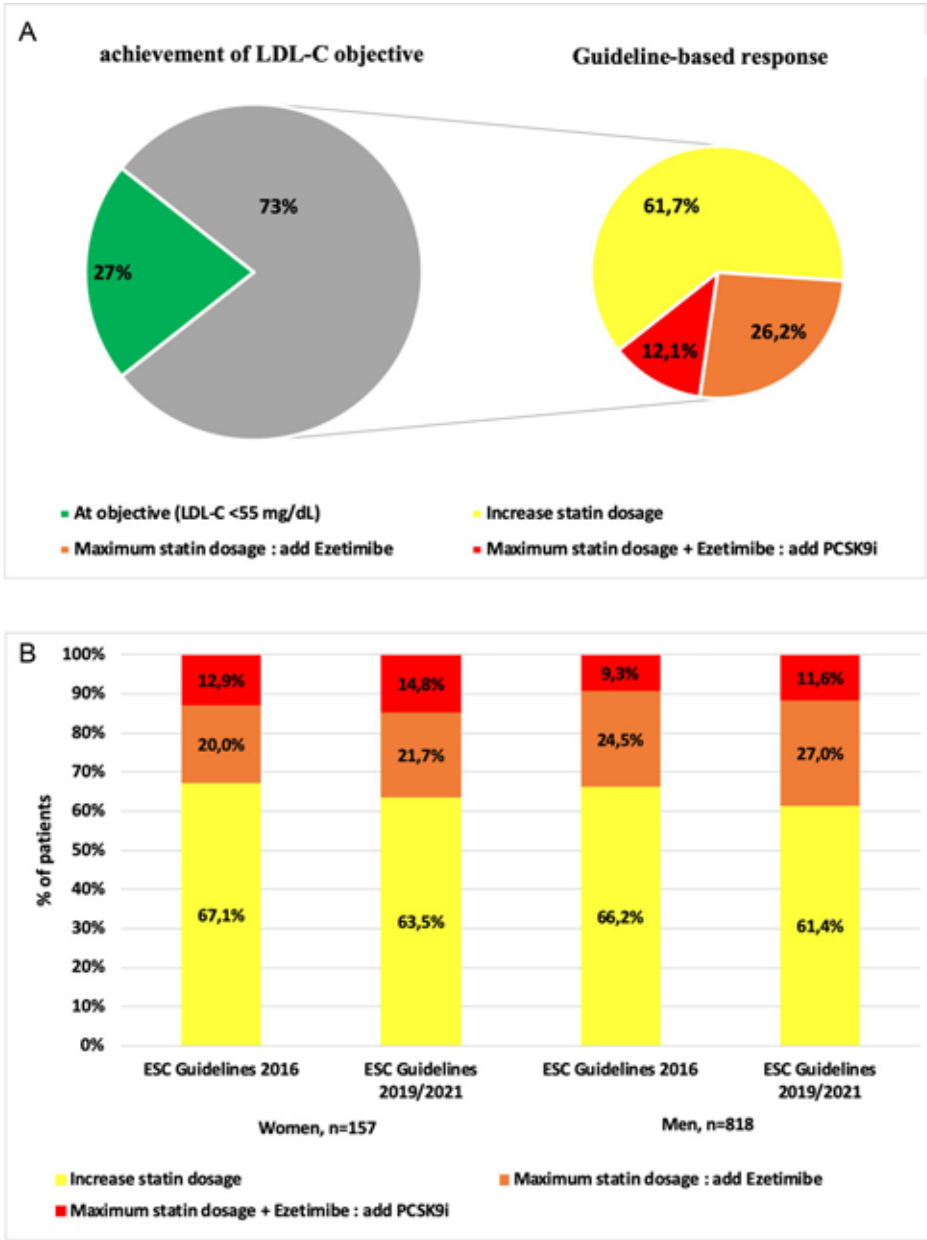


Figure 3 Guideline-based response to low-density lipoprotein cholesterol >55 mg/dL (>1.4 mmol/L) in a real-life setting with comparison of 2016 and 2019/2021 recommendations overall (*A*) and according to sex (*B*).

of the patients on statins reached LDL-C < 70 mg/dL at 1 year, highlighting that at least 70% of the patients would need a PCSK9i to reach the recommended goal of 55 mg/dL.[19]

Thus, the immediate implementation of PCSK9 after a first STEMI could be the next important step to reduce cardiovascular death or events and enable an effective and rapid reduction in LDL-C levels, especially as evolocumab and alirocumab were associated with a reduction of 15–20% of cardiovascular events, including death.[20,21] The ongoing AMUNDSEN (Acute Myocardial Infarction Upbound to PCI Immediately or in the Next Three Days and Randomized to Subcutaneous Evolocumab or Normal Strategies to Reach Guidelines LDL Objectives in the Real-world) trial (NCT04951856) is the largest study to evaluate the direct introduction of evolocumab vs. standard of care in individuals admitted for an ACS. Better strategies are needed to improve the control of cardiovascular risk factors after a first STEMI. Persistent smoking was present in one out of three individuals, and new-onset diabetes in 10% of the population. These results are consistent with the observations of Sverre *et al.*: in a nationwide Norwegian registry of post-MI patients, half of the individuals continued smoking, and 46% with persistent high blood pressure.[22] Beyond pharmacological interventions, education about

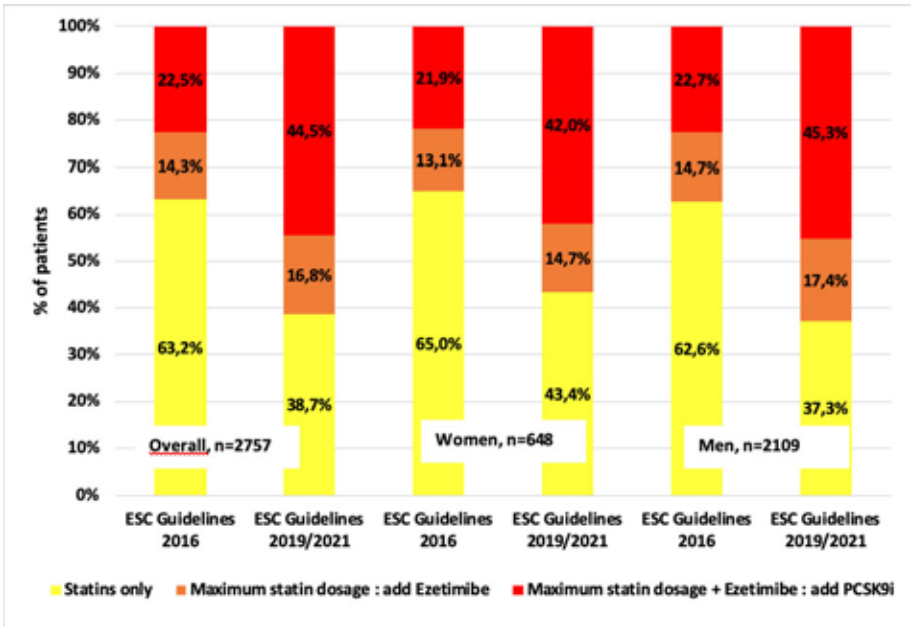


Figure 4 Eligibility for intensive lipid-lowering therapy after a first myocardial infarction according to 2016 European Society of Cardiology guidelines and 2019/2021 European Society of Cardiology guidelines based on expected follow-up low-density lipoprotein cholesterol.

Table 3 Control of other risk factors during follow-up according to sex

	Overall	Men	Women	*P*-value	Data (*n*)
At least one uncontrolled risk factor	381 (39%)	310 (38%)	71 (45%)	0.085	975
Blood pressure control					
Number of drugs	2.00(1.00—2.00)	2.00(1.00—2.00)	2.00(1.00—2.00)	0.76	625
Systolic arterial pressure (mmhg)	130(116–140)	128(116–140)	133(117–144)	0.1	534
Diastolic arterial pressure (mmhg)	75.0(68.0–80.0)	75.0(69.0–80.0)	70.0(65.5–80.0)	0.09	534
PAS > 140 mmHg, *n* (%)	269 (28%)	217 (27%)	52 (33%)	0.09	975
Diabetes					
HbA1c (%)	6.25 (5.70–7.00)	6.20(5.70–7.00)	6.40(5.60–7.30)	0.33	202
>6.5%, *n* (%)	102 (50%)	81 (47%)	21 (68%)	0.032	204
Smoking status					
Active smoking, *n* (%)	86 (31%)	78 (35%)	8 (14%)	<0.01	281

cardiovascular risk and change of lifestyle remain a cornerstone to improve the outcomes of patients admitted with a first STEMI. We demonstrated that lifestyle intervention alone, or before therapeutic intervention, was recommended in most patients before their first STEMI.

Study limitations

The present study contains limitations. First, risk modifiers such as coronary artery calcium score (CACS), carotid plaques, and CT coronary angiography (CTCA) were not collected or used in the algorithms to determine eligibility for statins. As a result, we could have underestimated the proportions of patients eligible for primary prevention statins, but this also reflects the simple clinical decision tools used in daily practice. Secondly, patients with non-st-elevation myocardial infarction (NSTEMI) were not analysed in this study, as our cohort only includes STEMI patients. Thirdly, our simulated analysis did not take into consideration individual variations in response to treatments and compliance, which may have led to an overestimation of eligibility. LDL-C levels were measured on samples taken within the hour of admission for STEMI and used as baseline LDL-C, based on studies showing very minimal variations between LDL-C before and after ACS.[23,24] Tolerance of statins in secondary prevention was not collected to decide whether an increase in the dosage was permitted, leading

to a potential underestimation of patients eligible for ezetimibe and a PCSK9i during follow-up. Eventually, our real-life follow-up LDL-C was incomplete, but our findings were consistent with prior descriptions.

Conclusions

The *2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice* improve the identification of subjects at risk for a first STEMI compared with the 2019 and 2016 guidelines, in both men and women. However, one-third of individuals admitted for a first STEMI would not have met the criteria provided by the 2021 ESC/EAS guidelines for primary prevention statin therapy. In secondary prevention, a vast majority of patients kept LDL-C levels above the goal of 55 mg/dL, for whom increasing the statin dose and adding ezetimibe were the most frequently recommended therapeutic actions. Ongoing trials are currently challenging this stepwise approach vs. the direct introduction of PCSK9is after a first STEMI.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Updates from the American Heart Association Scientific Sessions: cardiovascular pharmacotherapy

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Results from highly anticipated pharmacological trials were presented at the American Heart Association (AHA) Scientific Sessions 2021. Herein, we summarize key findings (*Table 1*).

More evidence favouring sodium–glucose cotransporter 2 inhibitor use in heart failure

A subgroup analysis of the EMPEROR-Preserved trial investigated whether the benefit of empagliflozin seen in heart failure (HF) patients with an ejection fraction (EF) >40% persisted when limited to patients with an EF>50%. In the primary analysis of patients with class II–IV HF and EFs ≥40% randomized to empagliflozin versus placebo, a significant reduction in the primary composite outcome of cardiovascular death and HF hospitalization was seen (event rate 13.8% vs. 17.1%).[1] The subgroup analysis among 'true' heart failure with preserved ejection fraction (HFpEF) patients demonstrated a 17% relative reduction in the primary outcome and 22% reduction in first HF hospitalization. In addition, empagliflozin had comparable and significant symptomatic improvement [change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score and New York Heart Association (NYHA) functional class]. Thus, the benefits of empagliflozin were comparable in heart failure with mid-range ejection fraction (HFmrEF) and HFpEF patients.

CHIEF-HF, a novel, virtually conducted randomized trial with no in-person visits, canagliflozin versus placebo in HF patients, found a significant improvement in symptoms among HF patients, regardless of diabetic status or EF (60% HFpEF). The 12-week change in the KCCQ total symptom score (TSS), the study's primary endpoint, was 4.3 points greater with canagliflozin. Additionally, this study demonstrated the feasibility and safety of utilizing virtual technologies in conducting pragmatic/digital trials.

The EMPULSE trial answered a crucial question regarding in-hospital initiation of empagliflozin in patients with acute decompensated HF. Empagliflozin was found to have a significant benefit over placebo with a primary composite outcome of death, number of HF events, time-to-first HF event, and 90-day change in KCCQ TSS, evidenced by a stratified win ratio of 1.36 in favour of the therapy, with no safety concerns.

Omecamtiv mecarbil and stroke risk in systolic heart failure

A secondary analysis of the GALACTIC-HF trial, which randomized patients with symptomatic HF and EF ≤35% to omecamtiv mecarbil or placebo, reported a significant stroke reduction. The therapy reduced the risk of first stroke by 35% (fatal or non-fatal stroke) and fatal strokes by 44%. These findings may be related to the increase in atrial and ventricular contractility and decrease in atrial fibrillation/flutter events seen with this selective cardiac myosin activator.

Milvexian for the prevention of venous thromboembolism

The AXIOMATIC-TKR trial investigated the efficacy and safety of milvexian, an oral factor-Xia inhibitor, in patients undergoing knee arthroplasty. Milvexian was compared with prophylactic dose enoxaparin, and found to have similar effectiveness in venous thromboembolism (VTE) prevention and a low bleeding risk.[2] Rates of VTE prevention, but not bleeding, were dose-dependent.

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Table 1 Summary of the design and main findings of key late-breaking trials during the American Heart Association Scientific Sessions 2021

Clinical trial	Question	Design	*N*	Primary outcome	Findings
GIRAF (NCT01994265)	Effect of dabigatran compared with warfarin on cognitive endpoints in patients who are > 65 years old and have atrial fibrillation and a $CHADS_2VASc$ score of >1	Randomized, single-blind (outcomes assessor), active-controlled, parallel assignment, phase 4 design	200	Cognitive impairment at 2 years independent of cerebrovascular events	No difference between warfarin and dabigatran in Mini-Mental State Exam ($P = 0.75$), Neuropsychological Test Battery ($P = 0.40$), and computer-generated neuropsychological test ($P = 0.06$). Warfarin improved Montreal Cognitive Assessment compared with dabigatran ($P = 0.02$)
EMPEROR-Preserved (NCT03057951)	Efficacy of empagliflozin in patients with heart failure with preserved ejection fraction (≥50%)	Secondary analysis of randomized, double-blind, placebo-controlled, parallel assignment, phase 3 design	4005	Cardiovascular death or heart failure (HF) hospitalization	Empagliflozin significantly reduced the primary outcome [hazard ratio (HR) 0.83; 95% confidence interval (CI) 0.71, 0.98]
CHIEF-HF (NCT04252287)	Effect of canagliflozin on Kansas City Cardiomyopathy Questionnaire total symptom score (TSS) in patients with symptomatic HF	Virtual, randomized, double-blind, placebo-controlled, parallel assignment, phase 3 design	476	KCCQ	Canagliflozin significantly improved KCCQ TSS at 12 weeks compared with placebo (mean difference 4.3; $P = 0.016$)
EMPULSE (NCT04157751)	Efficacy and safety of empagliflozin in patients with acute HF	Randomized, double-blind, placebo-controlled, parallel assignment, phase 3 design	530	Composite of death, number of HF events, time to first HF event, and change in KCCQ TSS from baseline to 90 days	Empagliflozin significantly improved the primary outcome [stratified win ratio 1.36; 95% CI (1.09, 1.68)]
PREPARE-IT 2 (NCT04460651)	Efficacy and safety of icosapent ethyl (IPE) on COVID-19-related hospitalizations in non-hospitalized patients with COVID-19	Randomized, double-blind, placebo-controlled, parallel assignment, phase 3 design	2052	COVID-19–related hospitalization	No difference between IPE and placebo on the primary outcome [HR 0.84; 95% CI (0.65, 1.08)]
AXIOMATIC-TKR (NCT03891524)	Efficacy of milvexian, an oral factor XIa inhibitor, in preventing total venous thromboembolism (VTE) events in patients undergoing knee arthroplasty	Randomized, open-label, study drug-dose blind, parallel assignment, phase 2 design	1242	Number of patients with total VTE, defined as the composite of asymptomatic deep-vein thrombosis, symptomatic venous thromboembolism, or death from any cause	Incidence of VTE with twice daily milvexian was 12%, which was significantly lower than the pre-specified benchmark (30%); one-sided $P < 0.001$
REVERSE-IT (NCT04286438)	Effect of bentracimab, a recombinant human IgG1 monoclonal antibody fragment that binds to free ticagrelor, on reversing the antiplatelet effect of ticagrelor and haemostasis parameters in patients presenting with uncontrolled major or life-threatening bleeding or who require urgent surgery/invasive procedure	Multicentre, open-label, prospective single-arm study	150 (enrolment is ongoing in North America and Europe with a goal to include at least 200 patients)	The minimum percentage inhibition of platelet reactivity units (PRUs) within 4 h of bentracimab initiation	Primary reversal endpoint was successfully met (PRU < −50%, $P < 0.001$)

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Management of antithrombotic therapy in patients at high bleeding risk after percutaneous coronary intervention for acute coronary syndromes: a case report

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Background Choosing antithrombotic therapy for patients at high bleeding risk, particularly those requiring long-term anticoagulant therapy, who have acute coronary syndromes (ACS) and/or undergoing percutaneous coronary intervention (PCI) is becoming increasingly complex.

Case summary A 78-year-old women was hospitalized with chest pain and a diagnosis of non-ST-elevation ACS was made. It was decided that the patient should undergo coronary angiogram with a view for angioplasty. Subsequently, she underwent successful PCI to the left anterior descending artery. Shortly after PCI, she was noted to be in atrial fibrillation. Furthermore, she had per rectal bleeding and acute kidney injury, which were managed conservatively. Aspirin and ticagrelor were stopped and she was discharged on dual antithrombotic therapy with clopidogrel and apixaban.

Discussion Available evidence, driven mainly from expert consensus documents, advocates a case-by-case comprehensive evaluation that integrates patient- and procedure-related factors to assess patients for thrombotic and bleeding tendencies to identify those who may gain most net clinical benefit of antithrombotic combination therapy. In general, if thrombotic drivers prevail, an augmented antithrombotic regime with a view for a longer duration should be planned, and if bleeding drivers prevail, a de-escalated regime with a view for a shorter duration should be sought.

Keywords Antithrombotic therapy • Acute coronary syndromes • Bleeding • Thrombosis • Case report

ESC Curriculum 3.2 Acute coronary syndrome • 3.1 Coronary artery disease

Learning points

- A one size fits all approach is not ideal for the management of antithrombotic therapy after acute coronary syndromes (ACS).
- In patients with ACS at high bleeding risk, the ultimate goal is to identify a therapeutic window 'sweet spot' of optimal protection and safety, where the combined risk of recurrent thrombosis and bleeding is low.
- After ACS, a dynamic individualized assessment of thrombotic vs. bleeding risks is required as part of a tailored management approach, taking into consideration the patient's preference.

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Introduction

Patients who suffer from acute coronary syndromes (ACS) and/or undergo percutaneous coronary intervention (PCI) are usually prescribed dual antiplatelet therapy (DAPT, consisting of aspirin and a $P2Y_{12}$ inhibitor), with an aim to provide secondary prevention strategy and reduce mortality.[1] The commonest reason for the addition of oral anticoagulation (OAC) to DAPT is the coexistence of atrial fibrillation (AF). Of note, one-fifth of patients who have ACS or PCI would warrant such therapeutic regime.[1–3] Withholding OAC to reduce bleeding risk may lead to a higher risk of stroke and attempts to reduce DAPT put the patients at risk of stent thrombosis, recurrent myocardial infarction, and even death. Management of patients with ACS and high bleeding risk remains a clinical challenge. This case study highlights the complexity of treating this cohort, and the different treatment strategies currently evidenced to individualize these patients' care.

Timeline

Day 0	Admission with non-ST-elevation acute coronary syndrome and loading doses of dual antiplatelet therapy (aspirin 300 mg and ticagrelor 180 mg) were given
Day 1	Maintenance doses of dual antiplatelet therapy (aspirin 75 mg daily and ticagrelor 90 mg twice daily) were given. A transthoracic echocardiography showed anterior wall hypokinesia with preserved left ventricular systolic function and no significant valvular heart disease
Day 2	Successful percutaneous coronary intervention (PCI) using one drug-eluting stent to the mid left anterior descending artery. A new diagnosis of atrial fibrillation (AF) with controlled ventricular response on a 12-lead electrocardiogram was made shortly after PCI
Day 3	New episodes of per rectal bleeding secondary to haemorrhoids and Grade II acute kidney injury presumed secondary to contrast-induced nephropathy
Day 4	Ticagrelor was de-escalated to clopidogrel 75 mg daily after a loading dose of 600 mg ~24 h after the last dose of ticagrelor
Day 5	No further per rectal bleeding. Apixaban 5 mg twice daily was started
Day 7	Aspirin was stopped and the patient was discharged on dual antithrombotic therapy with clopidogrel 75 mg daily and apixaban 5 mg twice daily for 12 months, then apixaban monotherapy thereafter
3 months	The patient had a good recovery with no major issues highlighted

Short summary of case (hypothetical)

A 78-year-old Caucasian women with a past medical history of hypertension and Type II diabetes mellitus was hospitalized with chest pain and elevated high-sensitivity troponin tests. She was subsequently diagnosed with non-ST-elevation acute coronary syndrome (NSTE-ACS). Her admission electrocardiogram (ECG) was unremarkable. She had loading doses of DAPT (aspirin 300 mg and ticagrelor 180 mg), and maintenance doses were prescribed (aspirin 75 mg daily and ticagrelor 90 mg twice daily). Physical examination was unremarkable including cardiovascular examination. She was planned to have an inpatient coronary angiogram with a view for angioplasty within the next 48 h. A transthoracic echocardiography showed anterior wall hypokinesia with preserved left ventricular systolic function and no significant valvular heart disease. On day 2, she underwent successful PCI using one drug-eluting stent to the mid-left anterior descending artery. There was mild diffuse bystander coronary artery disease that was non-flow limiting. Shortly after PCI, she was noted to be in AF with a controlled ventricular response on a 12-lead ECG. Furthermore, she had episodes of per rectal bleeding secondary to haemorrhoids and Grade II acute kidney injury presumed secondary to contrast-induced nephropathy, which were managed conservatively with good recovery.

Whilst in-hospital for 7 days, the patient received maintenance daily doses of aspirin 75 mg and ticagrelor 90 mg. As she remained in AF, ticagrelor was de-escalated to clopidogrel 75 mg daily after a loading dose of 600 mg ~24 h after the last dose of ticagrelor. She was discharged on dual antithrombotic therapy (DAT) with clopidogrel 75 mg daily and apixaban 5 mg twice daily for 12 months, then apixaban monotherapy thereafter. Other medications included a proton pump inhibitor for gastric protection, in addition to a beta-blocker, an angiotensin-converting enzyme inhibitor and a statin. Aspirin was stopped at hospital discharge on Day 7. An outpatient clinic follow-up was carried out at 3 months from index event and no concerns were highlighted.

Discussion

After ACS, while the emphasis is to prevent morbidity and mortality from future ischaemic events, the risk of high bleeding events translating into mortality is receiving recognition.[1,2] In ACS patients at high bleeding risk (HBR), especially those requiring long-term OAC, the ultimate goal is to reduce the combined risk of recurrent thrombosis and bleeding events. In the subset of patients with NSTE-ACS and/or undergoing PCI, and after DAPT loading doses (ideally with aspirin and clopidogrel), current ESC guidelines recommend DAT with clopidogrel and a non-vitamin K oral anticoagulant (NOAC) at the lowest recommended dose for stroke prevention for at least 12 months, and after an initial short period of up to 1 week of triple antithrombotic therapy (TAT, aspirin, and DAT).[3] This recommendation is mainly derived from subgroups of randomized controlled trials (*Table 1*). Of note, subsequent meta-analyses of these trials have demonstrated significantly lower bleeding with DAT compared with TAT with no increase in overall ischaemic events.[10,11] However, a higher stent thrombosis rate was observed with DAT containing a

Table 1 Randomized controlled trials including patients with non-ST-segment elevation acute coronary syndrome requiring long-term anticoagulation

Study	Population (n)/duration	DES (%)	ACS (%)	AF (%)	Conclusions
WOEST[4]	573 Between 2008 and 2011	65	27	69	TIMI bleeding and all-cause mortality lower with DAT (VKA + C) vs. TAT (VKA + A + C) at 1 year. No difference in MI, ST, stroke, or TVR
ISAR-TRIPLE[5]	614 Between 2008 and 2013	99	32	84	No difference in MACE or TIMI major bleeding at 9 months with TAT (VKA + A + C) for 6 weeks followed by DAT (VKA + A) vs. TAT (VKA + A + C) for 6 months followed by DAT (VKA + A)
PIONEER AF-PCI[6]	2124 Between 2013 and 2015	66	52	100	Clinically significant bleeding, all-cause death and rehospitalization lower with DAT (rivaroxaban 15 mg/day + C for 12 months) or modified TAT (rivaroxaban 2.5 mg b.i.d. + A + C for 1, 6, or 12 months) vs. TAT (VKA + A + C for 1, 6, or 12 months). No difference in cardiovascular death, MI or stroke
RE-DUAL PCI[7]	2725 Between 2014 and 2016	83	50	100	Major or clinically relevant non-major bleeding lower with DAT (dabigatran 110 or 150 mg b.i.d. + C or T) vs. TAT (VKA + A + C) up to 3 months. No difference in death, MI, stroke, systemic embolism or unplanned revascularization
AUGUSTUS[8]	4614 Between 2015–2018	NR	37	100	Major or clinically relevant non-major bleeds lower with DAT (apixaban 5 mg b.i.d. + C or T or P) vs. DAT (VKA + C or T or P) or TAT (apixaban 5 mg b.i.d. + A + C or T or P) or TAT (VKA + A + C or T or P). Death and hospitalization lower with apixaban
ENTRUST-AF PCI[9]	1506 Between 2017 and 2018	NR	52	100	Major or clinically relevant non-major bleeds non-inferior between DAT (edoxaban 60 mg + C or T or P) or TAT (VKA + A + C or T or P). No difference in cardiovascular death, MI, ST, stroke, or systemic embolism

A, aspirin, ACS, acute coronary syndrome, AF, atrial fibrillation, b.i.d., twice a day, C, clopidogrel, DAT, dual antithrombotic therapy, DES, drug-eluting stent, MI, myocardial infarction, NR, not reported, P, prasugrel, T, ticagrelor, ST, stent thrombosis, TAT, triple antithrombotic therapy, TIMI, Thrombolysis In Myocardial Infarction, TVR, target vessel revascularization, VKA, vitamin K antagonist

NOAC and an antiplatelet.[10,12] It is important to highlight that these studies were primarily designed to assess bleeding events and therefore may have lacked power to provide meaningful results on ischaemic events.

Choice of antiplatelet agent

No trials have evaluated the comparison of DAT containing aspirin vs. a $P2Y_{12}$ inhibitor. However, an expert consensus document in 2016 recommended $P2Y_{12}$ inhibitors over aspirin because of their higher efficacy and better gastrointestinal tolerance.[13] Currently, there is limited data to support the use of DAT containing either ticagrelor or prasugrel after PCI, as clopidogrel was chosen in >90% of cases in available trials. Therefore, the use of ticagrelor or prasugrel as part of TAT should be avoided due to the absence of safety data. In all patients requiring a combination of antiplatelet and anticoagulant therapy, gastric protection with a proton pump inhibitor is recommended.[3]

Balancing the risk of ischaemia and bleeding after acute coronary syndrome

In ACS patients at HBR and requiring long-term OAC, an expert consensus document in 2018 recommended shortening DAT duration to 6 months by withdrawing the ongoing antiplatelet therapy, especially with newer generation drug-eluting stents.[14] In contrast, for patients at high thrombotic risk requiring long-term OAC, TAT (aspirin and DAT) is suggested to continue for up to 1 month, followed by DAT for up to 12 months.[14] Recently, the AFIRE randomized trial of 2236 AF patients treated with PCI discouraged the need to continue with a single antiplatelet agent in combination with rivaroxaban beyond 12 months.[15] However, the trial had several limitations with results that are difficult to explain considering the known biologic effects of antithrombotic therapy.

An individualized approach of shortened vs. extended therapy according to patients' combined bleeding/thrombotic risk profile has therefore been advocated and is probably responsible for the wide variation observed in clinical practice.[16]

Atrial fibrillation and acute coronary syndromes

Concomitant AF exists in up to 16% of ACS patients with an increased risk of future stroke and death compared to patients without AF. This is mainly due to lack of OAC prescription in those at high risk of thrombosis [i.e. CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74, sex category female) ≥2].[17] In AF patients with a relatively low stroke risk (CHA_2DS_2-VASc of 1 in men or 2 in women), an expert consensus document in 2016 suggested treating upfront with only DAPT for the first 4 weeks after ACS/PCI,[1] although numerically more myocardial infarction events occurred when aspirin plus clopidogrel were used.[18] Thus, a more potent $P2Y_{12}$ inhibitor

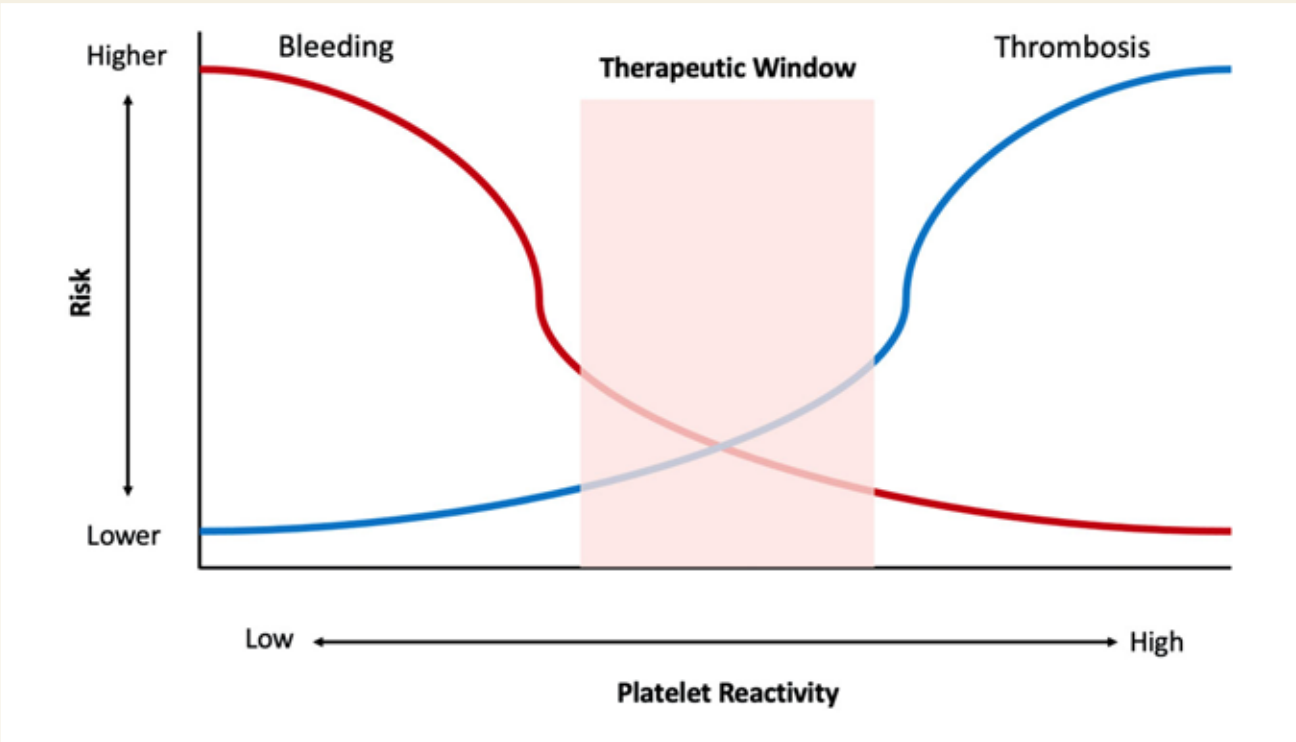

Figure 1 Therapeutic window of platelet inhibition after acute coronary syndromes. ***Bleeding risk*** is increased with advanced age, uncontrolled hypertension, Stage ≥4 chronic kidney disease, combined antiplatelet and anticoagulant use, prior bleeding events or bleeding tendencies/diathesis, active malignancy, low body weight and anaemia. ***Thrombotic risk*** is increased with advanced age, uncontrolled hypertension, Stage ≥4 chronic kidney disease, diabetes, prior myocardial infarction, acute coronary syndromes, extensive coronary artery disease, prior stent thrombosis, suboptimal stenting, greater stent length, small stent diameter, and bifurcation stenting.

(i.e. ticagrelor or prasugrel) may be preferable in this situation. In AF patients with ACS undergoing coronary artery bypass graft surgery, antithrombotic therapy, preferably with DAT, should be resumed as soon as the post-operative bleeding is controlled.

Identifying the 'sweet spot'

It is important to highlight that the evidence informing ESC practice guidelines generally reflects population-level data. The lack of a reliable individualized risk stratification tool to assess patients for thrombotic and bleeding tendencies to identify a safe therapeutic window, where the net clinical benefit is the highest, has led to limited use of potent antithrombotic drugs in many patients. However, it is important to note that this therapeutic window is likely variable, factorial and patient-specific.[13] Extremes of on-treatment platelet reactivity are associated with recurrent adverse events. Patients with high on-treatment platelet reactivity are at risk of thrombotic events, whilst those with low on-treatment platelet reactivity are at risk of bleeding. The ultimate goal of any antithrombotic management regime is to identify a therapeutic 'sweet spot' of optimal protection and safety, where the risk of thrombotic and bleeding events is low (*Figure 1*).

Given the trade-off between ischaemic and bleeding risks for antithrombotic medications, the use of risk stratification scores might be useful to guide individualized prescription. However, such scores have yet to be developed or validated for patients with AF and concomitant ACS/PCI. Several scores are mentioned in current ESC guidelines.[3] To assess the bleeding risk, the PRECISE-DAPT score, enclosing a five-item prediction model (age, creatinine clearance, haemoglobin, white blood cell count and prior spontaneous bleeding), or the ARC-HBR score are recommended, with a high risk identified as PRECISE-DAPT ≥25 or the ARC-HBR criteria met.[19] For the latter, patients are considered at HBR if they meet at least one major or two minor criteria. Major criteria included anticipated long-term anticoagulation after PCI, severe, or end-stage chronic kidney disease (eGFR <30 mL/min), anaemia (haemoglobin <11 g/dL), spontaneous bleeding requiring hospitalization or transfusion in the previous 6 months or at any time, if recurrent, moderate or severe thrombocytopenia (platelet count $<100 \times 10^9$/L), chronic bleeding diathesis, cirrhosis with portal hypertension, active malignancy in the previous 12 months, presence of brain arteriovenous malformation, previous spontaneous intracranial haemorrhage (ICH) at any time, previous traumatic ICH in the previous 12 months, moderate or severe ischaemic stroke in the previous 6 months, non-deferrable major surgery on DAPT, major surgery or major trauma in the 30 days before PCI. Minor criteria included ≥75 years, moderate chronic kidney disease (eGFR, 30–59 mL/min), haemoglobin 11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women, spontaneous bleeding requiring hospitalization or transfusion in the previous 12 months not meeting the major criterion, long-term use of oral non-steroidal anti-inflammatory drugs or steroids, any ischaemic stroke at any time not meeting the major criterion. The HASBLED (Hypertension,

abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly [>65 years], drugs and alcohol) score of ≥3 was also incorporated in the guidelines to identify AF patients at HBR but should not be directly used in patients with AF and ACS/PCI. Available scoring systems are derived mainly from clinical characteristics, which often overlap in predicting the risk (e.g. advanced age, uncontrolled hypertension, and chronic kidney disease). Designing risk stratification tools incorporating clinical, procedural, and rheological biomarkers may perhaps better risk-individualize patients.

The AUGUSTUS trial was the only randomized trial offering insight into the use of NOAC therapy (in the form of Apixaban), without aspirin combination, in patients with AF undergoing PCI.[8] Apixaban monotherapy resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischaemic events. Such results were very promising in showing a safety and efficacy benefit of NOAC monotherapy vs. regimens that included a vitamin K antagonist, aspirin, or both. There is a need for further trials to stratify patients based on risk prediction models to tailored treatments vs. standard care taking into consideration the thrombotic and bleeding risks, as well as the patient's values and preferences.

High bleeding risk in the elderly

Another HBR cohort, although not limited to, is that of the elderly. Bleeding risk increases with advanced age, with frequent concomitant comorbidities adding another burden to the choice of antithrombotic therapy following ACS/PCI in this cohort. Although the relationship between age and bleeding risk appears to be continuous, one must bear in mind that biological and chronical age are two separate entities and therefore patients should be assessed on an individualized basis with regards to their bleeding risk. Furthermore, one must acknowledge that bleeding risk must be balanced against thrombotic risk and that a balanced approach should guide the duration of antiplatelet therapy after ACS/PCI in this cohort.

Three randomized trials investigating short DAPT durations were completed in patients undergoing PCI perceived to be at increased bleeding risk.[20–22] In all three trials involving >5000 patients, advanced age was the commonest factor associated with increased bleeding (64% in LEADERS FREE, 51% in ZEUS, and 100% in SENIOR). To this effect, bleeding risk scores have been incorporated to help risk-stratify these patients, in particular the PRECISE-DAPT and the ARC-HBR.[3]

Conclusions

Patients with ACS requiring long-term OAC are at high risk of bleeding due to the need for combined antithrombotic therapy, as recommended by current practice guidelines, irrespective of whether invasive or conservative approaches are followed. A careful consideration of thrombotic and bleeding risks as well as the patient's preference is warranted to reduce the combined risk of ischaemic and bleeding events. More comparative randomized trials are needed to evaluate the efficacy and safety of antithrombotic therapies to guide clinical decisions.

Lead author biography

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