IMR Press

Review

Current management and prognosis of patients with recurrent myocardial infarction

Leonardo De Luca[1,*], Luca Paolucci[2], Annunziata Nusca[2], Rita Lucia Putini[1], Fabio Mangiacapra[2], Enrico Natale[1], Gian Paolo Ussia[2], Furio Colivicchi[3], Francesco Grigioni[2], Francesco Musumeci[4], Domenico Gabrielli[1]

[1] *Department of Cardiosciences, Division of Cardiology, A. O. San Camillo-Forlanini, 00152 Rome, Italy*

[2] *Department of Medicine, Unit of Cardiovascular Science, Campus Bio-Medico University, 00128 Rome, Italy*

[3] *Division of Cardiology, San Filippo Neri Hospital, 00186 Rome, Italy*

[4] *Department of Cardiosciences, Cardiac Surgery Unit and Heart Transplantation Center, A. O. San Camillo-Forlanini, 00152 Rome, Italy*

*Correspondence: leo.deluca@libero.it (Leonardo De Luca)

DOI:10.31083/j.rcm2203080

Submitted: 30 May 2021 Revised: 29 July 2021 Accepted: 4 August 2021 Published: 24 September 2021

Recurrent myocardial infarction (re-MI) is a common event following acute coronary syndrome (ACS), especially during the first year. According to epidemiological studies, patients who experience re-MI are at higher risk of all-cause cardiovascular events and mortality. The cornerstones of re-MI prevention include complete functional coronary revascularization, effective dual antiplatelet therapy and secondary prevention strategies. Notwithstanding this, some controversy still exists on the definition and management of re-MI, and no dedicated studies have been designed or conducted so far in this setting. We here provide an overview of epidemiological and prognostic data on ACS patients experiencing re-MI, along with current available treatment and preventive options.

Keywords

Recurrent myocardial infarction; Acute coronary syndrome; Secondary prevention; Dual antiplatelet therapy; Percutaneous coronary intervention

1. Introduction

Recurrent myocardial infarction (re-MI) is one of the most common adverse cardiovascular (CV) events that may occur after an episode of acute coronary syndrome (ACS). According to the 4th Universal Definition of Myocardial Infarction, re-MI is defined as the MI that occurs after 28 days following the index MI event. Differently, an MI that occurs within 28 days of the first index event is defined as reinfarctions [1]. However, current studies investigating ACS rarely use this distinction and adopt generic definitions as "MI" or "new MI". In the present review, re-MI is applied to any acute coronary events following the index MI. The main objectives of this review are to summarize evidence on the incidence and prognosis of re-MI and to discuss the most effective strategies that proved successful in significantly reducing re-MI rates in the current revascularization era.

2. Epidemiology and prognosis

Hospitalization rates due to MI have steadily decreased over the last 30 years [2, 3]. Obviously, re-MI incidence has dramatically changed as well.

From 1980s to the early 1990s, re-MI incidence appeared to be extremely high, without significant changes over time [4]. Later, a number of studies documented a progressive and slow decrease in re-MI occurrence, though case fatality tended to be stable [5, 6]. Buch *et al.* [6] compared two different cohorts of first MI survivors developing re-MI included in the National Danish Patient Registry between 1985–1989 and 2000–2002. In 1985–1989, early re-MI (within 30 days) and late re-MI (31–365 days after the index MI) occurred in 2.5% and 9% of patients, respectively. In 2000–2002, early re-MI and late re-MI occurred in 4.4% and 6.6% of patients, respectively, with a significant decline in related mortality.

In the era of percutaneous coronary intervention (PCI), the overall incidence of re-MI dramatically decreased over time, though rates were not consistent across registries [7–9]. In a sample of 48,688 US patients of Medicare beneficiaries who suffered MI between 2001 and 2009, a progressive decline in 1-year re-MI occurrence from 7.6% to 5.8% was observed [7]. In a larger cohort of patients hospitalized for acute MI from 1999 to 2010 (2.3 millions), re-MI rates declined from 12.1% in 1999 to 8.9% in 2010, with a relative reduction of 26.4% [8]. These data were confirmed in a recent study that reported a reduction in re-MI rates at 3 years from 7.1% to 5.1% in 4169 patients during a more contemporary period [10].

Regarding the incidence of in-hospital re-MI, i.e., re-MI occurring during the first hospitalization and often related to a PCI procedure (Type 4 MI), the FAST-MI registry showed comparable rates of re-MI for ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI) with values approaching 1% [10]. Similar data from other European registries have recently been published [11, 12].

Differently, after the in-hospital phase, re-MI incidence seems to be strongly related to readmission rates during the first year after the index MI. Based on the results from sev-

eral studies evaluating this event in contemporary cohorts, 30-day rehospitalization rates after MI vary from 12% to 20%, with almost 70% occurring within the first 2 weeks [13, 14]. As reported by Kim *et al.* [14], 11.3% of these patients may experience re-MI. Despite evidence that re-MI may represent one of the major causes of readmission during the first 30 days after the index MI [15], there are discordant data regarding the relative burden of re-MI in readmission causes at follow-up longer than 30 days. Culler *et al.* [16] retrospectively evaluated readmissions rates and causes of re-hospitalization in 143,286 patients discharged alive after MI in US during 2014. At 90 days, 28% experienced at least one readmission and 8% had more than one readmission. The main reasons for readmission were heart failure (HF) and need for cardiac surgery (15.3% and 10.1%, respectively), while re-MI occurred in 2.1% of patients with an average number of days to MI recurrence of 35.3 $\pm$ 29.7. In another study investigating readmissions in 296,965 US patients discharged after NSTEMI, 58.4% of total readmissions at 90 days were due to CV causes, with re-MI being the most frequent [17]. Notably, the risk of re-MI persists even at longer follow-up and re-MI rates actually tend to rise over the years after the index MI (13–16% at 7 years), though more than half of events occur within the first year [18, 19].

The prognostic impact of re-MI may be dramatic in patients surviving a first coronary event. Significantly higher mortality rates both at 30 days and 1 year have been reported in patients suffering re-MI compared to patients with no re-MI [20, 21]. In a substudy of TRITON-TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) including 13,608 patients with ACS, those who experienced a new MI had a significantly higher rate of CV death at 6 months compared to patients who had no re-MI (6.5% vs 1.3%; $p < 0.001$) [21]. The prognostic impact of re-MI may be related to its timing. In a recent prospective cohort of 3387 patients, the average mortality rate at 1 year in re-MI patients was 32.2%, reaching 53.3% in those with early recurrences. In this population, re-MI was associated with a 25-fold increased risk of death at 1 year compared to patients with a single acute coronary event [19].

3. Risk factors associated with re-MI

Due to its frequent occurrence and prognostic implications, re-MI is routinely included in the composite outcome of major adverse CV events (MACE) of studies conducted in patients with ACS [22]. Therefore, re-MI and global MACE tend to share many common risk factors. Conditions frequently associated with MACE in the ACS setting include age, female sex, prior MI, prior stroke, diabetes, left ventricular dysfunction, failed or not attempted revascularization, high Killip class, low systolic blood pressure, and renal failure [23–27].

Older age has been shown to be significantly associated with re-MI in several studies [19, 28] and is occasionally considered as one of the most important predictive factors of re-MI [29, 30]. Similar considerations may apply to diabetes [29–31], smoking status [32], female sex [28, 31, 33] or socio-demographic status [34]. In patients with STEMI and a prior history of stroke that account for 9% of all-comers STEMI, a two-fold increased risk of suffering re-MI has been observed during the first 30 days after the index coronary event when compared to other STEMI patients [35]. In addition, re-MI is not just a major cause of readmission in patients surviving the first MI, but it can also occur in patients hospitalized for other clinical reasons. As recently demonstrated by Wang and colleagues in a retrospective wide population of Medicare fee-for-service beneficiaries, there are at least 11 disease categories causing readmission that are significantly associated with re-MI, including diabetes, anemia, hypertension, coronary artery disease and HF [20]. This evidence supports the relevance of specific medical strategies designed to prevent all-cause readmissions in order to reduce re-MI rates and improve global patient's prognosis.

4. Role of revascularization

Coronary revascularization has been one of the most debated topics regarding MI recurrence. Although PCI is universally recognized as the most effective strategy in reducing MACE and mortality following ACS [36, 37], some authors have suggested that PCI itself may be a risk factor for re-MI [19, 28, 31–33]. In a prospective cohort of 3283 ACS patients, prior coronary artery bypass grafting (CABG) and prior PCI were respectively the first and second strongest predictors of re-MI at 1-year follow-up [28]. Similarly, prior CABG and PCI were significantly associated with re-MI in a prospective population of 9615 patients [31]. It should be noted, however, that both studies enrolled patients starting from 2004–2005, long before the modern antiplatelet strategies and second-generation drug-eluting stents (DES) have become available [16, 17, 19, 38–42].

Growing evidence suggesting a protecting role of PCI on re-MI events comes from modern randomized clinical trials (RCTs) investigating complete revascularization of non-infarct-related artery (IRA) vessels in STEMI patients [39]. Since 2013, a number of studies [40–44] have been conducted with the purpose of demonstrating how routine revascularization of significant non-culprit lesions may improve outcomes, i.e., mortality and MACE (including re-MI). All these trials differ significantly by sample size and methods, and this has led to varying results on the effectiveness of PCI in reducing re-MI rates. Gupta *et al.* [45] included data from two trials, DANAMI-3-PRIMULTI (Primary PCI in Patients with ST-elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) (n = 627) and Compare-Acute (Comparison Between FFR guided Revascularization versus Conventional Strategy in Acute STEMI Patients with MVD) (n = 885), with the aim to assess if a fractional flow reserve (FFR)-guided strategy of complete revascularization could improve outcomes during

a follow-up of 12 to 44 months. A similar analysis design, adding another minor RCT to the previous two ones, was used by Wang and colleagues in a more recent meta-analysis [46]. Both studies demonstrated a significant reduction in MACE rates and unplanned or ischemia-driven coronary interventions, with no evidence of of a higher risk of re-MI in patients undergoing complete revascularization.

Recently, the results from the COMPLETE trial (Complete vs Culprit-only Revascularization to Treat Multi-Vessel Disease after Early PCI for STEMI) have been published. In this trial, 4041 patients were randomized to an IRA-only strategy versus complete revascularization. At a mean follow-up of 36.2 months, complete revascularization significantly reduced the co-primary outcome of CV death and new MI (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.60–0.91). This result was mainly driven by the lower incidence of new MI in the IRA-only PCI group compared to the complete-revascularization group (HR 0.68, 95% CI 0.53–0.86), whereas no significant differences were reported in CV death (HR 0.93, 95% CI 0.65–1.32) or all-cause death (HR 0.91, 95% CI 0.69–1.20) [44]. After the publication of the COMPLETE trial, other meta-analyses showed significantly improved outcomes associated with complete revascularization. In an analysis including 10 RCTs for a total of more than 7000 patients, this strategy was found to be effective in reducing both CV death (OR 0.69, 95% CI 0.48–0.99) and re-MI (OR 0.68, 95% CI 0.49–0.96). In patients undergoing complete revascularization, re-MI incidence was 5.1% at a median follow-up of 29.5 months (compared to 6.9% in the IRA-only group, $p = 0.03$) [47]. Consistent results were reported in two additional meta-analyses with a comparable study design [48–50]. Notably, the recent FLOWER-MI trial (FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation Myocardial Infarction) (n = 1163 with STEMI) suggested that an FFR-guided strategy may not be superior to an angiography-guided strategy in STEMI patients undergoing complete revascularization (primary outcome: HR 1.32, 95% CI 0.78–2.23; non fatal re-MI: HR 1.77, 95% CI 0.82–3.84) [51]. All these data strongly support the hypothesis that PCI can significantly reduce re-MI after ACS and that the increased risk of type 4 MI associated with aggressive revascularization is largely counterbalanced by a reduction in type 1 re-MI incidence [52–57] (Table 1, Ref. [45–50]). In the STEMI setting, strict monitoring of ST-elevation resolution following PCI can be an effective tool in predicting the risk of recurrent events, including re-MI, at short and long-term follow-up [53].

5. Pharmacological strategies to reduce re-MI

Dual antiplatelet therapy (DAPT) is the cornerstone of pharmacological treatment of ACS. Since the early stages of both pharmaco-invasive and percutaneous treatment of MI, DAPT combining clopidogrel and aspirin showed to be strongly effective in reducing all-cause death, CV death, stent thrombosis (ST), and re-MI [54, 55]. Recently, new oral antiplatelet drugs and DAPT strategies have been investigated and approved in the MI setting, and currently either prasugrel or ticagrelor are strongly recommended by international guidelines [36, 37, 56].

In TRITON-TIMI 38, prasugrel proved superior to clopidogrel in reducing both re-MI (7.4% vs 9.7%; HR 0.76, 95% CI 0.67–0.85) and ST (1.1% vs 2.4%; HR 0.48, 95% CI 0.36–0.64) at 15 months, with no differences in overall mortality between treatment groups [57, 58]. In PLATO (Platelet Inhibition and Patient Outcomes) (n = 18,624), ticagrelor at a maintenance dose of 90 mg twice daily significantly reduced the rates of all-cause mortality, CV death, and MACE in patients with ACS compared with clopidogrel [59]. Re-MI incidence at 12 months was also significantly lower in the ticagrelor arm (5.8% vs 6.9%; HR 0.84, 95% CI 0.75–0.95). In PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) (n = 21,162 with previous MI), a prolonged DAPT duration with aspirin and ticagrelor 60 mg twice daily vs. placebo significantly reduced re-MI rates at 3-year follow-up (HR 0.84, 95% CI 0.72–0.98) [60]. These findings have been confirmed in real-world registries suggesting that both prasugrel and ticagrelor are highly effective in reducing CV outcomes compared to clopidogrel, without major safety concerns [61, 62].

The ISAR-REACT 5 trial (Prospective, Randomized Trial of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome) was designed to compare the efficacy of ticagrelor and prasugrel in reducing all-cause death, cardiac death, and MACE. More than 4000 patients with ACS were randomized to receive ticagrelor or prasugrel, with PCI performed in more than 80% of cases. At 1 year, the composite primary endpoint (death, MI, or stroke) was significantly reduced in the prasugrel vs. the ticagrelor group (6.9% vs 9.3%; HR 1.36, 95% CI 1.09–1.70). The lower incidence of the primary endpoint was primarily driven by a reduction in re-MI incidence (3.0% vs 4.8%; HR 1.63, 95% CI 1.18–2.25), while the other individual components of the composite outcome were not significantly different between the treatment groups [63].

Cangrelor is a strong $P2Y_{12}$ parental inhibitor and the latest to have been approved for clinical use. Differently from oral antiplatelet agents, cangrelor provides a prolonged inhibition of platelet activity with extremely rapid onset (2 min) and offset (60–90 min) periods [64]. Cangrelor efficacy in reducing ischemic endpoints was compared to clopidogrel standard treatment in the CHAMPION Program (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition), consisting of three RCTs enrolling both stable and unstable patients and differing each other by sample size and timing of clopidogrel administration. Both CHAMPION-PLATFORM (n = 5362 with stable and unstable CAD) and CHAMPION-PCI (n = 8877 with stable and unstable CAD) failed to demonstrate a significant reduction of the primary endpoint (death, MI, and ischemia-driven

Table 1. Complete revascularization and re-MI rates in recent major meta-analysis.

Author and year	No. of RCTs	Major RCTs included*	No. of patients	Follow-up (months)	Main results	Re-MI and complete revascularization
Gupta *et al.* 2018 [45]	2	Compare-Acute; DANAMI-3-PRIMULTI	1512	12–44	Reduced urgent/planned revascularizations	RR 0.71 (95% CI 0.39–1.31; $p = 0.28$)
Wang *et al.* 2019 [46]	3	Compare-Acute; DANAMI-3-PRIMULTI	1631	12–44	Reduced repeat revascularizations	OR 0.96 (95% CI 0.60–1.56; $p = 0.88$)
Pavasini *et al.* 2020 [50]	6	Compare-Acute; DANAMI-3-PRIMULTI; PRAMI; CvLPRIT; COMPLETE	6528	12–36	Reduced CV death, re-MI and repeat revascularizations	HR 0.65 (95% CI 0.53–0.80; $p < 0.0001$)
Levett *et al.* 2020 [49]	9	Compare-Acute; DANAMI-3-PRIMULTI; PRAMI; CvLPRIT; COMPLETE	6751	6–36	Reduced re-MI and repeat revascularizations (trends in favor of reduced CV and all-cause mortality)	RR 0.64 (95% CI 0.48–0.84)
Bainey *et al.* 2020 [47]	10	Compare-Acute; DANAMI-3-PRIMULTI; PRAMI; CvLPRIT; COMPLETE	7030	29.5 (median)	Reduced CV death and re-MI	OR 0.70 (95% CI 0.57–0.85; $p < 0.001$)
Ahmad *et al.* 2020 [48]	10	Compare-Acute; DANAMI-3-PRIMULTI; PRAMI; CvLPRIT; COMPLETE	7542	31.4 (median)	Reduced CV death, re-MI and unplanned revascularizations	RR 0.65 (95% CI 0.54–0.79; $p < 0.0001$)

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

*Major RCTs: defined as RCT with more than 250 patients enrolled.

Table 2. Major DAPT trial designs, populations, results and reported re-MI/MI incidences.

Study and year	$P2Y_{12}$ inhibitors	DAPT duration	No. of patients and ACS type	Follow-up	Main results	Re-MI/MI and DAPT strategy
TRITON-TIMI 38 2007 [57]	Prasugrel vs Clopidogrel	6–15 months	13,608 UA/NSTEMI, n = 10,074 STEMI, n = 3534	15 months	Reduced re-MI, urgent TVR and ST	HR 0.76 (95% CI 0.67–0.85; $p < 0.001$)
PLATO 2009 [59]	Ticagrelor vs Clopidogrel	12 months	18,624 UA, n = 3112 NSTEMI, n = 3950 STEMI, n = 7026 Undefined, n = 531	12 months	Reduced all-cause and CV death, re-MI, ST	HR 0.84 (95% CI 0.75–0.95; $p = 0.005$)
CHAMPION-PLATFORM* 2009 [66]	Cangrelor vs Clopidogrel	2–4 h; followed by standard DAPT	5362 UA, n = 1848 NSTEMI, n = 3174	48 h	Not superior to clopidogrel in reducing primary endpoint Reduced all-cause death and ST	OR 0.92 (95% CI 0.74–1.13; $p = 0.42$)
CHAMPION-PCI* 2009 [65]	Cangrelor vs Clopidogrel	2–4 h; followed by standard DAPT	8877 UA, n = 2185 NSTEMI, n = 4363 STEMI, n = 996	48 h	Not superior to clopidogrel in reducing primary endpoint	OR 1.09 (95% CI 0.91–1.29; $p = 0.36$)
CHAMPION-PHOENIX* 2013 [68]	Cangrelor vs Clopidogrel	2 h-PCI time; followed by standard DAPT	11,145 NSTEMI, n = 2810 STEMI, n = 1992	48 h	Reduced re-MI and ST	OR 0.80 (95% CI 0.67–0.97; $p = 0.02$)
DAPT* 2014 [88]	Clopidogrel (65%) or Prasugrel (35%)	12 vs 30 months	9961 UA, n = 1363 NSTEMI, n = 1543 STEMI, n = 1045	33 months	Reduced re-MI and ST	HR 0.47 (95% CI 0.37–0.61; $p < 0.001$)

Table 2. Continued.

Study and year	$P2Y_{12}$ inhibitors	DAPT duration	No. of patients and ACS type	Follow-up	Main results	Re-MI/MI and DAPT strategy
PEGASUS-TIMI 54 2015 [60]	Ticagrelor vs Placebo	DAPT beyond 1 year after MI vs ASA alone	21,162 NSTEMI, n = 8593 STEMI, n = 11,329 Undefined, n = 1205	33 months	Reduced coronary death, re-MI, stroke from any cause	Tic 90 mg vs plac: HR 0.81 (95% CI 0.69–0.95; $p = 0.01$) Tic 60 mg vs plac: HR 0.84 (95% CI 0.72–0.98; $p = 0.03$)
PRAGUE 18 2016 [89, 90]	Prasugrel vs Ticagrelor	12 months	1230 (prematurely interrupted for futility) NSTEMI, n = 67 STEMI/BBB, n = 1163	12 months	Not superior to ticagrelor in reducing primary endpoint	HR 1.1 (95% CI 0.6–2.3; $p = 0.61$)
GLOBAL LEADERS* 2018 [91]	Ticagrelor (vs Clopidogrel in CCS)	1 month DAPT (ASA and Ticagrelor) + 23 months Ticagrelor monotherapy vs 12 months DAPT	15,968 UA, n = 2022 NSTEMI, n = 3373 STEMI, n = 2092	24 months	Not superior to standard DAPT in reducing primary endpoint	New Q MI: RR 0.80 (95% CI 0.60–1.07; $p = 0.14$) Non Q MI: RR 1.00 (95% CI 0.84–1.19; $p = 0.98$)
ISAR-REACT 5 2019 [63]	Ticagrelor vs Prasugrel	12 months	4018 UA, n = 510 NSTEMI, n = 1855 STEMI, n = 1653	12 months	Reduced primary endpoint with prasugrel (only driven by re-MI)	HR 1.63 (95% CI 1.18–2.25)
TWILIGHT-ACS (substudy) 2020 [92]	Ticagrelor	3 month DAPT + 12 months Ticagrelor monotherapy vs 15 months DAPT	4114 All NSTEMI	15 months	Reduced bleedings Not increased ischemic endpoints	HR 1.00 (95% CI 0.72–1.39; $p = 0.99$)
TICO 2020 [93]	Ticagrelor	3 months DAPT + 9 months Ticagrelor monotherapy vs 12 months DAPT	3056 UA, n = 926 NSTEMI, n = 1027 STEMI, n = 1103	12 months	Reduced bleedings Not increased ischemic endpoints	HR 0.55 (95% CI 0.20–1.48; $p = 0.24$)

ACS, acute coronary syndrome; BBB, bundle branch block; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; RR, relative risk; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

*Trials including patients with chronic coronary syndrome.

revascularization) at 48 h in the cangrelor arm, despite some evidence suggesting a reduction in isolated death and ST [65, 66]. In a pooled analysis of these two trials that used a more precise definition of periprocedural MI, cangrelor was found to be associated with a significant reduction in early ischemic events when compared with clopidogrel [67]. Later results from the large CHAMPION PHOENIX trial (n = 11,145 with stable and unstable CAD) demonstrated a significant reduction of the primary efficacy endpoint (death, MI, ischemia-driven revascularization, and ST) in patients treated with cangrelor compared with patients treated with clopidogrel (4.7% vs 5.9%; OR 0.78, CI 95% 0.66–0.93). Notably, the benefit from cangrelor was mainly driven by lower rates of MI and ST (MI: 3.8% vs 4.7%; OR 0.80, 95% CI 0.67–0.97) [68]. A pooled analysis of these three trials, including ~25,000 patients, definitely confirmed these findings [69]. It should be considered that the CHAMPION trials (particularly CHAMPION PHOENIX) included a large proportion of stable patients, so that most of the reported MIs during follow-up cannot be properly reclassified as re-MIs. Thus, even if more than half of patients enrolled in these trials experienced an ACS, specific trials investigating cangrelor efficacy in the acute setting are lacking [70] (Table 2).

Additional pharmacological treatments are currently recommended to further reduce CV events following MI. In the ACS setting, several RCTs and meta-analyses have proven that statins dramatically reduce short- and long-term outcomes, including re-MI [71–73]. Indeed, an intensive statin regimen may decrease non-fatal MI rates by 15% [74, 75]. Moreover, in the acute setting, a high-dose statin pretreatment may be associated with a reduced rate of procedural MI and injury [76–78]. At present, the European Society of Cardiology ACS guidelines strongly recommend statin therapy (if not contraindicated) to reduce MACE, MI, and CV death, regardless of baseline LDL-cholesterol levels [36, 37]. Other lipid-lowering agents have shown to be effective in reducing CV events and MI in patients with ACS. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), more than 18,000 ACS patients were randomized to simvastatin vs. simvastatin plus ezetimibe. At 7-year follow-up, the combined lipid-lowering therapy effectively reduced the composite endpoint of CV death, nonfatal MI, unstable angina requiring hospitalization, reintervention of coronary revascularization, and nonfatal stroke. Notably, re-MI was strongly reduced by ezetimibe combined therapy (HR 0.87, 95% CI 0.80–0.95; $p = 0.002$) [79]. As for PCSK9 inhibitors, both evolocumab and alirocumab have been shown to significantly reduce CV events (including MI) in patients with established atherosclerotic CV disease or ACS, respectively [80, 81]. Besides lipid-lowering therapies, in the recent REDUCE-IT trial (n = 8179 with multiple CV risk factors), icosapent ethyl (targeting triglycerides) proved effective in reducing MACE (including MI) and CV death in high-risk patients (HR 0.75, 95% CI 0.68–0.83) [82].

The effects of non-antiplatelet drugs in the post-MI setting are critically influenced by other pathological conditions that may frequently coexist. Among these, left ventricular systolic dysfunction confers a much higher risk of re-MI and drugs such as beta-blockers and angiotensin-converting enzyme inhibitors can dramatically improve outcomes after ACS, including re-MI [83].

The relationship between beta-blockers and CV events in patients with ACS without HF is still a matter of debate. A large meta-analysis on this topic including 16 observational studies failed to demonstrate any relationship between beta-blocker therapy and survival improvement [84]. Conversely, in a recent prospective study enrolling more than 13,000 Asian patients, beta-blocker treatment was associated with reduced CV death at 1-year follow-up (HR 0.70, 95% CI 0.589–0.834; $p < 0.001$) [85]. Accordingly, there are data supporting the hypothesis that these agents may further reduce coronary events following an index ACS [89–91].

6. Conclusions

Re-MI is one of the most frequent complications occurring after an ACS episode.

Few dedicated epidemiological studies have tried to systematically evaluate the incidence and prognosis of re-MI in contemporary cohorts. It seems that the risk of re-MI persists for many years after the index event and approved secondary prevention strategies are able to only partially reduce its incidence, especially in subgroups at high risk. Novel pharmacological therapies and non-pharmacological strategies are highly needed in order to reduce the burden of re-MI and the overall residual risk after ACS.

Author contributions

LDL and LP drafted the paper; all other authors revised it critically.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Thanks to all the authors and peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al.* Fourth Universal Definition of Myocardial Infarction (2018). European Heart Journal. 2019; 40: 237–269.

[2] Dalen JE, Alpert JS, Goldberg RJ, Weinstein RS. The epidemic of the 20(th) century: coronary heart disease. American Journal of Medicine. 2014; 127: 807–812.

[3] Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. New England Journal of Medicine. 2010; 362: 2155–2165.
[4] Marques-Vidal P, Ruidavets JB, Cambou JP, Ferrières J. Incidence, recurrence, and case fatality rates for myocardial infarction in southwestern France, 1985 to 1993. Heart. 2000; 84: 171–175.
[5] Messner T, Lundberg V, Boström S, Huhtasaari F, Wikström B. Trends in event rates of first and recurrent, fatal and non-fatal acute myocardial infarction, and 28-day case fatality in the Northern Sweden MONICA area 1985-98. Scandinavian Journal of Public Health. 2003; 61: 51–59.
[6] Buch P, Rasmussen S, Gislason GH, Rasmussen JN, Køber L, Gadsbøll N, *et al.* Temporal decline in the prognostic impact of a recurrent acute myocardial infarction 1985 to 2002. Heart. 2007; 93: 210–215.
[7] Brown TM, Deng L, Becker DJ, Bittner V, Levitan EB, Rosenson RS, *et al.* Trends in mortality and recurrent coronary heart disease events after an acute myocardial infarction among Medicare beneficiaries, 2001–2009. American Heart Journal. 2015; 170: 249–255.
[8] Chaudhry SI, Khan RF, Chen J, Dharmarajan K, Dodson JA, Masoudi FA, *et al.* National trends in recurrent AMI hospitalizations 1 year after acute myocardial infarction in Medicare beneficiaries: 1999–2010. Journal of the American Heart Association. 2014; 3: e001197.
[9] Krumholz HM, Normand ST, Wang Y. Twenty-Year Trends in Outcomes for Older Adults with Acute Myocardial Infarction in the United States. JAMA Network Open. 2019; 2: e191938.
[10] Hanssen M, Cottin Y, Khalife K, Hammer L, Goldstein P, Puymirat E, *et al.* French Registry on Acute ST-elevation and non ST-elevation Myocardial Infarction 2010. FAST-MI 2010. Heart. 2012; 98: 699–705.
[11] García-García C, Oliveras T, Serra J, Vila J, Rueda F, Cediel G, *et al.* Trends in Short- and Long-Term ST-Segment–Elevation Myocardial Infarction Prognosis over 3 Decades: a Mediterranean Population-Based ST-Segment–Elevation Myocardial Infarction Registry. Journal of the American Heart Association. 2020; 9: e017159.
[12] De Luca L, Leonardi S, Cavallini C, Lucci D, Musumeci G, Caporale R, *et al.* Contemporary antithrombotic strategies in patients with acute coronary syndrome admitted to cardiac care units in Italy: the EYESHOT Study. European Heart Journal. Acute Cardiovascular Care. 2015; 4: 441–452.
[13] Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, *et al.* Diagnoses and Timing of 30-Day Readmissions after Hospitalization for Heart Failure, Acute Myocardial Infarction, or Pneumonia. Journal of the American Medical Association. 2013; 309: 355–363.
[14] Kim LK, Yeo I, Cheung JW, Swaminathan RV, Wong SC, Charitakis K, *et al.* Thirty-Day Readmission Rates, Timing, Causes, and Costs after ST-Segment–Elevation Myocardial Infarction in the United States: a National Readmission Database Analysis 2010–2014. Journal of the American Heart Association. 2018; 7: e009863.
[15] Southern DA, Ngo J, Martin B, Galbraith PD, Knudtson ML, Ghali WA, *et al.* Characterizing types of readmission after acute coronary syndrome hospitalization: implications for quality reporting. Journal of the American Heart Association. 2014; 3: e001046.
[16] Culler SD, Kugelmass AD, Cohen DJ, Reynolds MR, Katz MR, Brown PP, *et al.* Understanding Readmissions in Medicare Beneficiaries during the 90-Day Follow-up Period of an Acute Myocardial Infarction Admission. Journal of the American Heart Association. 2019; 8: e013513.
[17] Sreenivasan J, Abu-Haniyeh A, Hooda U, Khan MS, Aronow WS, Michos ED, *et al.* Rate, causes, and predictors of 90-day readmissions and the association with index hospitalization coronary revascularization following non-ST elevation myocardial infarction in the United States. Catheterization and Cardiovascular Interventions. 2021; 98: 12–21.
[18] Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circulation. Cardiovascular Quality and Outcomes. 2012; 5: 532–540.
[19] Song J, Murugiah K, Hu S, Gao Y, Li X, Krumholz HM, *et al.* Incidence, predictors, and prognostic impact of recurrent acute myocardial infarction in China. Heart. 2021; 107: 313–318.
[20] Wang Y, Leifheit E, Normand ST, Krumholz HM. Association Between Subsequent Hospitalizations and Recurrent Acute Myocardial Infarction Within 1 Year After Acute Myocardial Infarction. Journal of the American Heart Association. 2020; 9: e014907.
[21] Bonaca MP, Wiviott SD, Braunwald E, Murphy SA, Ruff CT, Antman EM, *et al.* American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation Universal Definition of Myocardial Infarction Classification System and the Risk of Cardiovascular Death: Observations from the TRITON-TIMI 38. Circulation. 2012; 125: 577–583.
[22] Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. Journal of the American College of Cardiology. 2008; 51: 701–707.
[23] Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. European Heart Journal. 2015; 36: 1163–1170.
[24] Zafrir B, Adawi S, Khalaily M, Jaffe R, Eitan A, Barnett-Griness O, *et al.* Long-Term Risk Stratification of Patients Undergoing Coronary Angiography According to the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention. Journal of the American Heart Association. 2019; 8: e012433.
[25] Zhao X, Liu C, Zhou P, Sheng Z, Li J, Zhou J, *et al.* Estimation of Major Adverse Cardiovascular Events in Patients With Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Risk Prediction Score Model From a Derivation and Validation Study. Frontiers in Cardiovascular Medicine. 2020; 7: 603621.
[26] Nguyen OK, Makam AN, Clark C, Zhang S, Das SR, Halm EA. Predicting 30-Day Hospital Readmissions in Acute Myocardial Infarction: The AMI "READMITS" (Renal Function, Elevated Brain Natriuretic Peptide, Age, Diabetes Mellitus, Nonmale Sex, Intervention with Timely Percutaneous Coronary Intervention, and Low Systolic Blood Pressure) Score. Journal of the American Heart Association. 2018; 7: e008882.
[27] Jimenez-Quevedo P, Brugaletta S, Cequier A, Iñiguez A, Serra A, Mainar V, *et al.* Long-term impact of diabetes in patients with ST-segment elevation myocardial infarction: Insights from the EXAMINATION randomized trial. Catheterization and Cardiovascular Interventions. 2019; 94: 917–925.
[28] Arnold SV, Smolderen KG, Kennedy KF, Li Y, Shore S, Stolker JM, *et al.* Risk factors for rehospitalization for acute coronary syndromes and unplanned revascularization following acute myocardial infarction. Journal of the American Heart Association. 2015; 4: e001352.
[29] Mal K, Awan I, Shaukat F. Evaluation of Risk Factors Associated with Reinfarction: A Multicenter Observational Study. Cureus. 2019; 11: e6063.
[30] Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M, *et al.* Incidence, predictors, and subsequent mortality risk of recurrent myocardial infarction in patients following discharge for acute myocardial infarction. Circulation Journal. 2013; 77: 439–446.

[31] Yudi MB, Clark DJ, Farouque O, Andrianopoulos N, Ajani AE, Brennan A, *et al.* Trends and predictors of recurrent acute coronary syndrome hospitalizations and unplanned revascularization after index acute myocardial infarction treated with percutaneous coronary intervention. American Heart Journal. 2019; 212: 134–143.
[32] Stone SG, Serrao GW, Mehran R, Tomey MI, Witzenbichler B, Guagliumi G, *et al.* Incidence, predictors, and implications of reinfarction after primary percutaneous coronary intervention in ST-segment-elevation myocardial infarction: the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Trial. Circulation: Cardiovascular Interventions. 2014; 7: 543–551.
[33] Thune JJ, Signorovitch JE, Kober L, McMurray JJV, Swedberg K, Rouleau J, *et al.* Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction. European Journal of Heart Failure. 2011; 13: 148–153.
[34] Wang M, Vaez M, Dorner TE, Rahman SG, Helgesson M, Ivert T, *et al.* Sociodemographic, labour market marginalisation and medical characteristics as risk factors for reinfarction and mortality within 1 year after a first acute myocardial infarction: a register-based cohort study of a working age population in Sweden. BMJ Open. 2019; 9: e033616.
[35] Tian L, Yang Y, Zhu J, Liu L, Liang Y, Li J, *et al.* Impact of Previous Stroke on Short-Term Myocardial Reinfarction in Patients With Acute ST Segment Elevation Myocardial Infarction: An Observational Multicenter Study. Medicine. 2016; 95: e2742.
[36] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2021; 42: 1289–1367.
[37] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018; 39: 119–177.
[38] Kytö V, Prami T, Khanfir H, Hasvold P, Reissell E, Airaksinen J. Usage of PCI and long-term cardiovascular risk in post-myocardial infarction patients: a nationwide registry cohort study from Finland. BMC Cardiovascular Disorders. 2019; 19: 123.
[39] Spitaleri G, Moscarella E, Brugaletta S, Pernigotti A, Ortega-Paz L, Gomez-Lara J, *et al.* Correlates of non-target vessel-related adverse events in patients with ST-segment elevation myocardial infarction: insights from five-year follow-up of the EXAMINATION trial. EuroIntervention. 2018; 13: 1939–1945.
[40] Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, *et al.* Randomized Trial of Preventive Angioplasty in Myocardial Infarction. New England Journal of Medicine. 2013; 369: 1115–1123.
[41] Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, *et al.* Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. Journal of the American College of Cardiology. 2015; 65: 963–972.
[42] Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, *et al.* Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015; 386: 665–671.
[43] Smits PC, Abdel-Wahab M, Neumann F, Boxma-de Klerk BM, Lunde K, Schotborgh CE, *et al.* Fractional Flow Reserve–Guided Multivessel Angioplasty in Myocardial Infarction. New England Journal of Medicine. 2017; 376: 1234–1244.
[44] Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, *et al.* Complete Revascularization with Multivessel PCI for Myocardial Infarction. New England Journal of Medicine. 2019; 381: 1411–1421.
[45] Gupta A, Bajaj NS, Arora P, Arora G, Qamar A, Bhatt DL. FFR-guided multivessel stenting reduces urgent revascularization compared with infarct-related artery only stenting in ST-elevation myocardial infarction: a meta-analysis of randomized controlled trials. International Journal of Cardiology. 2018; 252: 63–67.
[46] Wang L, Han S, Zhang X, Jin Y. Fractional flow reserve-guided complete revascularization versus culprit-only revascularization in acute ST-segment elevation myocardial infarction and multivessel disease patients: a meta-analysis and systematic review. BMC Cardiovascular Disorders. 2019; 19: 49.
[47] Bainey KR, Engstrøm T, Smits PC, Gershlick AH, James SK, Storey RF, *et al.* Complete vs Culprit-Lesion-only Revascularization for ST-Segment Elevation Myocardial Infarction: A Systematic Review and Meta-analysis. JAMA Cardiology. 2020; 5: 881–888.
[48] Ahmad Y, Howard JP, Arnold A, Prasad M, Seligman H, Cook CM, *et al.* Complete Revascularization by Percutaneous Coronary Intervention for Patients with ST-Segment–Elevation Myocardial Infarction and Multivessel Coronary Artery Disease: an Updated Meta-Analysis of Randomized Trials. Journal of the American Heart Association. 2020; 9: e015263.
[49] Levett JY, Windle SB, Filion KB, Cabaussel J, Eisenberg MJ. Meta-Analysis of Complete versus Culprit-only Revascularization in Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Coronary Disease. American Journal of Cardiology. 2020; 135: 40–49.
[50] Pavasini R, Biscaglia S, Barbato E, Tebaldi M, Dudek D, Escaned J, *et al.* Complete revascularization reduces cardiovascular death in patients with ST-segment elevation myocardial infarction and multivessel disease: systematic review and meta-analysis of randomized clinical trials. European Heart Journal. 2020; 41: 4103–4110.
[51] Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, *et al.* Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. New England Journal of Medicine. 2021; 385: 297–308.
[52] Kilic S, Kocabas U, Can LH, Yavuzgil O, Zoghi M. The Severity of Coronary Arterial Stenosis in Patients with Acute ST-Elevated Myocardial Infarction: a Thrombolytic Therapy Study. Cardiology Research. 2018; 9: 11–16.
[53] Spitaleri G, Brugaletta S, Scalone G, Moscarella E, Ortega-Paz L, Pernigotti A, *et al.* Role of ST-Segment Resolution in Patients with ST-Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention (from the 5-Year Outcomes of the EXAMINATION [Evaluation of the Xience-V Stent in Acute Myocardial Infarction] Trial). American Journal of Cardiology. 2018; 121: 1039–1045.
[54] Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, *et al.* Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. New England Journal of Medicine. 2005; 352: 1179–1189.
[55] Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, *et al.* Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366: 1607–1621.
[56] Valgimigli M, Bueno H, Byrne RA, Collet J, Costa F, Jeppsson A, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. European Journal of Cardio-Thoracic Surgery. 2018; 53: 34–78.
[57] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine. 2007; 357: 2001–2015.
[58] Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, *et al.* Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for

ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009; 373: 723–731.
[59] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine. 2009; 361: 1045–1057.
[60] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, *et al.* Long-term use of ticagrelor in patients with prior myocardial infarction. New England Journal of Medicine. 2015; 372: 1791–1800.
[61] De Luca L, Zeymer U, Claeys MJ, Dörler J, Erne P, Matter CM, *et al.* Comparison of P2Y12 receptor inhibitors in patients with ST-elevation myocardial infarction in clinical practice: a propensity score analysis of five contemporary European registries. European Heart Journal - Cardiovascular Pharmacotherapy. 2021; 7: 94–103.
[62] Cesaro A, Taglialatela V, Gragnano F, Moscarella E, Fimiani F, Conte M, *et al.* Low-Dose Ticagrelor in Patients with High Ischemic Risk and Previous Myocardial Infarction: a Multicenter Prospective Real-World Observational Study. Journal of Cardiovascular Pharmacology. 2020; 76: 173–180.
[63] Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, *et al.* Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine. 2019; 381: 1524–1534.
[64] Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and Pharmacodynamics of a Bolus and Infusion of Cangrelor: a Direct, Parenteral P2Y12 Receptor Antagonist. Journal of Clinical Pharmacology. 2010; 50: 27–35.
[65] Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, *et al.* Platelet inhibition with cangrelor in patients undergoing PCI. New England Journal of Medicine. 2009; 361: 2318–2329.
[66] Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, *et al.* Intravenous platelet blockade with cangrelor during PCI. New England Journal of Medicine. 2009; 361: 2330–2341.
[67] White HD, Chew DP, Dauerman HL, Mahaffey KW, Gibson CM, Stone GW, *et al.* Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. American Heart Journal. 2012; 163: 182–190. e4.
[68] Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, *et al.* Effect of platelet inhibition with cangrelor during PCI on ischemic events. New England Journal of Medicine. 2013; 368: 1303–1313.
[69] Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, *et al.* Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet. 2013; 382: 1981–1992.
[70] Grimfjärd P, Lagerqvist B, Erlinge D, Varenhorst C, James S. Clinical use of cangrelor: nationwide experience from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). European Heart Journal - Cardiovascular Pharmacotherapy. 2019; 5: 151–157.
[71] Navarese EP, Kowalewski M, Andreotti F, van Wely M, Camaro C, Kolodziejczak M, *et al.* Meta-Analysis of Time-Related Benefits of Statin Therapy in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. American Journal of Cardiology. 2014; 113: 1753–1764.
[72] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, *et al.* Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. Journal of the American Medical Association. 2001; 285: 1711–1718.
[73] Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, *et al.* Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE it-TIMI 22 trial. Journal of the American College of Cardiology. 2005; 46: 1405–1410.
[74] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376: 1670–1681.
[75] Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015; 385: 1397–1405.
[76] Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, *et al.* Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. Journal of the American College of Cardiology. 2007; 49: 1272–1278.
[77] Zhai C, Cong H, Liu Y, Zhang Y, Liu X, Zhang H, *et al.* Effect of High-Dose Statin Pretreatment on the Incidence of Periprocedural Myocardial Infarction in Patients Undergoing Percutaneous Coronary Intervention: Grading the Evidence through a Cumulative Meta-analysis. Clinical Cardiology. 2015; 38: 668–678.
[78] Berwanger O, Santucci EV, de Barros E Silva PGM, Jesuíno IDA, Damiani LP, Barbosa LM, *et al.* Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: the SECURE-PCI Randomized Clinical Trial. Journal of the American Medical Association. 2018; 319: 1331–1340.
[79] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine. 2015; 372: 2387–2397.
[80] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. New England Journal of Medicine. 2017; 376: 1713–1722.
[81] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, *et al.* Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. New England Journal of Medicine. 2018; 379: 2097–2107.
[82] Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, *et al.* Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. New England Journal of Medicine. 2019; 380: 11–22.
[83] De Luca L. Established and Emerging Pharmacological Therapies for Post-Myocardial Infarction Patients with Heart Failure: a Review of the Evidence. Cardiovascular Drugs and Therapy. 2020; 34: 723–735.
[84] Dahl Aarvik M, Sandven I, Dondo TB, Gale CP, Ruddox V, Munkhaugen J, *et al.* Effect of oral β-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. European Heart Journal - Cardiovascular Pharmacotherapy. 2019; 5: 12–20.
[85] Hwang D, Lee JM, Kim HK, Choi KH, Rhee T, Park J, *et al.* Prognostic Impact of β-Blocker Dose after Acute Myocardial Infarction. Circulation Journal. 2019; 83: 410–417.
[86] Bangalore S, Bhatt DL, Steg PG, Weber MA, Boden WE, Hamm CW, *et al.* B-blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. Circulation. Cardiovascular Quality and Outcomes. 2014; 7: 872–881.
[87] Neumann A, Maura G, Weill A, Alla F, Danchin N. Clinical Events after Discontinuation of β-Blockers in Patients without Heart Failure Optimally Treated after Acute Myocardial Infarction: A Cohort Study on the French Healthcare Databases. Circulation: Cardiovascular Quality and Outcomes. 2018; 11: e004356.
[88] Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, *et al.* Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. New England Journal of Medicine. 2014; 371: 2155–2166.

[89] Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, *et al.* Prasugrel Versus Ticagrelor in Patients with Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation. 2016; 134: 1603–1612.

[90] Motovska Z, Hlinomaz O, Kala P, Hromadka M, Knot J, Varvarovsky I, *et al.* 1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated with Prasugrel Versus Ticagrelor. Journal of the American College of Cardiology. 2018; 71: 371–381.

[91] Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, *et al.* Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet. 2018; 392: 940–949.

[92] Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, *et al.* Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. European Heart Journal. 2020; 41: 3533–3545.

[93] Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, *et al.* Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. Journal of the American Medical Association. 2020; 323: 2407–2416.