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炎症与他汀负荷对冠状动脉介入治疗围术期心肌梗死影响的研究进展

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[关键词]　经皮冠状动脉介入治疗；　炎症；　他汀负荷；　围术期心肌梗死

[摘　要]　围术期心肌梗死(PMI)是经皮冠状动脉介入治疗(PCI)术后常见并发症，它与患者远期死亡风险增加有关。炎症在动脉粥样硬化性心血管疾病(ASCVD)的发生、发展及其预后中起着十分重要的作用。研究表明炎症与 PMI 发生有关。他汀具有调脂、抗炎等作用。冠心病患者 PCI 术前给予他汀负荷能降低 PMI 发生率，并改善临床预后。该综述主要目的是分析炎症与他汀负荷以及 PMI 三者之间的关系。

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Research progress in impacts of inflammation and statin loading on periprocedural myocardial infarction after percutaneous coronary interventions

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[**KEY WORDS**]　percutaneous coronary intervention;　inflammation;　statin loading;　periprocedural myocardial infarction

[**ABSTRACT**]　Periprocedural myocardial infarction (PMI), a common complication after percutaneous coronary intervention (PCI), is associated with an increased risk of mortality.　Inflammation is pivotal in the initiation, progression and prognosis of arteriosclerotic cardiovascular disease (ASCVD).　Studies showed that inflammation plays an important role in the PMI.　Statin therapy can both lipid-lowering and anti-inflammatory effects.　Pretreatment with high-dose statin may have a lower incidence of PMI and improve clinical outcomes in patients with coronary heart disease undergoing PCI.　The main purpose of this review is to analyze the relationships between inflammation, statin loading and PMI.

目前，经皮冠状动脉介入治疗(percutaneous coronary interventions, PCI)已成为冠心病患者最主要的治疗手段，并且应用逐渐增加。随着技术的进步，使得 PCI 操作即刻成功率提高和并发症降低，但术后仍有一些并发症发生，包括心肌梗死、血栓形成、卒中、大出血和死亡，严重影响患者预后，在这些并发症中以围术期心肌梗死(periproceduralmyocardial infarction, PMI)最为常见[1-2]。PMI 与患者术后死亡风险增加有关[2-3]。研究表明，患者 PCI 所致肌酸激酶 MB 同工酶(creatine kinase-MB，CK-MB)和心肌肌钙蛋白(cardiac troponin，cTn)即使轻度升高，其远期死亡风险也会明显增加[4-6]。由于各研究检测的心肌生物标志物和采用的 PMI 定义标准不同，其发生率也有所差异，发生率为 5% ~ 30%[7-8]。研究发现炎症与 PMI 有关[9-11]。他汀除具有调脂作用外，还有抗炎效应[12]。冠心病患者 PCI 期间给予他汀负荷可显著降低 PMI 发生率，改善其临床预后[13-17]。2011 年美国指南推荐 PCI 术前给予他汀负荷可减少 PMI 发生率[18]。该综述主要目的是分析炎症与他汀负荷以及 PMI 三者之间的关系。

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1 围术期心肌梗死定义

2013 美国心血管造影与介入学会(SCAI)对 PMI 进行定义[19],至少应满足以下条件之一:(1)若术前心肌标志物正常,术后 48 h 内 CK-MB≥10 倍正常值上线(upper limits of normal, ULN)或≥5 倍 ULN,同时心电图新发完全性左束支传导阻滞或至少 2 个连续导联新发病理性 Q 波;若无 CK-MB 基线值,术后 48 h 内 cTn 应≥70 倍 ULN 或≥35 倍 ULN,同时心电图存在上述改变;(2)若术前 CK-MB 或 cTn 升高后稳定或回落,术后 CK-MB 绝对增量≥10 倍 ULN 或 cTn 绝对增量≥70 倍 ULN;(3)若术前心肌标志物持续升高,术后 CK-MB 绝对增量≥10 倍最近测量值或 cTn 绝对增量≥70 倍最近测量值,同时存在心电图 ST 段抬高或压低和心肌梗死一致的征象(如新发或恶化的心衰、持续性低血压)。

2018 年在欧洲心脏病协会(ESC)学术年会期间,公布了第 4 版心肌梗死全球定义[20],其中对 PMI 的定义为:(1)cTn 基线正常,cTn 升高≥5 倍参考值上线(upper limits of reference, ULR)99 百分位值;(2)术前 cTn 基线值升高但稳定(差异≤20%)或下降时,术后 cTn 升高>20%,同时 cTn 绝对值需超过 5 倍 ULR 99 百分位值。另外,至少符合以下情况之一:新发缺血性心电图改变;新进展的病理性 Q 波;与缺血相符合的影像学证据表明新发心肌活力丧失或新的节段性室壁运动异常;血管造影显示手术导致血流受限如冠状动脉夹层、大的冠状动脉或边支血管闭塞/血栓、侧支循环破坏、远端栓塞。

从上述两个定义可知,ESC 对 PMI 的定义相对宽松。然而,对于 ESC 的定义,颜红兵等[21]认为,或许需持谨慎态度,因为在临床实践中,若按照这一标准,会发现 PMI 发生率可高达 20%,而这些患者在随访中有相当一部分患者临床事件发生率并没有显著升高。此外,ESC 没有对心肌标志物持续升高情况下的 PMI 进行定义。

2 炎症与动脉粥样硬化和围术期心肌梗死的关系

含有大量炎性细胞的动脉粥样硬化斑块破裂是引发心血管事件的常见始发因素[22]。T 细胞、巨噬细胞和肥大细胞在病变处被激活,导致炎性细胞因子(例如干扰素 γ、白细胞介素 1 和肿瘤坏死因子)分泌,进而降低斑块的稳定性,此外,激活巨噬细胞和肥大细胞,还导致金属蛋白酶和半胱氨酸蛋白酶的释放,后两者能直接抑制纤维帽中的胶原蛋白和细胞外基质的合成,使纤维帽变薄,导致斑块不稳定[23]。研究表明,炎症反应标志物,如 C 反应蛋白(C-reactive protein, CRP)、高敏 C 反应蛋白(high-sensitivityC-reactiveprotein, hs-CRP)白细胞介素 6(interleukin-6, IL-6)以及血小板淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)等升高与心血管不良事件发生风险增加密切相关[24-30]。

CANTOS 研究[31]是一项涉及近 40 个国家 10 061 例心肌梗死后的稳定型冠心病患者的多中心、随机、双盲、安慰剂对照的临床试验,所有患者中约有 93.4% 的患者常规接受降脂治疗,其中他汀使用比例 91.1%,但仍有残余炎症风险(hs-CRP ≥2 mg/L)。结果表明,卡纳单抗(人源性抗 IL-1β 单克隆抗体)150 mg 每 3 个月皮下注射 1 次,在不影响血脂水平的情况下,能显著降低主要终点事件(包括非致死性心肌梗死、非致死性卒中和心血管死亡)的发生率(HR=0.85, P=0.021)。

CANTOS 研究[31]第一次证明通过抗炎治疗也能降低冠心病患者的心血管事件风险,将动脉粥样硬化的“炎症假说”上升到了“炎症理论”。然而,近期公布的 CIRT 研究[32],共纳入 4 786 例既往心肌梗死或冠状动脉多支病变且合并 2 型糖尿病或代谢综合征的稳定型冠心病患者。结果表明,与安慰剂相比,小剂量甲氨蝶呤并不能降低 IL-1β、IL-6、hsCRP 水平和心血管事件风险。同样都是以稳定型冠心病且均已充分接受降脂治疗的高危患者为研究对象,但 CIRT 研究却未能得出与 CANTOS 研究一样的结论,分析其原因:(1)CANTOS 研究纳入的对象是炎症反应较高的患者,其研究人群的 hs-CRP 和 IL-6 浓度中位数水平分别为 4.2 mg/L 和 2.6 ng/L,而 CIRT 研究纳入人群的 hs-CRP 和 IL-6 浓度中位数水平均低于 CANTOS 研究,分别为 1.6 mg/L、2.4 ng/L,患者基线炎症水平的不同很可能影响了抗炎治疗的效应;(2)可能与卡纳单抗能直接抑制 IL-1β/IL-6 信号通路有关,而该通路在动脉粥样硬化血栓形成中具有重要作用;虽然甲氨蝶呤作为类风湿关节炎首选药物,具有抗炎作用,但其作用机制尚不清楚,可能与其能增加腺苷介导的抗炎作用有关[33-34],而与动脉粥样硬化的炎症机制关系并不清楚。对于抗炎治疗能否改善急性冠状动脉综合征(acute coronary syndromes, ACS)患者的预后,尚需进一步研究证实。

关于炎症与 PMI 的临床研究发现,PCI 术前的

炎症状态与 PMI 的发生风险有关[9-11]，可能机制为，基线炎症水平越高，PCI 术后炎症反应越强，进而导致更多白细胞活化，分泌更多炎症介质、生长因子和组织因子加剧内皮细胞损伤、引发冠状动脉痉挛、刺激血小板聚集和激活外源性凝血途径，这一系列的反应最终导致小血管闭塞或微血栓形成[35-36]。此外，也有研究报道，认为 PMI 发生与冠状动脉介入治疗部位斑块负荷大小有关，因为斑块负荷越重，在经球囊扩张和支架释放时会造成更多斑块内容物碎屑被挤出至血管腔内，并随血流送往冠状动脉远端，进而发生微栓塞；另外，支架植入造成边支血管闭塞，可能也 PMI 有关[7]。

3　他汀的抗炎效应

Ridker 等[37] 早在 1998 年就发现他汀既能调脂，也能抗炎。他汀抗炎假说认为，他汀可以抑制单核细胞表达促炎因子（例如：肿瘤坏死因子 α 和 IL-1β）以及 CRP 基因转录[38-39]，和促进内皮细胞中抗炎因子和细胞保护因子的表达[40]，并且其抗炎效应与调脂无关[39]。此外，有研究表明，他汀可以使动脉粥样硬化斑块中核因子 κB（nuclear factor kappa B，NF-κB）活性降低、巨噬细胞和 T 细胞浸润减少[41]。最近来自 ESC 的共识进一步支持了他汀的抗炎效应[42]。一些临床研究发现无论是“健康”人群，还是冠心病患者，通过他汀的抗炎效应均能够取得临床获益[12, 43-45]。而在这些研究中，最为人所熟知的是 JUPITER 研究[12]，该研究共纳入 hs-CRP ≥2 mg/L，但低密度脂蛋白胆固醇（low density lipoprotein cholesterol，LDLC）< 3.4 mmol/L 的患者 17 802 例，结果表明，接受瑞舒伐他汀 20 mg/d 治疗，随访 1.9 年（最长 5 年），与安慰剂比较，LDLC 和 hs-CRP 分别降低 50% 和 37%，主要不良心血管事件（major adverse cardiac events，MACE）风险降低了 54%，该研究认为对于胆固醇不高，但 hs-CRP 升高的人群，瑞舒伐他汀治疗同样可以显著降低 MACE 的发生风险。

PCI 可导致冠状动脉局部发生栓塞并发症，并促进炎症活性[46-48]。早期他汀负荷对 PCI 治疗的冠心病患者带来的临床获益可能或多或少还与该类药物的抗炎作用有关[49-51]，因为他汀抗炎能在服药后短时间内起效[13]。MIRACL 的一项子研究对 2 402 例患者进行分析[52]，表明在 ACS 患者中他汀负荷治疗具有抗炎作用。2018 年 11 月份，《美国心脏协会杂志》（JAHA）发表了一项韩国的研究[53]，该研究表明采用阿托伐他汀 40 mg 或 80 mg 或瑞舒伐他汀 20 mg 治疗较他汀常规剂量治疗，hs-CRP 较基线下降幅度更明显（34.8±6.6 比 24.6±2.1，P=0.04）。

关于其他非他汀类调脂药物的研究，如前蛋白转化酶枯草溶菌素 9（proproteinconvertasesubtilisin / kexin type 9，PCSK9）抑制剂，目前还没有充分证据表明具有抗炎效应[54-56]；而关于肠道胆固醇吸收抑制剂，有研究表明，辛伐他汀联合依折麦布较单用辛伐他汀更易使 LDLC 和 hs-CRP 双重达标（LDLC <1.8 mmol/L 且 hs-CRP<2 mg/L）[45]，机制性研究和加速动脉粥样硬化的动物模型研究认为，依折麦布可能具有抗炎效应，且与调脂作用无关[57-58]。

4　他汀负荷与围术期心肌梗死

一系列的观察性研究证实，在 PCI 术前给予负荷剂量的他汀能够显著降低 PMI 的发生率，改善患者临床预后，降低死亡风险[59-61]。一项纳入 1 552 例 PCI 治疗的稳定型心绞痛和不稳定型心绞痛患者的回顾性研究[62]，发现与对照组相比，他汀治疗可显著降低 PMI 发生率；此外，随着 hs-CRP 水平的增加，PMI 发生率也随之增加；他汀治疗的患者术后 hs-CRP 的水平更低。

ARMYDA 研究[14] 表明，对行择期 PCI 且未服用过他汀治疗的慢性稳定型心绞痛患者，阿托伐他汀 40 mg/d 连用 1 周可将 PMI 风险降低 81%，30 天的 MACE 发生率降低 13%，且该获益主要归因于 PMI 发生率的降低。NAPLES II 研究[13] 对未曾服用他汀治疗的 668 例行择期 PCI 的稳定型心绞痛患者进行分析发现，术前 24 h 内阿托伐他汀 80 mg 负荷可显著降低 PMI 发生率；在事后分析中发现，只有对 CRP 高的患者进行阿托伐他汀负荷才能降低 PMI 发生率，提示 PCI 术前他汀负荷能降低 PMI 发生率或许与他汀类药物的抗炎效应有关。由于 ARMYDA 研究入选人群为稳定型心绞痛患者。时隔 3 年后的 ARMYDA-ACS 研究[15] 和之后的 Yun KH 等人的一项随机对照研究[16]，对非 ST 段抬高型急性冠状动脉综合征（non-ST segment elevation acute coronary syndrome，NSTE-ACS）患者进行分析，结果同样证明了阿托伐他负荷可降低 PMI 和 30 天的 MACE 发生率，且 MACE 的降低主要与 PMI 发生减少有关；此外，ARMYDA-ACS 研究发现，在炎症水平高的患者中，阿托伐他汀负荷治疗具有更强的抗炎

作用。

无论是 ARMYDA 研究,还是之后的 ARMYDA-ACS 研究,其主要研究人群均是未服用过他汀治疗的冠心病患者。然而,在现实中,大部分冠心病患者都有长期他汀用药史,那么对于这些患者在 PCI 术前短期他汀负荷是否会有同样的获益呢? ARMYDA-RECAPTURE 研究[17]表明,他汀负荷对已长期接受他汀治疗的患者仍然能够取得同样的临床获益;此外,该研究还发现对 ACS 患者他汀负荷可能会有更明显的获益。SECURE-PCI 研究[63],对 2 710 例已行 PCI 治疗的患者分析发现,他汀负荷治疗的患者 30 天的 MACE 发生风险降低了 28%,提示对于行 PCI 治疗的 ACS 患者给予他汀负荷或许会有显著临床获益。

然而,来自东亚人群的两项试图证实他汀负荷对冠心病患者预后改善的多中心、随机对照研究却均以失败告终。ALPACS 研究[64],纳入中韩两国共 449 例拟行 PCI 治疗的 NSTE-ACS 患者(最终 335 例患者接受 PCI),在行 PCI 治疗前 12 h 和 2 h 分别给予阿托伐他汀 80 mg 和 40 mg,随后阿托伐他汀 40 mg/d 维持,结果表明,阿托伐他汀负荷治疗与阿托伐他汀 40 mg/d 治疗相比,并不能使患者获益。ISCAP 研究[65]纳入中国 50 个中心拟行 PCI 的 1202 例 NSTE-ACS 或稳定性冠心病患者,与常规治疗相比,在 PCI 术前连续服用阿托伐他汀 80 mg/d 共 2 天,继之 40 mg/d 用 30 天,结果显示大剂量阿托伐他汀序贯治疗仍然不能减少 PMI 和 MACE 发生率。

虽然 ALPACS 研究近似模拟了 ARMYDA-ACS 研究,但却得出了相反的结论,其中可能原因是 ALPACS 研究中 33%(164/499)的患者在冠状动脉造影后未再进一步行 PCI,而 ARMYDA-ACS 研究中仅有 10%(20/191)的患者在造影后未行 PCI 治疗,这一差异有可能会使得 ALPACS 研究中患者术后心血管风险将低,从而削弱了他汀负荷的心脏保护作用。而 ISCAP 研究与以往研究区别之一在于,它最后一次他汀给药是在术前头一天晚上,而以往的研究是在术前 2 ~4 h 内最后一次给药,同样这可能也会使得他汀的保护作用在手术期间被减弱。

综上所述,炎症在 PMI 的发病机制中可能发挥着重要作用。他汀类药物在降胆固醇作用之外具有一定程度的抗炎作用,在 PCI 术前合适的时间进行他汀负荷治疗可能会降低冠心病患者,尤其是炎症反应水平较高患者的 PMI 发生风险,并改善临床预后。虽然,国内指南[66]以及一些亚洲人群研究不建议 ACS 患者 PCI 术前给予他汀负荷治疗,但对于炎症反应水平较高的冠心病患者,术前给予他汀负荷治疗可能会有效降低 PMI 发生风险。当然,这一猜测尚需要相关的临床证据支持。

[参考文献]

[1] Cho MS, Ahn JM, Lee CH, et al. Differential rates and clinical significance of periprocedural myocardial infarction after stenting or bypass surgery for multivessel coronary disease according to various definitions[J]. JACC Cardiovasc Interv, 2017, 10 (15): 1498-1507.

[2] Zeitouni M, Silvain J, Guedeney P, et al. Periprocedural myocardial infarction and injury in elective coronary stenting[J]. Eur Heart J, 2018, 39 (13): 1100-1109.

[3] Park DW, Kim YH, Yun SC, et al. Frequency, causes, predictors, and clinical significance of peri-procedural myocardial infarction following percutaneous coronary intervention[J]. Eur Heart J, 2013, 34 (22): 1662-1669.

[4] Brener SJ, Ellis SG, Schneider J, et al. Frequency and long-term impact of myonecrosis after coronary stenting[J]. Eur Heart J, 2002, 23 (11): 869-876.

[5] Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention[J]. J Am Coll Cardiol, 2003, 42 (8): 1406-1411.

[6] Abdelmeguid AE, Topol EJ, Whitlow PL, et al. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions[J]. Circulation, 1996, 94 (7): 1528-1536.

[7] Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention[J]. N Engl J Med, 2011, 364 (5): 453-464.

[8] Babu GG, Walker JM, Yellon DM, et al. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection[J]. Eur Heart J, 2011, 32 (1): 23-31.

[9] Kleveland O, Kunszt G, Bratlie M, et al. Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial[J]. Eur Heart J, 2016, 37 (30): 2406-2413.

[10] Patti G, Mangiacapra F, Ricottini E, et al. Correlation of platelet reactivity and C-reactive protein levels to occurrence of peri-procedural myocardial infarction in patients undergoing percutaneous coronary intervention (from the ARMYDA-CRP study)[J]. Am J Cardiol, 2013, 111 (12): 1739-1744.

[11] Goldberg A, Gruberg L, Roguin A, et al. Preprocedural C-reactive protein levels predict myocardial necrosis after successful coronary stenting in patients with stable angina[J]. Am Heart J, 2006, 151 (6): 1265-1270.

[12] Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein[J]. N Engl J Med, 2008, 359 (21): 2195-2207.

[13] Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial in-

farction[J]. J Am Coll Cardiol, 2009, 54 (23): 2157-2163.
[14] Pasceri V, Patti G, Nusca A, et al. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (atorvastatin for reduction of myocardial damage during angioplasty) study[J]. Circulation, 2004, 110 (6): 674-678.
[15] Patti G, Pasceri V, Colonna 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[J]. J Am Coll Cardiol, 2007, 49 (12): 1272-1278.
[16] Yun KH, Jeong MH, Oh SK, et al. The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome[J]. Int J Cardiol, 2009, 137 (3): 246-251.
[17] Di Sciascio G, Patti G, Pasceri V, et al. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (atorvastatin for reduction of myocardial damage during angioplasty) randomized trial[J]. J Am Coll Cardiol, 2009, 54 (6): 558-565.
[18] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions[J]. J Am Coll Cardiol, 2011, 58 (24): e44-122.
[19] Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI)[J]. J Am Coll Cardiol, 2013, 62 (17): 1563-1570.
[20] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018)[J]. Eur Heart J, 2018, 13(4): 305-338.
[21] 颜红兵, 霍 勇. 解读《第4版心肌梗死通用定义》: 变化、意义与挑战[J]. 中国介入心脏病学杂志, 2018, 26 (9): 501-503.
[22] Libby P. Current concepts of the pathogenesis of the acute coronary syndromes[J]. Circulation, 2001, 104 (3): 365-372.
[23] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease[J]. N Engl J Med, 2005, 352 (16): 1685-1695.
[24] Yeh ET, Anderson HV, Pasceri V, et al. C-reactive protein: linking inflammation to cardiovascular complications[J]. Circulation, 2001, 104 (9): 974-975.
[25] Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men[J]. N Engl J Med, 1997, 336 (14): 973-979.
[26] Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease[J]. Circulation, 2001, 103 (13): 1813-1818.
[27] Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women[J]. N Engl J Med, 2000, 342 (12): 836-843.
[28] Buckley DI, Fu R, Freeman M, et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the US Preventive Services Task Force[J]. Ann Intern Med, 2009, 151 (7): 483-495.
[29] Swerdlow DI, Holmes MV, Kuchenbaecker KB, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis[J]. Lancet, 2012, 379 (9822): 1214-1224.
[30] Kurtul A, Murat SN, Yarlioglues M, et al. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes[J]. Am J Cardiol, 2014, 114 (7): 972-978.
[31] Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease[J]. N Engl J Med, 2017, 377 (12): 1119-1131.
[32] Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events[J]. N Engl J Med, 2018, 380(8): 752-762.
[33] Chan ES, Cronstein BN. Methotrexate: how does it really work?[J]. Nat Rev Rheumatol, 2010, 6 (3): 175-178.
[34] Cronstein BN, Naime D, Ostad E. The antiinflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation[J]. J Clin Invest, 1993, 92 (6): 2675-2682.
[35] Azar RR, Waters DD. The inflammatory etiology of unstable angina[J]. Am Heart J, 1996, 132 (5): 1101-1106.
[36] Saadeddin SM, Habbab MA, Sobki SH, et al. Association of systemic inflammatory state with troponin I elevation after elective uncomplicated percutaneous coronary intervention[J]. Am J Cardiol, 2002, 89 (8): 981-983.
[37] Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators[J]. Circulation, 1998, 98 (9): 839-844.
[38] Ferro D, Parrotto S, Basili S, et al. Simvastatin inhibits the monocyte expression of proinflammatory cytokines in patients with hypercholesterolemia[J]. J Am Coll Cardiol, 2000, 36 (2): 427-431.
[39] Kleemann R, Verschuren L, De Rooij BJ, et al. Evidence for anti-inflammatory activity of statins and PPAR alpha activators in human C-reactive protein transgenic mice in vivo and in cultured human hepatocytes in vitro[J]. Blood, 2004, 103 (11): 4188-4194.
[40] Ali F, Zakkar M, Karu K, et al. Induction of the cytoprotective enzyme heme oxygenase-1 by statins is enhanced in vascular endothelium exposed to laminar shear stress and impaired by disturbed flow[J]. J Biol Chem, 2009, 284 (28): 18882-18892.
[41] Martin-Ventura JL, Blanco-Colio LM, Gomez-Hernandez A, et al. Intensive treatment with atorvastatin reduces inflammation in mononuclear cells and human atherosclerotic lesions in one month[J]. Stroke, 2005, 36 (8): 1796-1800.
[42] Tunon J, Badimon L, Bochaton-Piallat ML, et al. Identifying the anti-inflammatory response to lipid lowering therapy: a position paper from the working group on atherosclerosis and vascular biology

of the European Society of Cardiology[J]. Cardiovasc Res, 2019, 115 (1): 10-19.

[43] Toso A, Leoncini M, Maioli M, et al. Relationship between inflammation and benefits of early high-dose rosuvastatin on contrast-induced nephropathy in patients with acute coronary syndrome: the pathophysiological link in the PRATO-ACS study (protective effect of rosuvastatin and antiplatelet therapy on contrast-induced nephropathy and myocardial damage in patients with acute coronary syndrome undergoing coronary intervention)[J]. JACC Cardiovasc Interv, 2014, 7 (12): 1421-1429.

[44] Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease[J]. N Engl J Med, 2005, 352 (1): 29-38.

[45] Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT [J]. Circulation, 2015, 132 (13): 1224-1233.

[46] Lansky AJ, Stone GW. Periprocedural myocardial infarction: prevalence, prognosis, and prevention[J]. Circ Cardiovasc Interv, 2010, 3 (6): 602-610.

[47] Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction[J]. Eur Heart J, 2012, 33 (20): 2551-2567.

[48] Abbate A, Van Tassell BW, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-anakinra remodeling trial (2) (VCU-ART2) pilot study][J]. Am J Cardiol, 2013, 111 (10): 1394-1400.

[49] Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study[J]. Jama, 2001, 286 (1): 64-70.

[50] Correia LC, Sposito AC, Lima JC, et al. Anti-inflammatory effect of atorvastatin (80 mg) in unstable angina pectoris and non-Q-wave acute myocardial infarction[J]. Am J Cardiol, 2003, 92 (3): 298-301.

[51] Macin SM, Perna ER, Farias EF, et al. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study[J]. Am Heart J, 2005, 149 (3): 451-457.

[52] Kinlay S, Schwartz GG, Olsson AG, et al. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study[J]. Circulation, 2003, 108 (13): 1560-1566.

[53] Kim J, Park KT, Jang MJ, et al. High-intensity versus non-high-intensity statins in patients achieving low-density lipoprotein cholesterol goal after percutaneous coronary intervention[J]. J Am Heart Assoc, 2018, 7 (21): e009517.

[54] Cui CJ, Li S, Zhu CG, et al. Enhanced pro-protein convertase subtilisin/kexin type 9 expression by C-reactive protein through p38 MAPK-HNF 1 alpha pathway in HepG2 cells[J]. J Cell Mol Med, 2016, 20 (12): 2374-2383.

[55] Bohula EA, Giugliano RP, Leiter LA, et al. Inflammatory and cholesterol risk in the fourier trial[J]. Circulation, 2018, 138 (2): 131-140.

[56] Pradhan AD, Aday AW, Rose LM, et al. Residual inflammatory risk on treatment with pcsk9 inhibition and statin therapy[J]. Circulation, 2018, 138 (2): 141-149.

[57] Gomez-Garre D, Munoz-Pacheco P, Gonzalez-Rubio ML, et al. Ezetimibe reduces plaque inflammation in a rabbit model of atherosclerosis and inhibits monocyte migration in addition to its lipid-lowering effect[J]. Br J Pharmacol, 2009, 156 (8): 1218-1227.

[58] Qin L, Yang YB, Yang YX, et al. Anti-inflammatory activity of ezetimibe by regulating NF-kappa B/MAPK pathway in THP-1 macrophages[J]. Pharmacology, 2014, 93 (1-2): 69-75.

[59] Ko DT, Wijeysundera HC, Yun L, et al. Effectiveness of preprocedural statin therapy on clinical outcomes for patients with stable coronary artery disease after percutaneous coronary interventions [J]. Circ Cardiovasc Qual Outcomes, 2011, 4 (4): 459-466.

[60] Chan AW, Bhatt DL, Chew DP, et al. Early and sustained survival benefit associated with statin therapy at the time of percutaneous coronary intervention[J]. Circulation, 2002, 105 (6): 691-696.

[61] Herrmann J, Lerman A, Baumgart D, et al. Preprocedural statin medication reduces the extent of periprocedural non-Q-wave myocardial infarction[J]. Circulation, 2002, 106 (17): 2180-2183.

[62] Chan AW, Bhatt DL, Chew DP, et al. Relation of inflammation and benefit of statins after percutaneous coronary interventions[J]. Circulation, 2003, 107 (13): 1750-1756.

[63] Berwanger O, Santucci EV, De Barros ESPGM, 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 [J]. Jama, 2018, 319 (13): 1331-1340.

[64] Jang Y, Zhu J, Ge J, et al. Preloading with atorvastatin before percutaneous coronary intervention in statin-naive Asian patients with non-ST elevation acute coronary syndromes: a randomized study[J]. J Cardiol, 2014, 63 (5): 335-343.

[65] Zheng B, Jiang J, Liu H, et al. Efficacy and safety of serial atorvastatin load in Chinese patients undergoing elective percutaneous coronary intervention: results of the ISCAP (intensive statin therapy for Chinese patients with coronary artery disease undergoing percutaneous coronary intervention) randomized controlled trial [J]. European Heart J Suppl, 2015, 17 (suppl B): B47-B56.

[66] 中华医学会心血管病学分会介入心脏病学组, 中国医师协会心血管内科医师分会血栓防治专业委员会, 中华心血管病杂志编辑委员会. 中国经皮冠状动脉介入治疗指南(2016)[J]. 中华心血管病杂志, 2016, (5): 382-400.

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