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NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

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Most Promising Therapies in Interventional Cardiology

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Abstract

Purpose of Review The last 40 years of clinical research in interventional cardiology were extraordinarily innovative. This article will review the most promising up and coming interventional cardiovascular therapies, with a primary focus on the treatment of coronary artery disease.

Recent Findings From the first stent, to the first transcatheter aortic valve implantation (TAVI), and the left appendage closure technique, percutaneous interventions revolutionized the treatment of multiple diseases and dramatically improved the prognosis of many patients. While these advances have decreased the risk of mortality in some patients (such as ST-elevation myocardial infarction), 15% of acute coronary syndrome (ACS) patients still experience recurrent ischemic events within the first year, challenging us to develop new pharmaceutical targets and new devices.

Summary The continued emergence of data supporting inflammation as a risk factor and pharmacologic target as well as data supporting the importance of cholesterol efflux have identified novel therapeutic targets that may play a major role in the improvement of prognosis of patients with coronary artery disease. In addition, novel medical devices are being developed to allow even earlier detection of acute cardiac events and to support high-risk percutaneous coronary interventions. Advances in computing and the ability to analyze large datasets will allow us to use artificial intelligence to augment the clinician patient experience, both in and out of the catheterization laboratory, with live procedural guidance as well as pre- and post-operative prognostication tools.

Keywords Percutaneous coronary intervention · Implantable device · Acute coronary syndrome · Coronary artery disease

Abbreviations

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
BMS	Bare-metal stent
BVS	Bioresorbable vascular scaffold
DAPT	Dual anti-platelet therapy
DES	Drug-eluting stent
HDL	High-density lipoprotein
IVUS	Intravascular Ultra sound
LDL	Low-density lipoprotein
OCT	Optical coherence tomography
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
TAVI	Transcatheter aortic valve implantation

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Introduction

The last 40 years of clinical research in interventional cardiology were extraordinarily prolific. From the first percutaneous coronary intervention (PCI), to the first transcatheter aortic valve implantation (TAVI), and the left appendage closure technique, percutaneous interventions revolutionized the treatment of multiple diseases and dramatically improved the prognosis of many patients [1–4]. These advances would not have been possible without simultaneous innovation in pharmacotherapy, including development of potent antithrombotic agents and therapies that effectively lower low-density lipoprotein (LDL). [5]

While these advances have decreased the risk of mortality, 15% of acute coronary syndrome (ACS) patients still experience recurrent ischemic events within the first year, challenging us to develop new pharmaceutical targets and new devices [6, 7]. The evolution of the residual inflammatory risk model and the cholesterol efflux hypothesis has identified novel therapeutic targets that may play a major role in the improvement of prognosis of patients with coronary artery disease (CAD) [8, 9]. Novel medical devices are being developed to allow early detection of acute cardiac events and to support high-risk PCI [10]. Advances in computing and the ability to analyze large datasets will allow us to use artificial intelligence to augment the clinician patient experience, both in and out of the catheterization laboratory, with live procedural guidance as well as pre- and post-operative prognostication tools [11]. This article will review the most promising interventional cardiovascular therapies in the next 10 years for patients with ACS and CAD.

Will the "Old" PCI Still Be the Recommended Treatment for Stable Single-Vessel CAD in the Next 10 Years?

While there is no doubt that PCI changed the prognosis of patients with ST-elevation myocardial infarction (STEMI) over the past 40 years, leading to a 40% absolute reduction in mortality, the evidence supporting the use of PCI has been less robust among patients with stable angina [12]. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study failed to demonstrate a benefit for PCI on the composite ischemic endpoint compared to optimal medical therapy [13]. In contrast, the FAME 2 (Fractional Flow Reserve (FFR)-Guided Percutaneous Coronary Intervention (PCI) Plus Optimal Medical Treatment (OMT) Verses OMT) trial was stopped prematurely due to overwhelming efficacy of PCI compared to medically treated subjects [14]. Until last year, these conflicting results were interpreted in line with the several studies conducted over the past 20 years, including the ACME (Angioplasty Compared to Medicine) Trial, which demonstrated that revascularization improves angina in severe single-vessel disease [15, 16]. In 2017, the first sham-controlled PCI randomized trial was conducted to shed further light on this question. The ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial failed to demonstrate that PCI among patients with stable single-vessel disease (approximately 10% of the PCI volume) was associated with greater symptom relief compared with optimal medical therapy alone [17]. The accompanied editorial entitled "last nail in the coffin for PCI in stable angina" questioned the utility of PCI in this setting, suggesting that PCI should not be recommended in stable patients [18]. Despite the strengths of this sham-controlled trial, some limitations should curb its impact on daily practice. First, it is difficult to generalize their findings, as one third of patients had a fractional flow reserve > 0.8, a group that likely would not have been revascularized in real practice settings. Second, patients were called 2–4 times per week during the first 6 weeks to optimize medical therapy, which may be unrealistic in real clinical settings. Third, the difference in baseline exercise time between the PCI and sham group (38 s) was larger than the anticipated effect size of the intervention (30 s). The standard deviation of exercise time was greater than planned, and the trial was therefore underpowered. Finally, the "sham nature" of the trial effectively selected the lowest-risk patients, as one-in-five deemed eligible, declined participation which may explain (at least in part) how the mean baseline exercise time was > 8 min, while 39% of patients in the trial had a class 3 angina. Current guidelines recommend PCI for single-vessel disease only when significant symptoms and ischemia are present, despite maximally tolerated medical therapy [19]. Based on the previous studies and according to these limitations, the next round of guidelines will likely not be impacted by the ORBITA Trial.

The ongoing ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) Trial aims to assess whether an initial invasive strategy of catheterization and revascularization (PCI or coronary artery bypass grafting (CABG)) + optimal medical therapy (OMT) is superior to a conservative strategy of OMT alone, among 8000 patients with CAD and a moderate or severe ischemia [20•]. With results expected as late as 2020, the ISCHEMIA trial is expected to shed light on this much-debated issue.

What Future for the Stent?

From the first to the fourth generation of drug-eluting stents, major progress has been made in the reduction of stent-related complications [21]. However, with advances in stent technology, interventional cardiologists have more choices than ever before [22]. New stents with bio-absorbable polymers may increase the safety profile of the stent and improve their efficacy compared to durable polymer drug-eluting stent [23]. Although a drug-eluting stent (DES) may now become "bare-metal stent (BMS)-like" in 3 to 4 months, the complexity of the elution profile still remains a limitation. The development of new polymer-free DES may have several advantages: attenuating late adverse effects that might be related to the polymer, improving the surface integrity since there is no polymer to be sheared from the stent struts, and finally shortening the duration of dual anti-platelet therapy (DAPT) [24].

Different promising technologies to achieve this goal include drug release via a porous-eluting stent (Biosensor) or a drug elution controlled by diffusion physics stent (Medtronic) [25]. Whatever the technology, metallic stents with bio-absorbable polymers or polymer-free systems, the safety and efficacy profiles of new stents will need to be compared to the newest DES with non-erodable polymers and also with fully bio-absorbable stents.

A goal of interventional cardiology is to reduce the risk of complications. This desire was the basis for the radial approach as well as the use of bioresorbable vascular scaffolds (BVS). BVS was developed to overcome the long-term stent-related complications and leave the coronary artery free of any device. The presence of a stent, which limits the vasomotion and promotes chronic inflammation, is a well-known cause of late-stent thrombosis and neoatheroma. The ABSORB III (A Clinical Evaluation of Absorb™ BVS, the Everolimus-Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) randomized trial demonstrated that the everolimus-eluting bioresorbable vascular scaffold (Absorb) was non-inferior to the everolimus-eluting cobalt-chromium (Xience) stent with respect to target lesion failure, resulting in FDA regulatory approval [26]. However, 3-year data showed that BVS was associated with higher rates of target vessel myocardial infarction and thrombosis [27]. Similarly, the AIDA (Amsterdam Investigator-initiated Absorb Strategy All-comers Trial) trial was stopped prematurely due to higher rates of thrombosis in the BVS group [28]. Despite this setback, there is still hope for BVS in the future as similar struggles in the development of early generation DES that were subsequently overcome by improvements in technology [29]. Indeed, new BVS (DESolve (Elixir Medical Corporation; Milpitas, CA), ART Pure (Arterial Remodeling Technologies SA; Paris, France), Magmaris and Fantom stents (REVA Medical, Inc.; San Diego, CA)) have been developed with an improved profile which simplifies the delivery of the stent and facilitates the reendothelization process.

The Future Intracoronary Imaging

The quality of the stent is only one of the factors that can be improved to help reduce the risk of complication and recurrent events. The sizing, the apposition, and the early recognition of any mechanical complication, such as dissection, are also strong predictors of acute ischemic events [30]. There is a growing body of evidence which supports the clinical use of intravascular imaging to reduce the risk of recurrent ischemic events and guide the placement of the stent [19]. However, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) remains markedly underused in the USA and Europe [31].

There are many reasons that may be contributing to the low rate of use of these techniques. The large number of images acquired by OCT can make it difficult to interpret and requires a high level of training to be adequately comprehended. Therefore, it can be difficult to make a clinical decision based on these images. However, new-generation OCT systems have software which automates some tasks and reduces some of the burden imposed by manual processes. For example, the Ilumien Optis I System (St. Jude Medical, St. Paul, Minnesota) has automated luminal profile measurements which facilitate selection of stent diameter and length and aids in the real-time assessment of stent deployment combined with tracking-based angiography to allow co-registration. The inability of programs to automatically identify different plaque characteristics has also hampered widespread use of these tools, as it can be time consuming. To our knowledge, automated plaque characterization with OCT is still not available. Progress is being made, however, with respect to the development of algorithms for automated classification using tissue characteristics on OCT [32].

Other reasons for the underuse of OCT include the increased amount of radio-contrast needed for each run of OCT (15–30 ml), which increases the risk of contrast-induced nephropathy [33]. This is particularly undesirable in patients with chronic kidney disease. Alternative biocompatible non-contrast flush media with adequate optical transparency are needed to limit the risk of renal insufficiency [34]. Lastly, the additional cost of intravascular imaging may limit its use in some countries. Reimbursement of IVUS and OCT in Japan resulted in widespread utilization [31]. Cost-effectiveness studies are needed to justify the costs to health insurers and increase the use of this technology.

New Devices Can Improve the Symptom to Balloon Time

Both American and European guidelines recommended a reperfusion strategy based on a network of primary PCI-capable and non-PCI-capable hospitals [34]. The ultimate goal of this recommendation is to decrease the transfer time of patients with ACS to the catheterization laboratory. In contrast, little is done to reduce the delay in time from patient's onset of symptoms to reporting to an emergency room, known as symptom-to-door time. Currently, recommendations rely solely on patient education and patient recognition of symptoms. This is particularly difficult as patients may experience atypical symptoms or no symptoms at all [35]. An implantable medical device, the AngelMed Guardian system, was recently approved by the Food and Drug Administration (FDA). The device, designed for use in ACS patients at high risk for a recurrent event, detects rapidly progressive ST segment deviations and subsequently alerts the patient to seek medical attention via an internal and an external device [36]. The ultimate goal of this device is to detect potentially silent MIs and decrease event-to-door time in an effort to improve clinical outcomes. In a clinical trial (AngeLmed Early Recognition and Treatment of STEMI), subjects with the AngelMed Guardian System is being evaluated to determine if there is a decrease in a composite of cardiac/unexplained death, development of new Q-Wave MI, and late arrival at a medical facility for an ACS event (time-to-door > 2 h) compared to subjects with the device implanted, but deactivated. Further, the device is being evaluated to determine if it increases the positive predictive value for presentation at emergency room for an MI compared to presentation for symptoms alone coupled with a decrease in the false-positive rate.

Lowering LDL Cholesterol

Despite maximal medical therapy, recurrent ACS events have been related, in part, to elevated levels of low-density lipoprotein cholesterol (LDL-C) [37]. Studies consistently demonstrated a reduction in risk when LDL-C is lowered with statin therapy compared with placebo [5]. This efficacy of LDL-C-lowering therapy has been shown both with high-intensity statin therapy compared with moderate-intensity statin therapy, and finally with ezetimibe (a non-stating therapy), compared with placebo, when added to a statin [38, 39]. A recent meta-analysis demonstrated that LDL-C lowering below the lowest current targets (as low as 21 mg/dL) was associated with a 20% reduction in cardiovascular risk for every 38.7 mg/dL reduction in LDL-C, independent of baseline levels [40].

Additional avenues for LDL-C reduction include Proprotein convertase subtilisin/kexin type 9 (PCSK9), which is a validated target for risk reduction in stable atherosclerotic cardiovascular disease [41, 42]. A fully human monoclonal antibody against PCSK9 produces substantial and sustained reductions in LDL-C and other atherogenic lipoproteins [42]. Studies of PCSK9 inhibitors have demonstrated that it is safe and well-tolerated [43]. In the ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) Trial, enrolling approximately 19,000-patient placebo-controlled trial, including many patients treated for ≥ 3 years, there was no safety signal with alirocumab other than injection site reactions. Further, compared with placebo in ACS patients, alirocumab 75 or 150 mg subcutaneous targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL, was associated with a reduction of the composite endpoint of major cardiac events (MACE), MI, and ischemic stroke. It was also associated with a lower rate of all-cause death as a secondary endpoint [44]. Similarly, the FOURIER trial randomized 27,564 subjects to receive subcutaneous injections of evolocumab, another PCSK9 inhibitor, or a matched placebo. Evolocumab was associated with a reduced incidence of major adverse cardiovascular events, MI, and stroke but a similar rate of mortality compared to placebo [40]. In a secondary analysis of FOURIER, evolocumab demonstrated a 42% relative reduction in major adverse limb events including acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia compared to placebo [45].

Improving HDL Function

High-density lipoprotein (HDL) has historically demonstrated an inverse relation with the occurrence of MACE, such that patients with low HDL are at an increased risk of experiencing a MACE event compared to patients with normal or elevated HDL levels [46, 47]. This observation became the basis for the "HDL hypothesis," which suggested HDL was a potential modifiable risk factor, and therefore, a possible pharmacologic target. Surprisingly, therapies that invoked a substantial increase in HDL concentrations consistently failed to demonstrate efficacy on hard outcomes [48, 49]. Lack of efficacy in these trials was attributed to the agents not influencing the function of HDL, leading to an evolution in the HDL hypothesis [50]. Subsequent therapies have since focused the attention on raising HDLs cholesterol efflux capacity, instead of simply raising concentrations of HDL [51]. Cholesterol efflux capacity is the HDL molecule ability to effectively transport cholesterol from atherosclerotic plaque to the liver [52].

CSL112 is a human plasma-derived apolipoprotein A1 (ApoA1) that has been tested in subjects post-acute myocardial infarction (AMI), when cholesterol efflux is substantially impaired [53]. The AEGIS-I phase 2b trial demonstrated that four weekly infusions of CSL112 with either a 2 or 6 g dose was not associated with hepatotoxicity or renal toxicity compared to placebo among subjects with normal renal function or mild renal impairment [54••]. CSL112 administrated was also associated with increases in plasma ApoA1, and total cholesterol efflux capacity and ATP-binding cassette A1-depdendent cholesterol efflux capacity. CSL112 may influence future HDL therapies pending an adequately powered phase 3 trial on hard MACE endpoints.

New Strategies that Target Inflammation

Twenty years ago, atherosclerosis was first hypothesized to be, at least partly, a modifiable inflammatory disease [9]. Inflammation has consistently been associated with cardiovascular disease in apparently healthy adults [55]. It was not until the JUPITER trial was conducted 10 years ago that clinicians understood that in patients without hyperlipidemia but with elevated inflammatory markers, statins impacted clinical outcomes by reducing inflammation, independently of lipid lowering [56]. The CANTOS trial validated this finding and demonstrated that Canakinumab, which targets the interleukin-1β innate immune pathway and has no effect on LDL, was associated with significant 15% relative reduction in MACE compared with placebo, independently of baseline LDL levels [57••]. Additional anti-inflammatory trials, such as the Cardiovascular Inflammation Reduction Trial (NCT01594333), which is evaluating low-dose methotrexate compared to placebo among 7000 stable coronary artery disease patients, are currently underway.

Research is also being conducted on the role of inflammation in the acute coronary setting. Two small phase II trials demonstrated a reduction in hsCRP with anakinra, an interleukin-I receptor inhibitor, among subjects with AMI [58, 59]. Other inflammatory pathways such as T cell activation signaling, synthetic inhibitors of tyrosine phosphatase, low doses of IL-2, and infusion of autologous regulatory T cells have risen as potential targets for reduction of residual inflammatory risk in ACS patients.

Factor XI and XII Inhibitors: Promising Drugs?

Current research and development of new thrombosis agents are focusing on more specific and direct anticoagulant therapies, which are expected to have improved efficacy and safety. Recent investigations are targeting factor XI and XII (FXI and FXII), which are part of the intrinsic and contact pathways for coagulation and play an important role in thrombus stabilization and growth. Interestingly, deficiencies in FXI and FXII are associated with a low hemorrhagic risk [60, 61]. Further epidemiological studies established a link between low concentrations of FXI and FXII and low rates of arterial or venous thromboembolism. As a result, recent trials are evaluating new anticoagulant drugs, antibodies, or peptides or antisense oligonucleotides (ASO), which directly inhibit of FXI and FXII. The proof of concept for FXI and FXII inhibitors was established for thromboprophylaxis after surgery, with the FXI-ASO-IONIS trial, which demonstrated superiority on hard outcomes with a 300-mg dose regimen of IONIS-FXIRx compared to enoxaparin [62]. Notably, bleeding events were similar between the two treatment groups. Additional research and trials are required to fully evaluate FXI and FXII inhibitor's potential benefits in acute coronary syndrome and periprocedural anticoagulation. However, it should be noted that FXI and FXII inhibitors could offer a wide range of pharmacological possibilities: with a peptide form in the acute setting allowing a quick on-off action or a longer effect with antibodies or ASO suitable for chronic situations.

Artificial Intelligence

One would be remiss to review the future of the interventional cardiology without mentioning the potential role of "big data." Indeed, "artificial intelligence" or "machine learning" were words unknown or only used by a limited number of statisticians and mathematicians just a few years ago. Facebook, Google, and Amazon have disseminated these concepts, which are now broadly used across various industries. Although their application in medicine is still in an early stage, many researchers are trying to figure out how exactly big data and artificial intelligence can improve healthcare [11]. Utilization of powerful computing to find structure in large datasets may transform the role of clinicians in the next 10 years. Artificial intelligence (AI) offers the possibility of identifying patients with high-risk profiles, and to estimate treatment effects according to their characteristics. Diagnostic and imaging applications of machine learning algorithms have shown the most promise [63]. In the cath lab, AI has the potential to provide live procedural guidance for angiography, intravascular imaging, and to provide real-time support to interventional cardiologists. Like most innovations, advancements in technology precede the clinical application. Bringing complex AI algorithms to clinical practice requires a concerted effort to standardize reporting of AI performance metrics in the scientific literature and to objectively assess their implementation on patient outcomes.

Conclusion

For patients with CAD, many promising therapies are under development including innovative devices, pharmacological therapies, and data solutions. The identification of novel pharmacologic targets has the potential to modify the residual risk of major adverse cardiovascular events. Further development of intravascular imaging and stent technology are expected to further improve outcomes. Widespread use of novel therapeutics is often challenged by identification of a target population that would derive the largest treatment benefit and the least harm. Powerful computational techniques now allow us to utilize complex machine learning algorithms for early diagnostics, prognostication, and derivation of personalized benefit-risk profiles that enable the delivery of targeted therapeutics based on individualized benefit-risk profiles. This review showcases the most promising ongoing advancements in coronary interventions and highlights a promising future for our patients.

Compliance with Ethical Standards

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Puymirat E, Simon T, Steg PG, Schiele F, Guéret P, Blanchard D, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA. 2012;308:998–1006.
2. Nguyen V, Michel M, Eltchaninoff H, Gilard M, Dindorf C, Iung B, et al. Implementation of transcatheter aortic valve replacement in France. J Am Coll Cardiol. 2018;71:1614–27.
3. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. J Am Coll Cardiol. 2017;70:2964–75.
4. Culler SD, Kugelmass AD, Brown PP, Reynolds MR, Simon AW. Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012. Circulation. 2015;131:362–70 Lippincott Williams & Wilkins Hagerstown, MD, discussion370.
5. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532–61.
6. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA American Medical Association. 2004;291:2727–33.
7. 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. Eur Heart J. 2015;36:1163–70.
8. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357:1301–10 Massachusetts Medical Society.
9. Ross R. Atherosclerosis—an inflammatory disease. Epstein FH, editor. N Engl J Med. 1999;340:115–26.
10. Kalra A, Rehman H, Khera S, Thyagarajan B, Bhatt DL, Kleiman NS, et al. New-generation coronary stents: current data and future directions. Curr Atheroscler Rep Springer US. 2017;19:14.
11. Johnson KW, Soto JT, Glicksberg BS, Shameer K, Miotto R, Ali M, et al. Artificial intelligence in cardiology. J Am Coll Cardiol. 2018;71:2668–79.
12. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13–20.
13. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503–16 Massachusetts Medical Society.
14. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991–1001 Massachusetts Medical Society.
15. Angioplasty versus Medical Therapy for Single-Vessel Coronary Artery Disease. N Engl J Med. 1992;326:1632–4 Massachusetts Medical Society.
16. Kereiakes DJ, Teirstein PS, Sarembock IJ, Holmes DR, Krucoff MW, O'Neill WW, et al. The truth and consequences of the COURAGE trial. J Am Coll Cardiol. 2007;50:1598–603.
17. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet. 2018;391:31–40.
18. Brown DL, Redberg RF. Last nail in the coffin for PCI in stable angina? Lancet. 2018;391:3–4.
19. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. Circ Cardiovasc Interv. 2016;9:e003700 Lippincott Williams & Wilkins Hagerstown, MD.
20.• ISCHEMIA Trial Research Group, Maron DJ, Hochman JS, O'Brien SM, Reynolds HR, Boden WE, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. Am Heart J. 2018;201:124–35 **This is the study design of the ISCHEMIA trial, that should provide in the next years a reliable answer to the question of whether a percutaneous coronary intervention should be performed among stable coronary artery disease patients.**
21. James SK, Stenestrand U, Lindbäck J, Carlsson J, Scherstén F, Nilsson T, et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med. Massachusetts Medical Society. 2009;360:1933–45.
22. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, et al. Report of a European Society of Cardiology-European Association of percutaneous cardiovascular interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur Heart J. 2015;36:2608–20.
23. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia-Garcia HM, et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet. 2017;390:1843–52.

24. Krackhardt F, Kočka V, Waliszewski MW, Utech A, Lustermann M, Hudec M, et al. Polymer-free sirolimus-eluting stents in a large-scale all-comers population. Open Heart. 2017;4:e000592.
25. Chen W, Habraken TCJ, Hennink WE, Kok RJ. Polymer-free drug-eluting stents: an overview of coating strategies and comparison with polymer-coated drug-eluting stents. Bioconjug Chem. 2015;26:1277–88.
26. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, et al. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. N Engl J Med. Massachusetts Medical Society. 2015;373:1905–15.
27. Kereiakes DJ, Ellis SG, Metzger C, Caputo RP, Rizik DG, Teirstein PS, et al. 3-year clinical outcomes with everolimus-eluting bioresorbable coronary scaffolds: the ABSORB III trial. J Am Coll Cardiol. 2017;70:2852–62.
28. Waksman R. Bioresorbable scaffolds versus metallic stents in routine PCI. N Engl J Med. 2017;377:1790–1.
29. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med. 2006;119:1056–61.
30. Elmariah S, Jang I-K. Acute stent thrombosis: technical complication or inadequate antithrombotic therapy? An optical coherence tomography study. JACC Cardiovasc Interv. 2012;5:e3–4.
31. Koskinas KC, Nakamura M, Räber L, Colleran R, Kadota K, Capodanno D, et al. Current use of intracoronary imaging in interventional practice—results of a European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Japanese Association of Cardiovascular Interventions and Therapeutics (CVIT) clinical practice survey. EuroIntervention Europa Digital & Publishing. 2018;14:e475–84.
32. Gan Y, Tsay D, Amir SB, Marboe CC, Hendon CP. Automated classification of optical coherence tomography images of human atrial tissue. J Biomed Opt. International Society for Optics and Photonics. 2016;21:101407.
33. Karimi Galougahi K, Zalewski A, Leon MB, Karmpaliotis D, Ali ZA. Optical coherence tomography-guided percutaneous coronary intervention in pre-terminal chronic kidney disease with no radio-contrast administration. Eur Heart J. 2016;37:1059–9.
34. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012:2569–619.
35. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the global registry of acute coronary events. Chest. 2004;126:461–9.
36. Rogers T, Steinvil A, Torguson R, Waksman R. The AngelMed Guardian system: is there a role for implantable devices for early detection of coronary artery occlusion? Cardiovasc Revasc Med. Elsevier. 2016;17:522–7.
37. Navarese EP, Robinson JG, Kowalewski M, Kołodziejczak M, Andreotti F, Bliden K, et al. Association between baseline LDL-C level and Total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. JAMA American Medical Association. 2018;319:1566–79.
38. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. Mass Med Soc. 2009;350:1495–504. https://doi.org/10.1056/NEJMoa040583.
39. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. Mass Med Soc. 2015;372:2387–97. https://doi.org/10.1056/NEJMoa1410489.
40. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. JAMA Cardiol. 2018;3:823–8.
41. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. Massachusetts Medical Society. 2017;376:1713–22.
42. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489–99.
43. Robinson JG, Rosenson RS, Farnier M, Chaudhari U, Sasiela WJ, Merlet L, et al. Safety of very low low-density lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. J Am Coll Cardiol. 2017;69:471–82.
44. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J. 2014;168:682–9.
45. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk). Circulation. 2018;137:338–50.
46. Olsson AG, Schwartz GG, Szarek M, Sasiela WJ, Ezekowitz MD, Ganz P, et al. High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. Eur Heart J. 2005;26:890–6.
47. Duffy D, Holmes DN, Roe MT, Peterson ED. The impact of high-density lipoprotein cholesterol levels on long-term outcomes after non-ST-elevation myocardial infarction. Am Heart J. 2012;163:705–13.
48. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. Massachusetts Medical Society. 2012;367:2089–99.
49. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, et al. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med. 2017;376:1933–42.
50. Siddiqi HK, Kiss D, Rader D. HDL-cholesterol and cardiovascular disease: rethinking our approach. Curr Opin Cardiol. 2015;30:536–42.
51. Tricoci P, D'Andrea DM, Gurbel PA, Yao Z, Cuchel M, Winston B, et al. Infusion of reconstituted high-density lipoprotein, CSL112, in patients with atherosclerosis: safety and pharmacokinetic results from a Phase 2a randomized clinical trial. J Am Heart Assoc. American Heart Association, Inc. 2015;4:e002171.
52. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med. 2011;364:127–35.
53. Shao B, Tang C, Sinha A, Mayer PS, Davenport GD, Brot N, et al. Humans with atherosclerosis have impaired ABCA1 cholesterol efflux and enhanced high-density lipoprotein oxidation by myeloperoxidase. Circ Res. Lippincott Williams & Wilkins Hagerstown, MD. 2014;114:1733–42.
54.•• Gibson MC, Korjian S, Tricoci P, Daaboul Y, Yee M, Jain P, et al. Safety and tolerability of CSL112, a reconstituted, infusible, plasma-derived apolipoprotein A-I, after acute myocardial infarction: the AEGIS-I trial (ApoA-I Event Reducing in Ischemic Syndromes I). Circulation. 2016;134:1918–30 **This trial is the first stone of new HDL hypothesis, suggesting that improving that HDL function may safely reduce the risk of ischemic outcomes among patients with MI.**
55. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation Lippincott Williams & Wilkins. 2004;109:II2–10.

56. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. Massachusetts Medical Society. 2008;359:2195–207.
57.•• Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377:1119–31 Massachusetts Medical Society, **This trial is the proof of concept of the inflammatory hypothesis in coronary artery disease (CAD). Administration of canakinumab, an IL 1 inhibitor, was associated with a reduction of the ischemic events among a large population of CAD patients.**
58. Abbate A, Kontos MC, Grizzard JD, Biondi-Zoccai GGL, Van Tassell BW, Robati R, et al. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling trial [VCU-ART] pilot study). Am J Cardiol. 2010;105:1371–1.
59. Abbate A, Van Tassell BW, Biondi-Zoccai G, Kontos MC, Grizzard JD, Spillman DW, 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]. Am J Cardiol. 2013;111:1394–400.
60. Renné T, Oschatz C, Seifert S, Müller F, Antovic J, Karlman M, et al. Factor XI deficiency in animal models. J Thromb Haemost Wiley/Blackwell (10.1111). 2009;7(Suppl 1):79–83.
61. Renné T, Pozgajová M, Grüner S, Schuh K, Pauer H-U, Burfeind P, et al. Defective thrombus formation in mice lacking coagulation factor XII. J Exp Med. 2005;202:271–81.
62. Büller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. N Engl J Med. Massachusetts Medical Society. 2015;372:232–40.
63. Al'Aref SJ, Anchouche K, Singh G, Slomka PJ, Kolli KK, Kumar A, et al. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. Eur Heart J. 2nd ed. 2018;359:1675.

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