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CARDIOLOGY CORNER

Cardiology News / Literature Review / 2018-2019

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1. COMPLETE study: PCI of non-culprit lesions in patients with STEMI

Approximately 50% of patients with ST-elevation myocardial infarction (STEMI) have multivessel disease (MVD) with significant non-culprit lesions identified at the time of primary percutaneous coronary intervention (pPCI) of the culprit lesion. PCI of the culprit lesion reduces the risk of cardiovascular death or myocardial infarction. Whether PCI of non-culprit lesions further reduces the risk of such events is unclear. The COMPLETE was a multinational, randomized trial that evaluated a strategy of Complete Vs. Culprit-Only Revascularization Strategies to Treat MVD after Early PCI for STEMI. At a median follow-up of 3 years, the first coprimary outcome had occurred in 158 of the 2016 patients (7.8%) in the complete-revascularization group as compared with 213 of the 2025 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91; P=0.004). The second coprimary outcome had occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (hazard ratio, 0.51; 95% CI, 0.43 to 0.61; P<0.001). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of non-culprit-lesion PCI (P=0.62 and P=0.27 for interaction for the first and second coprimary outcomes, respectively). Mehta SR, *et al. Am Heart J*. 2019 Sep;215:157-166. doi: 10.1016/j.ahj.2019.06.006.

2. PCI vs. CABG in 3VD or UPLMD: The 10-year results of SYNTAX trial

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial was a non-inferiority trial that compared percutaneous coronary intervention (PCI) using first-generation paclitaxel-eluting stents with coronary artery bypass grafting (CABG) in patients with de-novo three-vessel and left main coronary artery disease, and reported results up to 5 years. We now report 10-year all-cause death results. The SYNTAX Extended Survival (SYNTAXES) study is an investigator-driven extension of follow-up of a multicenter, randomized controlled trial done in 85 hospitals across 18 North American and European countries. Patients with de-novo three-vessel and left main coronary artery disease were randomly assigned (1:1) to the PCI group or CABG group. Patients with a history of PCI or CABG, acute myocardial infarction, or an indication for concomitant cardiac surgery were excluded. The primary endpoint of the SYNTAXES study was 10-year all-cause death, which was assessed according to the intention-to-treat principle. Pre-specified subgroup analyses were performed according to the presence or absence of left main coronary artery disease and diabetes, and according to coronary complexity defined by core laboratory SYNTAX score tertiles. From March 2005, to April 2007, 1800 patients were randomly assigned to the PCI (n=903) or CABG (n=897) group. At 10 years, 248 (28%) patients had died after PCI and 212 (24%) after CABG (hazard ratio 1·19 [95% CI 0·99–1·43], p=0·066). Among patients with three-vessel disease, 153 (28%) of 546 had died after PCI versus 114 (21%) of 549 after CABG (hazard ratio 1·42 [95% CI 1·11–1·81]), and among patients with left main coronary artery disease, 95 (27%) of 357 had died after PCI versus 98 (28%) of 348 after CABG (0·92 [0·69–1·22], pinteraction= 0·023). There was no treatment-by-subgroup interaction with diabetes (p interaction= 0·60) and no linear trend across SYNTAX score tertiles (p trend=0·20). At 10 years, no significant difference existed in all-cause death between PCI using first-generation paclitaxel-eluting stents and CABG. However, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with left main coronary artery disease.Thuijs DJFM *et al. Lancet*. 2019 12;394(10206):1325-1334. doi: 10.1016/S0140-6736(19)31997-X.

3. COLCOT Trial: Colchicine in patients with acute MI

Inflammation plays a central role in the pathophysiology of both atherosclerosis and acute coronary artery disease. However, previous studies have not demonstrated improved cardiovascular outcomes for therapy directly targeted at inflammation. Colchicine is an orally administered, potent anti-inflammatory medication that is indicated for the treatment of gout and pericarditis. In the COLCOT trial, over 4700 patients with myocardial infarction (MI) were randomly assigned to colchicine 0.5mg daily or placebo within 30 days of their event (2366 patients were assigned to the colchicine group,

and 2379 to the placebo group). At 2 years, the primary end point occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 (95% CI, 0.46 to 1.52) for death from cardiovascular causes, 0.83 (95% CI, 0.25 to 2.73) for resuscitated cardiac arrest, 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for urgent hospitalization for angina leading to coronary revascularization. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P=0.03). While the results of COLCOT appear promising, we do not treat MI patients with colchicine pending additional supportive evidence. Jean-Claude Tardif, et al. NEJM, 2019; 381:2497-2505 DOI: 10.1056/NEJMoa1912388

4. Percutaneous coronary intervention of bifurcation stenosis - 3-year results of DKCRUSH-V study.

In 2019, the 3-year follow-up data of the DKCRUSH-V study were published; similar to what has been reported at 1-year follow-up, DK-Crush technique was associated with a lower incidence of target lesion revascularization (TLR, 5.0% vs. 10.3%, P= 0.029) target vessel MI (1.7% vs. 5.8%, P= 0.017), and definite or probable stent thrombosis (0.4% vs. 4.1%, P = 0.006) compared to provisional T stenting. DK-Crush technique, however, is a challenging procedure and requires skills and expertise; therefore, considering that the findings of the DKCRUSH-V study may not be reproduced by centers with less experienced operators, the recently published 14th consensus document from the European Bifurcation Club advocates the use of provisional T-stenting technique for the treatment of bifurcations lesions and proposes a two stent strategy only in lesions with a complex anatomy, when access to the side branch is challenging, or when there is ostial disease in the side branches extending >5mm form the carina and/or increased calcification. In the case of a two stent strategy the European Bifurcation Club recommends the use of Culotte or TAP technique and when the crush technique is considered it proposes the use of the DK-crush. Banning AP, et al. *Euro-Intervention* 2019;15:90–98 doi: 10.4244/EIJ-D-19-00144.

5. Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO) trial

In 2019, the Euro-CTO Club published a consensus document that summarizes the current evidence discusses the indications for chronic total occlusion (CTO) revascularization, presents the advances in CTO equipment, and provides recommendations about training in CTO PCI. In line with the ESC guidelines on myocardial revascularization and taking into account the findings of randomized controlled (RCT) studies, the EuroCTO Club recommends CTO recanalization in the presence of symptoms despite optimal medical therapy; in asymptomatic patients, ischemic burden assessment is recommended and CTO revascularization is advised if there is evidence of increased ischemic burden (>_10% of the left ventricular mass). These recommendations are in line with the findings of the recently reported Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION CTO) trial. This is an open-label, multicenter, non-inferiority trial, in which 815 patients with a CTO were randomized in 1:1 ratio to complete revascularization or to the treatment of the obstructive non-CTO lesions whenever these were present. Only one-fourth of the patients included in the two groups had a single- vessel disease. At 4-year follow-up, there was no difference between the two groups for the combined endpoint of death, MI, stroke, or revascularization (22.4% vs. 22.3%, P = 0.86) or patients' quality of life. These findings indicate that in case of multivessel disease (MVD) revascularization of the non-CTO lesion and re-evaluation of the extent of ischemia and patient symptoms should be considered before advocating recanalization of a CTO. Limitations of the study included the high crossover rate (19.6%) from the non-CTO PCI group to the CTO-PCI group within the first days from randomization as well the fact that it was underpowered for the primary endpoint as patient recruitment was early terminated because of a slow enrolment rate. Moreover, the non-inferiority design is not suitable when comparing a more costly and potentially risky intervention with medical treatment alone. A superiority design and power calculation should have been used. In conclusion, both study groups (CTO-PCI and no CTO-PCI) were associated with substantial quality of life improvements that were sustained through 36 months, with no differences between groups in the primary quality of life analyses. However, the impact of CTO-PCI on clinical outcomes should be tested in large RCT that include higher-risk patients with more complex CTOs. Lee SW, et al. *Circulation* 2019;139: 1674–1683, doi: 10.1161/CIRCULATIONAHA.118.031313.

6. TWILIGHT study: Ticagrelor Monotherapy Lowers Bleeding Without Increasing Ischemic Events

TWILIGHT study is a double blind randomized trial, who examined the effect of ticagrelor alone as compared with ticagrelor plus aspirin with regard to clinically relevant bleeding among patients who were at high risk for bleeding or an ischemic event and had undergone PCI enrolling 9006 patients. From the study population 7119 underwent randomization after 3 months. After 3 months of treatment with ticagrelor plus aspirin, patients who did not have a major bleeding or ischemic event continued to take ticagrelor and were randomly assigned to receive aspirin or placebo for 1 year. The primary end point was Bleeding Academic Research Consortium

(BARC) type 2, 3, or 5 bleeding. Between randomization and 1 year, the incidence of the primary end point was 4.0% among patients randomly assigned to receive ticagrelor plus placebo and 7.1% among patients assigned to receive ticagrelor plus aspirin (hazard ratio, 0.56; 95% confidence interval [CI], 0.45 to 0.68; P<0.001). The difference in risk between the groups was similar for BARC type 3 or 5 bleeding (incidence, 1.0% among patients receiving ticagrelor plus placebo and 2.0% among patients receiving ticagrelor plus aspirin; hazard ratio, 0.49; 95% CI, 0.33 to 0.74). The incidence of death from any cause, nonfatal myocardial infarction, or nonfatal stroke was 3.9% in both groups (difference, −0.06 percentage points; 95% CI, −0.97 to 0.84; hazard ratio, 0.99; 95% CI, 0.78 to 1.25; p<0.001 for non-inferiority). Therefore the study concluded that among high-risk patients who underwent PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, myocardial infarction, or stroke. We must point out that AstraZeneca funded this study. Interestingly these results were maintained even among the subgroup of patients presenting with NSTE-ACS (STEMI patients were excluded from the trial), diabetes mellitus, and those undergoing complex PCI. These are interesting findings, and help advance our understanding of the optimal duration and type of antiplatelet agent post-PCI. Similar findings were noted with clopidogrel in the SMART-CHOICE and STOPDAPT-2 trials. These trials are thus likely to influence future guidelines regarding DAPT duration post-PCI. Mehran R et al. *NEJM*. 2019 Nov 21;381(21):2032-2042. doi: 10.1056/NEJMoa1908419. Epub 2019 Sep 26.

7. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes:

During the annual meeting in Paris, the ESC has released the new 2019 Guidelines for the diagnosis and management of chronic coronary syndromes (CCS) that will replace the 2013 Guidelines on stable coronary artery disease. The new terminology used (CCS) describes more accurately, compared to the previous, the different clinical presentations of the disease and is coherent with the term used to describe the acute coronary syndromes. The 2019 guidelines contain a number of new very positive issues including the central role of non-invasive testing for myocardial ischemia, the fact the optimal medical therapy remains paramount and the importance of myocardial revascularization in patients non responsive to anti-anginal treatment.

We report the most important key points:

1. Careful evaluation of patient history, including the characterization of anginal symptoms, and evaluation of risk factors and manifestations of CVD, as well as proper physical examination and basic testing, are crucial for the diagnosis and management of CCS.
2. Unless obstructive CAD can be excluded based on clinical evaluation alone, non-invasive functional imaging or anatomical imaging using coronary CTA may be used as the initial test to rule-out or establish the diagnosis of CCS.
3. Selection of the initial non-invasive diagnostic test is based on the PTP, the test's performance in ruling-in or ruling-out obstructive CAD, patient characteristics, local expertise, and the availability of the test.
4. For revascularization decisions, both anatomy and functional evaluation are to be considered. Non-invasive or invasive functional evaluation is required for the assessment of myocardial ischemia associated with angiographic stenosis, unless very high grade (>90% diameter stenosis).
5. Assessment of risk serves to identify CCS patients at high event risk who are projected to derive prognostic benefit from revascularization. Risk stratification includes the assessment of LV function.
6. Patients at high event risk should undergo invasive investigation for consideration of revascularization, even if they have mild or no symptoms.
7. Implementation of healthy lifestyle behaviors decreases the risk of subsequent cardiovascular events and mortality, and is additional to appropriate secondary prevention therapy. Clinicians should advise on and encourage necessary lifestyle changes in every clinical encounter.
8. Cognitive behavioral interventions such as supporting patients to set realistic goals, self-monitor, plan how to implement changes and deal with difficult situations, set environmental cues, and engage social support are effective interventions for behavior change.
9. Multidisciplinary teams can provide patients with support to make healthy lifestyle changes, and address challenging aspects of behaviour and risk.
10. Anti-ischemic treatment must be adapted to the individual patient based on comorbidities, co-administered therapies, expected tolerance and adherence, and patient preferences. The choice of anti-ischemic drugs to treat CCS should be adapted to the patient's heart rate, BP, and LV function.
11. Beta-blockers and/or CCBs remain the first-line drugs in patients with CCS. Beta-blockers are recommended in patients with LV dysfunction or HF with reduced ejection fraction.
12. Long-acting nitrates provoke tolerance with loss of efficacy. This requires prescription of a daily nitrate-free or nitrate-low interval of_10-14 h.
13. Antithrombotic therapy is a key part of secondary prevention in patients with CCS and warrants careful consideration. Patients with a previous MI, who are at high risk of ischemic events and low risk of fatal bleeding, should be considered for long-term DAPT with aspirin and either a P2Y12 inhibitor or very low-dose rivaroxaban, unless they have an indication for an OAC.
14. Statins are recommended in all patients with CCS. ACE

inhibitors (or ARBs) are recommended in the presence of HF, diabetes, or hypertension and should be considered in high-risk patients.
15. Proton pump inhibitors are recommended in patients receiving aspirin or combination antithrombotic therapy who are at high risk of gastrointestinal bleeding.
16. Efforts should be made to explain to patients the importance of evidence-based prescriptions to increase adherence to treatment, and repeated therapeutic education is essential in every clinical encounter.
17. Patients with a long-standing diagnosis of CCS should undergo periodic visits to assess potential changes in risk status, adherence to treatment targets, and the development of comorbidities. Repeat stress imaging or ICA with functional testing is recommended in the presence of worsening symptoms and/or increased risk status.
18. Assessment of myocardial and valvular function and dimensions, as well as a functional test to rule-out significant myocardial silent ischemia, may be contemplated every 3-5 years in asymptomatic patients with a long-standing diagnosis of CCS.
19. An assessment of coronary vasomotor function should be considered in patients with non-significant epicardial CAD and objective evidence of ischemia.

Knuuti J et al. *Eur Heart J*. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425.

STRUCTURAL HEART DISEASE

1. PARTNER 3 and EVOLUT trials Confirm Benefits of TAVR Over Surgery in Low-Risk Patients

Transcatheter aortic valve replacement (TAVR) has become a main stone in treatment for patients with severe aortic stenosis (AS) who are considered high- or intermediate risk surgical candidates. The use of TAVR in low-risk patients with severe AS is being explored as an alternative to surgical aortic valve replacement (SAVR). Recent results from the Medtronic Evolut Low Risk trial and the Placement of Aortic Transcatheter Valves (PARTNER) 3 trial shed light on the use of TAVR in low-risk surgical candidates. Both studies compared the outcomes of TAVR with those of SAVR in patients with severe AS and a low risk of death with SAVR.

In *PARTNER-3* 1,000 patients randomized to either TAVR with a 3rd-generation balloon-expandable valve or SAVR with a bioprosthetic valve. The primary endpoint was the composite of death from any cause, stroke or re-hospitalization at one year after the procedure. The assigned procedure was performed in 950 patients. Two patients in the TAVR group and four in the SAVR group died during the index hospitalization. At one year, the primary endpoint occurred in 8.5% of the TAVR group compared with 15.1% of the SAVR group, meeting the requirements for both non-inferiority ($p<0.001$) and superiority of TAVR vs. surgery ($p<0.001$). The Kaplan-Meir analysis of the primary endpoint components with TAVR vs. SAVR found mortality rates of 1.0% vs. 2.5%, stroke rates of 1.2 % vs. 3.1%, and re-hospitalization rates of 7.3% vs. 11.0%, respectively, confirming both non-inferiority and superiority in the TAVR group. The length of hospital stay was reduced from 7 to 3 days with TAVR.

In *EVOLUT* 1,468 patients were randomized to TAVR with a self-expanding bioprosthesis compared with SAVR. The primary endpoint was the composite of death from any cause or disabling stroke at 24 months. The as-treated cohort included 1,403 patients. At 24 months, death or disabling stroke occurred in 5.3 % of the TAVR group compared with 6.7 % of the SAVR group, meeting the pre-specified criteria for non-inferiority. The mortality rate from any cause was 4.5 % in both groups. The rate of disabling stroke was 1.1 % with TAVR vs. 3.5 % with SAVR. At 30 days, TAVR was statistically superior to SAVR for the secondary combined endpoint of all-cause mortality or disabling stroke (0.8 vs. 2.6 %). Patients receiving TAVR had significantly better quality of life and hemodynamics at 30 days. Thus the Evolut Low Risk trial thus concluded that TAVR was statistically non-inferior but not superior to SAVR.

Therefore both trials provide evidence that the use of TAVR extends beyond the scope of high and intermediate risk surgical patients and is at the very least equivalent to SAVR in the treatment low-risk surgical candidates when using a transfemoral approach in patients without bicuspid aortic valves. Given this data, it seems reasonable to consider moving TAVR in low risk patients to a class I guideline indication on par with surgery for patients with severe AS. Perella P and Anwar S. *NEJM*. 2019 May 2; 380(18):1695-1705. doi: 10.1056/NEJMoa1814052. Epub 2019 Mar 16.

2. Bicuspid Vs. Tricuspid Aortic Valve Stenosis (AS): Data from the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapies (TVT) Registry

As the FDA has already approved an expanded indication for several transcatheter heart valves (Sapien 3, Sapien 3 Ultra, CoreValve Evolut R and CoreValve Evolut PRO) to include patients with severe aortic valve stenosis (AS) at low surgical risk more often we are going to phase the issue of bicuspid aortic valve (BiC) stenosis. However, limited data are available on clinical outcomes in patients with BiC AS treated with transcatheter aortic valve implantation (TAVR). This is a multicenter propensity-matched registry-based prospective data from the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapies (TVT) Registry including 81,822 consecutive patients with AS undergoing TAVR for AS. 2,691 propensity-score matched pairs of BiC and tricuspid (TC) AS were analyzed (median age, 74 years; interquartile range [IQR], 66-81 years; 39.1% women; mean STS-predicted risk of mortality 4.9 ± 4.0% and 5.1 ± 4.2%, respectively). All-cause mortality was not significantly different between patients with BiC and TC

AS at 30 days (2.6% vs. 2.5%, hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.74-1.47) and 1 year (10.5% vs. 12.0%; HR, 0.90; 95% CI, 0.73-1.10). The 30-day stroke rate was significantly higher for BiC vs. TC AS (2.5% vs. 1.6%; HR, 1.57; 95% CI, 1.06-2.33). The risk of procedural complications requiring open-heart surgery was significantly higher in the BiC vs. TC cohort (0.9% vs. 0.4%, respectively; absolute risk difference [RD], 0.5%; 95% CI, 0-0.9%). There were no significant differences in valve hemodynamics and there were no significant differences in moderate or severe paravalvular leak (PVL) at 30 days (2.0% vs. 2.4%; absolute RD, 0.3%; 95% CI, −1.3 to 0.7%) and 1 year (3.2% vs. 2.5%; absolute RD, 0.7%; 95% CI, −1.3% to 2.7%). At 1 year, there was no significant difference in improvement in quality of life between the groups overall summary score, −2.4; 95% CI, −5.1 to 0.3; p = 0.08). This preliminary study using propensity-matched patients from the STS/ACC TVT Registry, suggests no significant differences among patients with BiC vs. TC AS in terms of 30-day and 1-year mortality, valve hemodynamics, moderate or severe PVL, or quality of life measured at 1 year; but higher rates of stroke and procedural complications requiring open-heart surgery associated with BiC anatomy. This retrospective, registry-based study cannot control for potential selection bias among patients with BiC AS who underwent TAVR rather than surgical AVR (SAVR). The study did not compare outcomes for TAVR and SAVR. Given the available evidence and pending prospective, randomized trials, it may be reasonable to use TAVR in at least some patients with BiC AS based upon estimates of risk. Raj R. Makkar et al. *JAMA*. 2019;321(22):2193-2202. doi:10.1001/jama.2019.7108

3. Mitral regurgitation and MITRA-FR vs. COAPT: Lessons from 2 trials with opposed results

The overall prevalence of mitral regurgitation (MR) in the general population is ∼2% and its etiology may be primary (or organic) or secondary (or functional). Secondary MR is a consequence of annular dilatation and geometrical distortion of the sub-valvular apparatus secondary to left ventricular (LV) remodeling associated with cardiomyopathy or coronary artery disease. Severe secondary MR is associated with a poor prognosis in patients with chronic heart failure (HF) and reduced left ventricular ejection fraction (LVEF). Percutaneous mitral valve repair using the Mitra-Clip device has been proposed to correct secondary MR. Recently, the results of two randomized controlled trials, that is MITRA-FR (Percutaneous Repair with the Mitra-Clip Device for Severe Functional/Secondary MR) and COAPT (Cardiovascular Outcomes Assessment of the Mitra-Clip Percutaneous Therapy for HF Patients with Functional Mitral Regurgitation), assessing the efficacy and safety of Mitra-Clip in patients with systolic HF and severe secondary MR were published in the *New England Journal of Medicine*. Although, these two trials targeted the same patient populations with the same disease using the same device the results were diametrically opposed, MITRA-FR being neutral and COAPT being highly positive with respect to efficacy of the MitraClip procedure.

In light of the results of the MITRA-FR and COAPT trials, it thus appears reasonable to conclude that the MitraClip procedure reduces HF hospitalization and mortality in patients meeting the following criteria:

- ≥ moderate-to-severe (3+) secondary MR defined as EROA ≥30 mm2 and/or regurgitant volume >45 mL;
- LVEF between 20% and 50% and LV end-systolic diameter <70 mm;
- Persistent HF symptoms (NYHA ≥ II) despite optimal (maximally tolerated) GDMT with cardiac resynchronization and coronary revascularization if appropriate.

Furthermore, the goal of the procedure should be to obtain an acute reduction of the MR severity to ≤ mild (1+) and the implantation of additional clips should be considered to achieve this goal. Indeed, a more aggressive strategy for correction of MR was applied in COAPT, as suggested by the larger number of clips implanted per patient in COAPT vs. in MITRA-FR. Furthermore, the rate of sustained reduction of MR was higher in COAPT than in MITRA-FR. At 1 year, 17% of the MITRA-FR patients randomized to MitraClip had ≥ moderate-to-severe (3+) residual MR compared with only 5% in COAPT. The lower sustained efficacy of the MitraClip procedure may also have contributed to the lack of benefit of the intervention in MITRA-FR.

Further insight will come from the results of the ReshapeHF2 trial [A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation (Reshape-HF2) (https://clinicaltrials.gov/ct2/show/NCT 02444338], which has the same inclusion criteria as those of the COAPT trial in terms of MR severity, with intermediary criteria COAPT and MITRA-FR in terms of LV dysfunction severity. Philippe Pibarot, Victoria Delgado, and Jeroen J. Bax. *European Heart Journal - Cardiovascular Imaging* (2019) 20, 620–624 doi:10.1093/ehjci/jez073.

4. Transcatheter strategies for tricuspid valve disease.

The tricuspid valve (TV), which is commonly referred to as the ‘‘forgotten valve’’ has received increasing attention in recent years. Transcatheter strategies for tricuspid disease remain in their early stages. Anatomical challenges include the large annulus, paucity of valve/annular calcification, adjacency of the right coronary artery, and fragility of the valve tissue. Current approaches under investigation in feasibility and early phase clinical trials include edge-to-edge repair, coaptation enhancement, annuloplasty, heterotopic caval valve implantation, and percutaneous tricuspid valve replacement. The supporting dataset is substantially smaller than for mitral interventions (which is itself limited) although promising early outcomes have been demonstrated with the Mitra-Clip device. Although recent studies have suggested potential advantages

of transcatheter intervention compared with medical therapy, major questions that need to be addressed by future trials include whether earlier intervention for tricuspid regurgitation may be beneficial, and whether combined mitral and tricuspid procedures improve procedural success and clinical outcomes. Taramasso M, et al. *J Am Coll Cardiol* 2019;doi: 10.1016/j.jacc.2019.09.028.

5. TRI-REPAIR study. Tricuspid Valve Reconstruction for Patients With Severe Tricuspid Regurgitation: 6-Month Outcomes.

This is a single-arm, multicenter, prospective trial in which between October 2016 and July 2017, 30 patients diagnosed with moderate to severe, symptomatic TR in the absence of untreated left-heart disease deemed inoperable were enrolled. TR reconstruction occurred with the use of the CaRdioband Transcatheter System. Six-month outcomes show that the system performs as intended and appears to be safe in patients with symptomatic and moderate to severe functional TR. Significant reduction of TR through decrease of annular dimensions, improvements in heart failure symptoms, quality of life, and exercise capacity were observed. Technical success was 100%. Through 6 months, 3 patients died. Between 6 months and baseline, echocardiography showed average reductions of annular septolateral diameter of 9% (42 mm vs. 38 mm; $p < 0.01$), proximal isovelocity surface area effective regurgitant orifice area of 50% (0.8 cm2 vs. 0.4 cm2; $p < 0.01$), and mean vena contracta width of 28% (1.2 cm vs. 0.9 cm; $p < 0.01$). Clinical assessment showed that 76% of patients improved by at least 1 NYHA functional class with 88% in NYHA functional class I or II. Six-minute walk distance improved by 60 m ($p < 0.01$), and Kansas City Cardiomyopathy Questionnaire score improved by 24 points ($p < 0.01$). Further studies are warranted to validate these initial promising results. (TrIcuspid Regurgitation RePAIr With CaRdioband Transcatheter System [TRI-REPAIR]; NCT02981953). Georg Nickenig et al. J Am Coll Cardiol. 2019 Apr 23;73(15):1905-1915. doi: 10.1016/j.jacc.2019.01.062.

HEART FAILURE

1. Clinical practice update on Heart Failure.

In 2019 the ESC has published new guidelines on heart failure (HF). Given the amount of new information that has become available since 2016, the HFA of the ESC recognized the need to review and summarize recent developments in a consensus document. This expert consensus report is neither a guideline update nor a position statement, but rather a summary and consensus view in the form of consensus recommendations. This report describes how these guidance statements are supported by evidence, it makes some practical comments, and it highlights new research areas and how progress there might change the clinical management of HF. We report interesting data regarding Heart Failure patients:

A. ***SGLT2 inhibitors in type 2 diabetes mellitus and Heart Failure. Data from clinical trials***

EMPA-REG enrolled 7020 patients with T2DM, about 10% of who had HF (LVEF was not measured) and showed that empagliflozin reduced the risk of hospitalization for HF and mortality. Within a few weeks of initiating empagliflozin, body weight, and blood pressure fell and hematocrit rose, consistent with a diuretic effect. Subsequent RCTs of other SGLT2i in T2DM had similar findings. Meta-analyses suggested that SGLT2i were the hypoglycaemic agents most likely to reduce incident HF, whilst observational data raises concerns about insulin therapy. A meta-analysis of RCTs of empagliflozin, canagliflozin, and dapagliflozin for T2DM, including >30 000 patients, showed benefit, at least for those with established CV disease. For the outcome of hospitalization for HF or CV death, the annual rate was about 0.6% for the 13 672 patients with multiple risk factors but without established CV disease, about 3% for the 20 650 patients with established atherosclerotic disease and about 6% for 3891 patients with HF at baseline; the relative risk reductions with SGLT2i in these populations were 16%, 24%, and 29%, respectively, without evidence of heterogeneity amongst agents. The largest of these trials, DECLARE, included 17 160 patients of whom 671 had HFrEF and 1316 had HFpEF or an unspecified LVEF. In a subgroup analysis, dapagliflozin reduced hospitalizations for HF and CV mortality for HFrEF but not for other patient-groups.

DAPA-HF enrolled 4744 patients and followed them for a median of 18.3 months, demonstrating that addition of dapagliflozin to guideline-recommended therapy for HFrEF-reduced hospitalizations for HF by 30% and mortality (mainly cardiovascular) by 18%, preventing 3–5 hospitalizations and 1–2 deaths per 100 patients treated per year. Patients were somewhat less likely to experience serious adverse events, especially renal, with dapagliflozin compared with placebo. The benefits appeared consistent across subgroups, although patients with evidence of more severe congestion (worse NYHA class or higher NT-pro-BNP) may have received less benefit. Importantly, benefits were similar for those with and without T2DM and regardless of age.

Dapagliflozin also improved quality of life, an effect that was confirmed in a smaller RCT (DEFINE) that followed 263 patients for 12 weeks; about one in six patients got a meaningful benefit, either prevention of worsening or an improvement in symptoms, compared with placebo. In DAPA-HF, the placebo-corrected decline in weight between baseline and 8months was 0.87 kg and this was associated with a small fall in NT-proBNP and systolic blood pressure and a small increase in haematocrit and serum creatinine. These findings are again consistent with the belief that SGLT2i exert at least some of their benefits by enhancing diuresis, through an osmotic effect of glycosuria or by interfering with sodium-hydrogen exchange in the nephron. The effects of SGLT2i appear early, consistent with an immediate hemodynamic effect. However,

alternative or additional explanations for the effect of SGLT2i have been proposed. A small RCT suggested that empagliflozin stimulated production of erythropoietin leading to a rise in hematocrit and a fall in ferritin, a marker.

B. ***MitraClip and heart failure,***

(see also Mitral regurgitation and MITRA-FR vs. COAPT): More experience and further data from RCTs may improve patient selection (RESHAPE-HF2: https://clinicaltrials.gov/ct2/show/NCT02444338). However, optimizing guideline-recommended therapy, including diuretic dose, may cause mitral regurgitation secondary to dilation of the LV and mitral ring to improve or resolve. Other technologies for secondary mitral and tricuspid regurgitation are being developed.

C. ***Atrial Fibrillation in Heart Failure:***

About a third of outpatients, perhaps more for those with HFpEF, and more than half of those admitted with HF will be in AF, which is associated with an adverse prognosis even after correcting for age and other risk factors. Controversy continues over whether medical management focused on rate control or restoration of sinus rhythm is the better strategy for AF and HF. In practice, the strategy needs to be tailored to the patient. When AF is the driver of symptoms and worsening cardiac function, restoration of sinus rhythm might be appropriate but when AF reflects the progression of underlying cardiac dysfunction, it may not. For new-onset or paroxysmal AF associated with a clear deterioration in symptoms, restoration of sinus rhythm may be warranted to improve symptoms. For long-standing AF and HF with markedly dilated atria, sustained restoration of sinus rhythm and atrial contraction is less likely. Optimal pharmacological management includes anticoagulation avoiding toxic anti-arrhythmic agents and lenient ventricular rate control. Beta-blockers are the agent of choice for rate control, a resting day-time ventricular rate of 70–90bpm is preferred, which may require only modest doses; digoxin should be used sparingly, if at all. Unfortunately, RCTs of rate vs. rhythm control for AF HF to optimize the rate control strategy in the above fashion. A meta-analysis of RCTs of rate vs. rhythm control included four trials (n= 2486) comparing pharmacological rhythm to rate control found no difference in mortality or thromboembolic events but an increase in hospitalizations, often due to recurrent AF, in the rhythm control group. Six trials (n= 1112) comparing AF ablation with rate control reported reductions in mortality (0.51; 95% CI 0.36–0.74), hospitalizations (0.44; 95% CI 0.26–0.76), and stroke (0.59: 95% CI 0.23–1.51) and an improved quality of life. However, none of the trials individually had a robust result, patients were highly selected and the rate control strategy was not optimal. As such, this meta-analysis should be considered hypothesis generating. Further trials are required with greater involvement of heart failure physicians.

D. ***Implanted electrical device in Heart Failure patients:***

The controversy over the role of high-energy devices for HF continues. Long-term follow-up of cardiac resynchronization therapy (CRT) in a French Registry showed a low rate of sudden death amongst patients who received CRT-Pacing (without a defibrillator). A systematic review of observational studies and RCTs reported that differences in the rate of sudden death with CRT-Pacing and CRT-D were narrowing. RCTs comparing CRT-Pacing and CRT-D are underway. Whether myocardial scar found on cardiac magnetic resonance imaging identifies patients with more to gain from an implantable cardioverter defibrillator (ICD) is also under investigation (CMR_GUIDE; https://clinical trials.gov/ct2/show/NCT01918215). Retrospective analysis of SCDHeFT found that patients with T2DM did not benefit from an ICD. An individual patient-data meta-analysis confirmed a reduction in sudden death with MRA. A systematic review identified 22 studies with post-mortem interrogation of ICDs; the analysis suggested that 24% of sudden deaths were not arrhythmic. A substantial multi-point pacing trial failed, so far, to show improvements in the clinical or echocardiographic response to CRT.

E. ***Rehabilitation:***

Systematic reviews suggest that exercise-based rehabilitation can improve patients' well-being and exercise capacity and reduce HF related and all-cause hospitalization but may not reduce mortality, despite potentially improving adherence to treatment. The best and most cost-effective service-model is a topic of active research.

John G.F. Cleland et al. *European Heart Journal* (2020) 41, 1232–1248. doi:10.1093/eurheartj/ehz949.

ARRYTHMIAS

1. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC)

This is the first guideline update for SVT by ESC in 16 years. The following are key points to remember from the 2019 European Society of Cardiology (ESC) guidelines for the management of patients with supraventricular tachycardia (SVT):

A. Amiodarone and digoxin are no longer mentioned in the new guidelines for the acute management of narrow complex tachycardia. Sotalol and lidocaine have been removed from the acute management of wide complex tachycardia algorithm.

B. Verapamil/diltiazem and catheter ablation are no longer recommended for inappropriate sinus tachycardia. Ivabradine alone, beta-blocker alone, or both agents taken together should now be considered in symptomatic patients (Class IIa).

C. Procainamide, sotalol, and digoxin are no longer recommended for the acute management of focal atrial tachycardia (AT). Amiodarone, sotalol, and disopyramide are not recommended for chronic suppression of focal AT. Catheter ablation is recommended for recurrent focal AT, especially if incessant or causing tachycardia cardiomyopathy. Beta-blockers should be considered for recurrent focal AT or atrial flutter, if ablation is not possible or successful.

D. For multifocal AT, treatment of an underlying condition is recommended as a first step (Class I). Verapamil, diltiazem, or a selective beta-blocker should be considered (Class IIa). Atrioventricular (AV) nodal ablation followed by biventricular or His-bundle pacing should be considered for patients with left ventricular dysfunction due to recurrent multifocal AT refractory to drug therapy (Class IIa).

E. Dofetilide, sotalol, flecainide, propafenone, procainamide, quinidine, and disopyramide are no longer recommended for chronic management of atrial flutter in the new guidelines. Patients with atrial flutter without atrial fibrillation (AF) should be considered for anticoagulation, but the threshold for initiation is not established (Class IIa).

F. In all re-entrant and most focal arrhythmias, catheter ablation should be offered as an initial choice to patients, after having explained in detail the potential risks and benefits. In post-AF ablation ATs, focal or macro–re-entrant, ablation should be deferred for >3 months after AF ablation, when possible.

G. Multiple drugs have been removed from both the acute and chronic management of AV nodal re-entrant tachycardia (AVNRT). Verapamil, diltiazem, and beta-blockers remain as options for the chronic management of AVNRT, but they were downgraded from Class I to Class IIa.

H. Catheter ablation is recommended in asymptomatic patients in whom electrophysiology testing with the use of isoprenaline identifies high-risk properties, such as shortest pre-excited RR interval during AF≤250ms, accessory pathway effective refractory period <250ms, multiple accessory pathways, and an inducible accessory pathway-mediated tachycardia (Class I).

I. Flecainide or propafenone should be considered for prevention of SVT in patients with WPW syndrome and without ischemic or structural heart disease (Class IIa).

J. SVTs have been reported as risk factors for sudden cardiac death in patients with adult congenital heart disease (ACHD). In ACHD, anticoagulation for focal AT or atrial flutter should be similar to that for patients with AF. Catheter ablation in experienced centers should be considered. Sotalol is not recommended as a first-line antiarrhythmic drug due to an increased risk of proarrhythmia and mortality (Class III). Flecainide and propafenone should be avoided in patients with left bundle branch block, or ischemic or structural heart disease (Class III).

K. In postural orthostatic tachycardia syndrome, a regular and progressive exercise program should be considered (Class IIa). The consumption of up to 2-3 L of water and 10-12 g of sodium chloride daily, as well as midodrine, low dose non-selective beta-blocker, pyridostigmine, and ivabradine may be considered (Class IIb).

L. Vagal maneuvers and adenosine are the treatments of choice for the acute therapy of SVT, and may also provide important diagnostic information.

M. In post-AF ablation ATs, focal or macro-re-entrant, ablation should be deferred for >_3 months after AF ablation, when possible.

N. If possible, avoid all antiarrhythmic drugs during the first trimester of pregnancy. If beta-blockers are necessary, use only beta-1 selective agents (but not atenolol). If ablation is necessary during pregnancy, use non-fluoroscopic mapping.

O. Patients with macro-re-entrant tachycardias following atrial surgery should be referred to specialized centers for ablation.

P. Ablate AVNRT, typical or atypical, with lesions in the anatomical area of the nodal extensions, either from the right or left septum. AVNRT, typical or atypical, can now be ablated with almost no risk of AV block.

Brugada J et al. Eur Heart J. 2020 Feb 1;41(5):655-720. doi: 10.1093/eurheartj/ehz467.

PREVENTIVE CARDIOLOGY

1. 2019 ESC/EAS Guidelines for the management of dyslipidemias: *lipid modification to reduce cardiovascular risk*: The Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

The 2019 Joint European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Dyslipidemia Guidelines were released on 31 August during the ESC Congress, Paris, France. These novel ESC/EAS Guidelines on lipids provide important new advice on patient management, which should enable more clinicians to efficiently and safely reduce CV risk through lipid modification emphasizing that lower LDL-C is better. Herein we present the most important key messages of the new guidelines regarding:

A. *Cholesterol and risk*

Prospective studies, randomized trials, and Mendelian randomization studies have all shown that raised LDL-C is a cause of ASCVD. Throughout the range of LDL-C levels, 'lower is better' with no lower threshold, at least down to _1 mmol/L. Lowering LDL-C may yield worthwhile benefits in patients with average or below average LDL-C who are already receiving LDL-C-lowering treatment. The proportional reduction in ASCVD risk achieved by lowering LDL-C (e.g. with a statin, ezetimibe, or PCSK9-inhibitor) depends on the absolute reduction in LDL-C, with each 1 mmol/L reduction corresponding to a reduction of about one-fifth in ASCVD.

B. ***PCSK-9 inhibitors***

Large trials have shown that PCSK9 inhibitors further reduce ASCVD risk when given on top of statin-based therapy and their use may need to be restricted to those at the highest risk for ASCVD (Subgroup analyses of the FOURIER and ODYSSEY OUTCOMES trials).

C. ***Use of cardiac imaging for risk stratification***

CAC score assessment with CT may be helpful in reaching decisions about treatment in people who are at moderate risk of ASCVD. Obtaining such a score may assist in discussions about treatment strategies in patients where the LDL-C goal is not achieved with lifestyle intervention alone and there is a question of whether to institute LDL-C-lowering treatment. Assessment of arterial (carotid or femoral) plaque burden on ultrasonography may also be informative in these circumstances.

D. ***Use of Apo-B in risk stratification***

Apo-B may be a better measure of an individual's exposure to pro atherogenic lipoproteins, and hence its use may be particularly helpful for risk assessment in people where measurement of LDL-C underestimates this burden, such as those with high TG, DM, obesity, or very low LDL-C.

E. Use of Lp(a) in risk stratification: A one-off measurement of Lp(a) may help to identify people with very high inherited Lp(a) levels who may have a substantial lifetime risk of ASCVD. A high Lp(a) plasma level may also be helpful in further risk stratification of patients at high risk of ASCVD, in patients with a family history of premature CVD, and to determine treatment strategies in people whose estimated risk is on the border of risk categories. The guidelines have emphasized that individuals with very high Lp(a), indicative of an inherited lipid disorder, are likely to have a lifetime ASCVD risk similar to that of individuals with heterozygous FH. The new emphasis on Lp(a) is important, given the fact that novel treatments that are specific to this lipoprotein abnormality are now entering phase III clinical trials in high and very high-risk patients. Current options for treatment of high Lp(a) are limited to the PCSK9 inhibitors which have been shown to reduce levels by 25-30% on average, with or without background statin therapy.

F. ***Intensification of treatment goals***

It is important to ensure that treatment of the highest-risk patients achieves the largest LDL-C reduction possible. These Guidelines aim to support this by setting both a minimum percentage LDL-C reduction (50%) and an absolute LDL-C treatment goal of <1.4 mmol/L (<55mg/dL) for very-high-risk patients, and <1.8 mmol/L (<70 mg/dL) for high-risk patients. It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk. Additionally, there has been further information from the IMPROVE-IT trial with ezetimibe, which demonstrated enhanced absolute cardiovascular benefit in very high-risk individuals with diabetes compared with those without, reflecting the higher absolute risk of this group.

G. ***Treatment of patients with recent ACS***

New randomized trials support a strategy of intensification of LDL-C-lowering therapy in very-high-risk patients with ACS (MI or unstable angina). If the specified LDL-C treatment goal is not achieved after 4-6 weeks with the highest tolerated statin dose and ezetimibe, it is appropriate to add a PCSK9 inhibitor. Moreover, If patients experience a second vascular event within 2 years (not necessarily of the same type as the first event) on maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.

H. Safety of low LDL cholesterol concentrations: To date there are no known adverse effects of very low LDL-C concentrations [e.g. <1 mmol/L (40 mg/dL)].

I. ***Management of statin 'intolerance'***

While statins rarely cause serious muscle damage (myopathy, or rhabdomyolysis in the most severe cases), there is much public concern that statins may commonly cause less serious muscle symptoms. Such statin 'intolerance' is frequently encountered by practitioners and may be difficult to manage. However, placebo-controlled randomized trials have shown very clearly that true statin intolerance is rare, and that it is generally possible to institute some form of statin therapy (e.g. by changing the statin or reducing the dose) in the overwhelming majority of patients at risk of ASCVD.

J. ***Statin treatment for older people***

A meta-analysis of randomized trials has shown that the effects of statin therapy are determined by the absolute reduction in LDL-C as well as the baseline ASCVD risk, and are independent of all known risk factors, including age. Statin therapy in older people should therefore be considered according to the estimated level of risk and baseline LDL-C, albeit with due regard to an individual's underlying health status and the risk of drug interactions. There is less certainty about the effects of statins in individuals aged >75 years, particularly in primary prevention. Statin therapy should be started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.

K. ***Triglyceride management***

While statin treatment remains the first choice for managing high triglycerides (TG, >200 mg/dL or 2.3 mmol/L), the new guidelines have taken account of evidence from REDUCE-IT and recommend n-3 PUFAs (particularly icosapent ethyl 2x2g daily) in high-risk patients with persistently elevated TG (between 135 - 499mg/dL or 1.5 and 5.6 mmol/L) despite statin treatment.

In high-risk patients at LDL-C goal with TG >200 mg/dL or >2.3 mmol/L, fenofibrate or bezafibrate may be considered in combination with statins. Mach F, et al. Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

2. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The global prevalence of diabetes mellitus (DM) has quadrupled over the past few decades, from an estimated 108 million adults living with diabetes in 1980 to 422 million adults living with diabetes in 2014. Just as worrying, the global burden of diabetes is projected to further increase by 10% in 2040. This poses a major challenge to societies and health care authorities as diabetes increases the risk for several diseases, including cardiovascular disease (CVD). Indeed, the total economic cost associated with DM was $327 billion in 2017 in the US alone. Clear and evidence-based recommendations for how to manage patients with diabetes have never been more important. The European Society of Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes (EASD) released 2019 guidelines for the prevention and management of CVD in patients with pre-diabetes and diabetes. The following Table summarizes the CVD risk categories, which developed from the 2016 ESC guidelines on CVD prevention in clinical practice.

Very high risk	High risk	Moderate risk
Patients with DM and CVD or DM with target organ damage.* Patients with DM with three or more major risk factors or with type 1 DM duration of >20 years	Patients with DM duration of ≥10 years without target organ damage plus any other additional risk factor	Young patients (type 1DM aged <35 years or type 2DM aged <50 years) with DM duration of <10 years without other risk factors

**Proteinuria or kidney failure (estimated GFR <30 mL/min/1.73m2), LV hypertrophy, or retinopathy*

Herein we present the most important key messages of the new guidelines regarding:

A. *Glucose Lowering Management*

Since the prior ESC guidelines published in 2013, there has been an unprecedented increase in new evidence indicating cardiovascular benefits from the use of novel glucose-lowering drugs based on large-scale cardiovascular outcome trials. In general, the new 2019 ESC recommendations for glucose lowering treatments are closely linked to recent results from the CVOTs. Thus, an SGLT-2 inhibitor or GLP1-RA should be immediately initiated or added to existing metformin treatment in patients with DM and CVD, or in patients at high or very high risk to reduce CV events. Metformin is the preferred initial glucose-lowering agent for the treatment of type 2 DM. The guideline also provides specific recommendations for SGLT2 and GLP1-RA based on results from individual CVOTs. Accordingly:

- *SGLT2 inhibitors* such as empagliflozin, canagliflozin, or dapagliflozin are recommended to lower the risk of heart failure hospitalization and to reduce the progression of diabetic kidney disease. Empagliflozin is recommended in patients with prevalent CVD, to reduce the risk of death.
- *GLP1-RAs* such as liraglutide, semaglutide and dulaglutide are recommended in patients with DM and CVD, or who are at very high/high CVD risk, to reduce CVD events. In addition, liraglutide has shown to significantly reduce CV death in DM and CVD, or for patients at very high/high CV risk.

The choice of drug to reduce CV events should be prioritized and individualized based on the presence of risk factors and CVD in patients with DM. For glycemic control, HbA1c l< 7% is advised for most patients, while a target of 8% or ≤9% may be adequate for elderly patients.

B. *Lipid Management*

The 2019 ESC diabetes guidelines endorse the same principle for management of blood cholesterol as the 2019 dyslipidemia guidelines, that is, by providing differentiated treatment targets for low-density lipoprotein cholesterol (LDL-C) based on estimated risk for CVD. These LDL-C targets have been lowered compared to the preceding guideline:

- Moderate risk: LDL-C <2.6 mmol/L (<100mg/dL)
- High risk: LDL-C <1.8 mmol/L (<70mg/dL) and LDL-C reduction of at least 50% is recommended
- Very high risk: LDL-C <1.4 mmol/L (<55mg/dL) and LDL-C reduction of at least 50% is recommended

To reach these targets, most patients will qualify for statin treatment. Currently, a PCSK9 inhibitor is recommended in very high-risk patients who have persistently high LDL-C levels even with maximal dose of statin and ezetimibe therapy or in patients who have statin intolerance.

C. *Blood Pressure Management*

As with lipid targets, the targets for blood pressure levels have been lowered in the new guidelines. Thus, a systolic blood pressure (SBP) goal of 130 mmHg (<130mmHg if well tolerated), and a diastolic blood pressure (DBP) goal of <80mmHg is recommended, compared to a previous target of <140/85 mmHg for all patients. In older adults aged >65 years, SBP target range of 130-139 mmHg is recommended. The guidelines emphasize an individualized approach for hypertension management. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is recommended as first line therapy for BP control in DM patients.

D. ***Antiplatelet Therapy***

The 2019 ESC guideline does not provide strong recommendations for antiplatelet therapy in DM patients without CVD. Therefore aspirin for primary prevention is not recommended in patients with DM at moderate CV risk. However, aspirin (75-100 mg/day) for primary prevention may be considered in patients with DM at very high/high risk in the absence of clear contraindications (IIb). In addition, concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or oral anticoagulant monotherapy who are at high risk of gastrointestinal bleeding finally, prolongation of DAPT beyond 12 months should be considered for ≤3 years in patients with DM at very high risk who have tolerated DAPT without major bleeding complications.

E. ***Imaging***

Screening for coronary artery disease (CAD) in asymptomatic patients with DM remains debatable. According to the new guidelines, screening of CAD with computed tomography coronary angiography (CTCA) or functional imaging such as radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography may be considered (IIb). Additionally, coronary artery calcium (CAC) score may be considered as a risk modifier in the CVD risk assessment of asymptomatic patients at moderate risk (IIb).

D. ***Revascularization strategies***

Angiographic studies have shown that patients with DM are more likely to have left main and multivessel CAD (MVD), and that coronary pathology is more frequently diffuse and involves the small vessels. The indications for myocardial revascularization, for both symptomatic and prognostic reasons, are the same in patients with and without DM (IA), and have been summarized in the 2018 ESC/ EACTS Guidelines on myocardial revascularization (see previous text). The appropriate revascularization modality in patients with DM and MVD should be discussed by the Heart Team, taking into consideration individual cardiac and extracardiac characteristics, as well as preferences of the well-informed patient. However, in patients with DM with low complexity of coronary anatomy (SYNTAX score ≤22), PCI using DES has achieved similar outcomes to CABG with respect to death and the composite of death, MI, or stroke. Therefore, PCI prevails to CABG in 1VD or 2VD without proximal LAD stenosis (IC vs. IIB), while has equivocal indication in LM disease and low SYNTAX score representing a good alternative. In patients with DM and 3VD CABG prevails PCI (IC vs. IIB). Overall, current evidence indicates that in stable patients with coronary anatomy suitable for both procedures and low predicted surgical mortality, CABG is superior to PCI in reducing the composite risk of death, MI, or stroke, as well as death. CABG is recommended for intermediate-to-high anatomical complexity (SYNTAX score >22) with the PCI being a good alternative in case of intermediate disease complexity (SYNTAX scorec 23 -32). While in case of HFrEF and DM, and two- or three-vessel CAD, CABG is the recommended approach. Although newer-generation DESs have improved outcomes in patients with DM, RCTs are needed to determine whether they can reduce the gap in outcomes between CABG and PCI. The best surgical coronary revascularization strategy and graft selection in patients with DM is still subject to debate. In case of CABG the first choice should be the internal mammary artery, and its impact on survival when grafted to the left anterior descending (LAD) coronary artery and the radial artery may be preferred as a second graft in view of better long-term patency of the radial artery compared with the saphenous vein, but further studies are needed (see the 2018 ESC/EACTS Guidelines on myocardial revascularization for further information). Interestingly in the Arterial Revascularization Trial (ART) which compared the BIMA with SIMA and an additional veins in 1554 patients, at 10 years showed no significant differences in the rate of death or the composite outcome of death, MI, or stroke suggesting that vein grafts is always a good option.

F. ***Heart failure and diabetes***

Patients with DM are at greater risk of HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF); conversely, HF increases the risk of DM. Indeed, findings from a large pan-European registry indicated that 36% of outpatients with stable HF had DM, while in patients hospitalized for acute HF, DM was present in ≤50%. Major causes of HF in patients with DM are CAD, CKD, hypertension, and direct effects of insulin resistance/ hyperglycaemia on the myocardium.

- The coexistence of DM and HF imparts a higher risk of HF hospitalization, all-cause death, and CV death.
- Guideline-based medical and device therapies are equally effective in patients with and without DM; as renal dysfunction and hyperkalaemia are more prevalent in patients with DM, dose adjustments of some HF drugs (e.g. RAAS blockers) are advised.
- Aliskiren (a direct renin inhibitor) is not recommended for patients with HFrEF and DM because of a higher risk of hypotension, worsening renal function, hyperkalaemia, and stroke.
- First-line treatment of DM in HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone, and rosiglitazone are not recommended for patients with DM and HF.

Cosentino F, et al. *Eur Heart J.* 2020 Jan 7;41(2):255-323. doi: 10.1093/eurheartj/ehz486.