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ROLE OF NEW DRUG THERAPIES AND INNOVATIVE PROCEDURES IN OLDER PATIENTS WITH HEART FAILURE: FROM TRIALS TO CLINICAL PRACTICE

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INTRODUCTION

Introduction

Heart failure (HF) is the leading cause of first hospitalization and re-hospitalization in older patients (1) and is associated with high risk of morbidity, disability, poor quality of life and frequent institutionalization in nursing homes (2). In the last decades, medical therapies have improved survival of patients affected by HF (3), although, in advanced aged patients, good medical therapy is difficult to maintain with dosage recommended by guidelines (4) due to the complex and severe comorbidity (5). In parallel, during earliest years, new drug-therapies and novel structural interventional therapies for HF have been designed to modify the detrimental effect of secondary valve diseases, adverse ventricular remodelling and persistent fluid overload (6). This new therapeutic era gives and will give much more therapeutic possibilities for several frail older HF patients, often excluded by cardiac surgery approach or candidate to a prohibitive surgery procedures (7). A multidisciplinary heart team approach is mandatory in this new therapeutic field, in which interventional cardiologists, cardiac surgeons, anesthesiologists and geriatricians could better define a correct decision-making process in a perioperative, as well as postoperative period, to reduce morbidity, mortality and global functional decline (8). Finally, we have to remember how, this innovative therapeutic era is probably to date, the gateway of regenerative therapies that first stems we see on the horizon.

NOVEL DRUG-THERAPIES INNOVATION ERA

Angiotensin receptor neprilysin inhibitor -ARNI

Sacubitril/valsartan is the first in class of angiotensin receptor neprilysin inhibitor (ARNI), a combination of two molecules which synergically act on the renin-angiotensin-aldosterone system (RAAS) and on the neutral endopeptidase pathway: indeed, on one side, sacubitril inhibits neprilysin and the degradation of the natriuretic peptides (NPs) with favorable effects on diuresis, natriuresis, myocardial relaxation, anti-remodeling and on reduction of secretion of renin and aldosterone, while, on the other side, valsartan blocks selectively AT1-receptors, keeping free the AT2-ones, with consequently reduction on vasoconstriction, sodium and water retention and myocardial hypertrophy, fibrosis and remodeling (9).

After the publication of the results of the PARADIGM-HF trial in 2014, ARNI has become a cornerstone of HF therapy (10-12). This phase III trial was conducted in 8399 patients with mean age 64 years, a New York Heart Association (NYHA) class II-IV and a left ventricular ejection fraction (LVEF) ≤40% (than amended to ≤35% during the study), randomly assigned to sacubitril/valsartan or enalapril (10). ARNI proved superior to angiotensin–converting enzyme inhibitor (ACEi) in reducing hospitalizations for worsening HF, cardiovascular (CV) mortality, overall mortality and in decreasing symptoms and physical limitations (10). Of note, this trial was interrupted early because of clear benefit, with a 20% reduction of the composite primary endpoint of CV mortality and HF hospitalization in sacubitril/valsartan group (10).

Later, Jhund et al. analyzed the efficacy and safety of sacubitril/valsartan according to age highlighting that the benefit of ARNI over ACEi was consistent across the age categories studied, with some uncertainty about fatal outcomes in oldest patients, as probable consequence of the modest number (n=121) of those aged 85 years and older (13). However, the effect of sacubitril/valsartan on HF hospitalization and quality of life even in the oldest patients seemed qualitatively and quantitatively similar to those observed in younger ones (13).

Despite the superiority of sacubitril/valsartan on enalapril, there are some safety issues to underline. Symptomatic hypotension was more common in the sacubitril/valsartan group (it occurred in 18% of patients of ARNI group vs. 12% of the enalapril group at age ≥75 years) and these events rarely required the discontinuation of treatment (10,13). Although this hypotensive effect may have consequences on renal function for reduction in perfusion, increases in serum creatinine or serum potassium levels and discontinuation because of renal impairment or hyperkaliemia were more common in enalapril group than in sacubitril/valsartan one (10). Of note, as compared with the value at randomization, the mean systolic blood pressure after 8 months of treatment was 3.2±0.4 mmHg, lower in the ARNI than in the enalapril group while no significant changes were observed in serum creatinine level (10).

Emerging real word data showed that patients in clinical practice were older and had a higher serum creatinine level, higher NYHA functional class, lower LVEF and have baseline characteristics indicative of more disease severity in comparison with those in the PARADIGM-HF trial (14-18). This resulted in a more pronounced drop in systolic blood pressure and lower drug dose usage in real word patient treated with ARNI; again, effects on serum creatinine or serum potassium levels were marginal and low events of renal failure or hyperkalaemia were reported (14-18). Vardeny et al. showed that the magnitude of benefit for patients on lower doses of sacubitril/valsartan relative to those on lower doses of enalapril was similar to that of patients on target doses (19). In this sub-analysis of the PARADIGM-HF trial, only hypotension was responsible for more dose reductions among those taking sacubitril/valsartan than enalapril; anyway, a higher proportion of participants in the sacubitril/valsartan group were re-up-titrated to target doses of study medication after initial down-titration (19). Analysing basal characteristics of patients who experienced a dose reduction, advanced age, lower systolic blood pressure, more severe symptoms of HF or greater renal impairment were more common and similar between treatment arms (19).

From these data, the necessity of a careful monitoring of renal function, serum potassium level and blood pressure, particularly in older patients, emerged in clinical management of HF patients. Parithi et al. highlighted the importance of a careful clinical attention to volume status assessment and to the management of diuretic prescription, especially to reach target dose (18). Anyway, few data are currently available on elderly, and mainly in old oldest patients, treated with sacubitril/valsartan (14-18). An international statement suggests a careful follow-up when ARNI is started or up-treated with close clinical control of systolic blood pressure and orthostatic hypotension and close laboratory monitoring of renal function and serum potassium level (11). Moreover, especially in elderly patients, mostly if low blood systolic pressure or impairment in renal function were recorded, sacubitril/valsartan should be started at low dosages and slowly up-titrated, fluid balance must be monitored, and diuretic dose adjusted (11). Of note, Damman et al. highlighted that an initial impairment after starting treatment with ARNI and ACEi were reported and that this impairment was higher in sacubitril/valsartan group; anyway, compared with enalapril, sacubitril/valsartan led to a slower rate of decrease in the estimated glomerular filtration rate (eGFR) and improved CV outcomes, even in patients with chronic kidney disease (CKD), despite causing a modest increase in urinary albumin/creatinine ratio (20).

Since 2014, doubts emerged regarding the effects of ARNI on cognitive status relating to the hypothesis that inhibition of neprilisyn might lead to amyloid accumulation in the brain and promote the onset of dementia. Anyway, Cannon et al. found that the incidence of dementia-related adverse events was similar in the two arms of PARADIGM-HF (21). Nevertheless, the effect of sacubitril/valsartan on cognitive function is currently under evaluation in the ongoing PERSPECTIVE study (NCT02884206).

To date, the indications for ARNI are limited to patients with LVEF≤35%. The hypothesis that patients affected by HF with preserved ejection fraction (HFpEF), notoriously more prevalent in older persons, could also benefit from sacubitril/valsartan was tested in a small phase II clinical trial (PARAMOUNT-HF), which showed a significantly higher reduction of N-terminal pro–B-type

natriuretic peptide (NT-proBNP) at 12 weeks compared to valsartan (22). Anyway, in the recently published PARAGON-HF trial, nearly 5000 patients aged 50+ years, in NYHA class II to IV, with a LVEF ≥45% within the previous 6 months, elevated level of NPs, evidence of structural heart disease and diuretic therapy were enrolled (23). After a median follow-up of 3 year, although sacubitril/valsartan reduced the primary composite outcome of total (first and recurrent) hospitalizations for HF and death from CV causes respect valsartan, statistical significance has been touched; only a sub-analysis showed possible beneficial in patients with LVEF between 45-57% to be explored with further studies (23).

Sodium-glucose co-transporter inhibitor-SGLT2i

Diabetes mellitus (DM) is among the most common non-CV comorbidities that affected HF patients. Anyway, its importance is not only for the association with worse prognosis but also for the recent evidence of a positive prognostic impact of a new class of drugs for treatments of type 2 DM in HF patients, the sodium-glucose co-transporter inhibitor (SGTL2i). Particularly, the EMPA-REG, CANVAS and DECLARE–TIMI 58 trials had showed a reduction in CV morbidity and mortality in patients with type 2 DM at high CV risk treated, respectively, with empagliflozin, canagliflozin and dapagliflozin, in addition to standard care and compared to placebo. Moreover, all three drugs showed a remarkable and significant reduction in HF hospitalization rate and a good safety profile (24-26).

Driven by these results, the application of SGLT2i were tested in two *ad-hoc* trial: the DAPA-HF and the EMPEROR-Reduced trial. In the DAPA-HF trial 4744 patients with symptomatic HF, LVEF ≤40% and elevated NT-proBNP were randomized to receive dapagliflozin or placebo, showed a significant reduction of the risk of first worsening HF events (HF hospitalization/urgent HF visit requiring intravenous diuretics) or CV, regardless of the presence or absence of DM (27). Martinez et al. conducted a *post-hoc* analysis showing that dapagliflozin reduced the risk of death and worsening HF and improved symptoms across the broad spectrum of age studied in DAPA-HF with no significant imbalance in tolerability or safety events, even in older individuals (28). Similarly, also the EMPEROR-Reduced trial, a double-blind trial which enrolled 3730 patients with symptomatic HF and LVEF < 40% randomized to empagliflozin or placebo in addition to recommended therapy, confirmed the reduction of the risk of CV death or hospitalization for HF in patients treated with empagliflozin regardless of the presence or absence of diabetes (29). Moreover, a slower decline of renal function was observed in empagliflozin group, also regardless of the severity of kidney impairment at baseline (30).

A nephroprotective effect of SGLT2i had already been demonstrated in the CREDENCE trial which assessed the effects of canagliflozin on renal outcomes in patients with type 2 DM and

albuminuric CKD (eGFR >30 ml/min/1.73 m^2) (31). The trial was stopped early because the event rate of the primary outcome, a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73 m^2), doubling of the serum creatinine level or death from renal or CV causes, was significantly lower with canagliflozin (31). Furthermore, DAPA-CKD, an international, multi-center, randomized, double-blinded trial designed to evaluate the efficacy of dapagliflozin, compared with placebo, in patients with CKD stages 2–4 and elevated urinary albumin excretion, with and without type 2 DM, was recently published (32). The independent data monitoring committee recommended stopping the trial early because of efficacy of dapagliflozin in reducing the primary composite endpoint of worsening renal function (defined as a composite of an eGFR decline ≥50%, onset of ESRD and death from CV or renal cause), regardless of the presence or absence of diabetes (32). Actually, the EMPA-KIDNEY (NCT03594110) is yet in recruiting status and will investigate the effect of empagliflozin on kidney disease progression or CV death versus placebo on top of standard of care in patients with pre-existing CKD.

Thanks to these results, SGLT2i will become more and more protagonists for the treatments of HF, increasing and complicating the armamentarium therapeutic for the treatment of HFrEF patients (11,12,33). More efforts will have to be made to define better their safety profile, especially in the elderly group with CKD and in treatments with RAAS inhibitors and diuretics. Solomon et al. showed that dapagliflozin was similarly efficacious and safe in patients who were and who were not taking sacubitril/valsartan in the DAPA-HF trial, suggesting that the use of both agents together could further lower morbidity and mortality in patients with HFrEF (34). On the other hand, Docherty et al. conducted a *post-hoc* analysis showing that the benefit of dapagliflozin was consistent regardless of background therapy for HF, suggesting that they act in a mechanistically independent and complementary way to other therapies for HFrEF (35). Although renal adverse events were less common with dapagliflozin than with placebo, an alert on volume status emerged: indeed, in patients treated with a diuretic, adverse events related to volume depletion occurred more frequently with dapagliflozin compared to placebo, with fewer events seen in those not on a diuretic

and randomized to dapagliflozin; moreover, renal adverse events were less common with dapagliflozin compared to placebo in those not on a diuretic at baseline with no difference in those treated with a diuretic (35).

Emerging real-word data highlight physicians' attention on a careful management of this therapy in association with RAAS inhibitors and diuretics, especially after its inception (36-38). International society have also aligned themselves with these alerts, suggesting frequently monitoring of fluid balance and reduction of diuretic posology, particularly during acute illnesses associated with hypovolemic states (fever, diarrhea, vomiting) and hot seasons, and a regular assessment of renal function and pressure profile to prevent renal failure and volume depletion (12).

Why this therapy has such a positive effect is still being studied although numerous mechanisms may underlie, like reduction in inflammation, oxidative stress, fibrosis, intraglomerular hypertension, activation of sympathetic nervous system, and improvement in mitochondrial function and myocardial efficiency (39).

Finally, to further expand our armamentarium, results of SOLOIST-WHF trial was published (40). In this double-blind, randomized, trial 1222 patients, with type 2 diabetes mellitus who were recently hospitalized for worsening HF, underwent randomization to placebo or sotagliflozin, an SGLT2 inhibitor that also provides some gastrointestinal SGLT1 inhibition (40). In patients treated with sotagliflozin, before or shortly after discharge, a significantly lower total number of deaths from CV causes and hospitalizations and urgent visits for HF were found than placebo, without significant differences between the two arms about hypotension and acute kidney injury (40). Interestingly, patients treated with ARNI, betablocker or loop diuretic were over 90% each one (40). Anyway, its safety profile was questioned by the similar SCORED trial, where a significantly higher percentage of adverse effects, like diarrhea, volume depletion, diabetic ketoacidosis and genital mycotic infection, were recorded in sotagliflozin group (41). Further studies will need to be conducted to define its safety profile, especially in the elderly.

Such effects have currently only been certified in HFrEF patients, although the mechanism of action is still under study. In October 2021 data from the EMPEROR-Preserved trial demonstrated for first time that empaglifozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. In the study 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% were randomized to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the treatment group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly driven by lower risk of hospitalization for heart failure in the empagliflozin group. The positive effects of empagliflozin appeared independent from presence of diabetes (42).

Potassium binders

As known, hyperkaliemia is a common electrolyte disturbance of HF patients, especially in the elderly patients with CKD, becoming, often, an important limiting factor to initiate or up-titrate RAAS inhibitors. The U.S. Food and Drug Administration and the European Medicines Agency approved two novel potassium absorbents, patiromer sorbitex calcium and sodium zirconium cyclosilicate (ZS-9), for the treatment of hyperkalaemia in patients receiving RAAS inhibitors. Both drugs have shown to be effective in reducing potassium levels in patients with CKD and hyperkalemia acting by increasing potassium loss via the gastrointestinal tract (43,44). Although the efficacy in reduction of potassium levels was proved, their use could be cautious for the possible adverse effect reported (45). Indeed, data from a recent meta-analysis showed that patiromer was associated with more gastrointestinal upset (7.6% constipation, 4.5% diarrhea) and electrolyte depletion (7.1% hypomagnesemia), whereas ZS-9 was associated with adverse effects of urinary tract infections (1.1%) and edema (0.9%); anyway, discontinuation of therapy due to an adverse effect occurred in 8% of patients on patiromer and 1% of patient on ZS-9 (45).

To help HF specialist in the management of hyperkaliemia and in making the optimization of guidelines-directed medical treatments more possible, these drugs are being evaluated for use in patients with HF and hyperkalemia. In the PEARL-HF trial, 105 patients with HF and a history of hyperkalaemia resulting in discontinuation of a RAAS inhibitor and/or beta-adrenergic blocking agent or CKD were randomized to double-blind treatment with 30 g/day patiromer or placebo for 4 weeks while spironolactone was started at 25 mg/day and increased to 50 mg/day after 15 days (46). At the end of treatment, patiromer group had significantly lowered serum potassium levels, a lower incidence of hyperkalaemia and a higher proportion of patients on spironolactone 50 mg/day (46). Of note, the most common adverse events were gastrointestinal disorders (e.g. flatulence, diarrhea. constipation, and vomiting), which were reported with higher frequency in patiromer group (21 vs. 6% of placebo group) with the majority of adverse events that were graded by the investigator as mild or moderate in intensity (46). A similar proportion of patients in each treatment group had an

adverse events that led to discontinuation of study drug (7% patiromer, 6% placebo) (46). Finally, hypomagnesemia occurred in 24% of the patients receiving patiromer versus 2% receiving the placebo (46). The HARMONIZE trial studied the effects of ZS-9 on serum potassium levels. In a *post hoc* analysis was found that 94 patients of 258 total enrolled, had HF history and baseline hyperkalaemia. These patients were treated, as required by the study design, with open label ZS9 for 48 h with the 93% that achieved normokalaemia without adjusting RAAS inhibitors doses and were randomized to daily ZS-9 (5, 10, or 15 g) or placebo for 28 days (47). During the randomized phase, patients in the 5 g, 10 g, and 15 g dose groups maintained lower serum potassium and a greater portion of normokalaemia compared with placebo group and efficacy findings were consistent regardless of continued concomitant RAAS inhibitors medications (47). Oedema was reported in 3.8% of the placebo group and up to 20.0% with the highest dose of ZS9 (47). Eight of the nine cases were peripheral oedema, four of which did not require treatment despite continued ZS-9 dosing, and no patient discontinued the study because of oedema (47). Generalized oedema occurred in one patient with severe HF and a history of oedema requiring diuretic treatment (47). Anyway, Six of the nine oedema patients entered the extension study, continuing once-daily ZS-9, and none have experienced new oedema (with 149 total exposure weeks) (47). No patient receiving 15 g doses of ZS-9 in the extension study has experienced oedema (with 278 total exposure weeks) (47).

Undoubtedly, these findings support the hypothesis that therapy with potassium binders could play a relevant role in the treatment of HF in the future. Anyway, the safety profile of both compounds in a real-world setting, as well as the effect of these drugs on harder endpoints, should be further evaluated particularly in HF patients. The ongoing DIAMOND-trial (NCT03888066) should have assessed whether patiromer reduces the risk of CV death or hospitalization in patients, with or without CKD, treated with RAAS inhibitors in accordance with HF treatment guidelines, but the primary outcome was change in the time to first occurrence of CV death or CV hospitalization because of the significant impact of COVID-19 on recruitment. On the other hand

the PRIORITIZE-HF (NCT03532009) trial will evaluate risks and benefits of using ZS-9 to initiate and up-titrate RAAS inhibitors in HF patients; anyway this study was stopped early due to the COVID-19 pandemic and results will be published soon.

Although greater efforts will need to be made to understand the levels of safety in a real word elderly population, from the results of these trials we will understand if potassium binders make us able to implement guidelines-recommended treatments in HF patients with high potassium levels and CKD.

Table 1

NOVEL DEVICE-THERAPIES FOR ELDERLY PATIENTS WITH HEART FAILURE

Interventional transcatheter therapies for heart failure with Secondary Valvular Heart Disease

Secondary mitral valve regurgitation and percutaneous valve repair or replacement : mitral regurgitation (MR) is the most common heart valve disease together with aortic stenosis in worldwide industrial countries (48) and the incidence increase with age (49). The mechanisms of MR can be summarized in 2 categories: in primary MR the core components of the valve are the target of insufficiency process due to rheumatic or fibroelastic degeneration, as well as due to different collagenopathies or infective disease infiltration (50). Conversely secondary (functional) MR is related to left cardiac side cameras modification with an enlargement of valve ring diameter with a substantial normal structure of the leaflets (50,51). In most frequent secondary MR, the insufficiency is related to incomplete coaptation of the valve leaflets with a conflict of closing and tethering forces often associated with anular enlargement, caused by secondary left ventricular remodelling with displacement of the papillary muscles, dilatation and significant modification of LV geometry secondary to ischemic or non ischemic cardiomyopathies (50,51).Furthermore, a mitral annular dilation can also develop progressively in patients with persistent/permanent atrial fibrillation because left atrium enlargement (50). The worsening of secondary MR is mostly due by acute or chronic loading variations and subsequent progressive increase in LV end-diastolic volumes (51) and different studies have demonstrated how secondary MR is associated with increase mortality and morbidity (51); although it still remains quite debated if worsening of secondary MR is directly associated with progression of LV adverse remodeling or conversely whether secondary MR “per se” significantly contributes to poor prognosis (52). Indeed, it is more clearly established that drug therapies able to modulate acute loading changes (i.e diuretics and ino-vadilatators) can contribute in acute phase to ameliorate symptoms and reduce hospitalization (52) as well as those therapies that positive influence reverse remodelling such RAAS inhibitors, betablockers, neprilysin inhibitors, reduce significantly the risk of long term mortality (52).

In addition, non pharmacological therapies such as cardiac resyncronization when clinical indicated, showed to reduce the grade of secondary MR (53) and promote positive reverse remodelling (54); finally patients with secondary MR seem to obtain significant prognostic advantage from myocardial revascularization when significant ischemia has been documented (55,56).

MITRAclip: As well known, surgery still remains the gold standard intervention in patients with severe primary MR regurgitation (57); differently and much more debated, remain the indication of surgical or transcatheter intervention in secondary MR (50). Many patients who need treatment of primary or secondary MR are old or oldest-old patients with several and clinical complex comorbidities, so cardiac surgery had prohibitive risk or clearly contraindicated. Thus, on the way of Alfieri cardiac surgery operation (58) a novel transcatheter mitral valve edge to edge repair technique- MitraClip (Abbott Vascular Inc, Santa Clara, CA, USA) is recently developed (Figure 1). This percutaneous technique is performed usually during general anaesthesia even if a new approach with deep sedation has been proposed, under fluoroscopic and trans-oesophageal echocardiographic guidance that permits to interventional operators to advance the catheter system composed by delivery-system handle and the MitraClip device (a 4-mm-wide cobalt–chromium implant with two arms) from femoral vein through a posterior and superior atrial transeptal puncture into the left atrium till above mitral leaflets (59). At this point, after positioning delivery-system handle just perpendicular above regurgitating orifice, Mitra-clip is advanced into the ventricle and withdrawn till the mitral leaflets rest on the arms and can be grasped lowering the grippers and closing the arms, resulting in a double-orifice mitral-valve reproducing the haemodynamic effect of the Alfieri intervention. It is possible , in the case of inadequate MR reduction assessed by transesophaegel view, positioning more than one clips to reach a good hemodynamic result (59). During procedure patients were treated with unfractioned heparin for maintaining an ACT equal or more 300 sec; in the follow-up period according to trials protocols (59) all patients are treated with an empiric antithrombotic therapy with aspirin (at a dose of 325 mg daily) for 6 months and with clopidogrel (at a dose of 75 mg daily) for 30 days (60) since there are

no randomized studies comparing the safety/efficacy balance of these anti-thrombotic regimes. In addition, many older patients with HF and moderate to severe secondary MR presented different types of atrial fibrillation with a class IA evidence for long-term anticoagulation. No data are present comparing different anticoagulant regimens including NOACs have been investigated in patients undergoing MITRAClip at this time; probably NOACs in guideline-recommended doses might be a better choice for elderly patients candidate to MITRAclip and atrial fibrillation (61) but this hypothesis must to be tested in the next future.

Since 2005-2010 period the safety and efficacy of this technique was tested predominantly in primary MR in sporadic experiences, in 2011 the first randomized trial (59) EVEREST II demonstrated in 279 patients with mean age 65 yrs and 30% aged more than 75 yrs affected by severe MR from both mechanisms that MITRAclip was less effective in reducing mitral regurgitation than cardiac surgery; but the procedure was associated with superior safety and equal improvements in primary composite end-point defined as freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months.

In the same issue of December 2018, New England Journal of Medicine published MITRA-FIR (62) and COAPT (63) randomized trials that tested the role of mitraclip in secondary severe MR. In the French MITRA-FIR study 304 patients were randomized to mitraclip plus medical therapy versus medical therapy alone; in this population with mean age of 70 yrs and one third over 75 yrs the rate of death or unplanned hospitalization for HF at 1 year was similar between patients who underwent MITRAclip and medical therapy and those who received medical therapy alone (54.6% vs 51.3%; odds ratio, 1.16; 95% CI: 0.73 to 1.84; p = 0.53) (62). Conversely, data from american COAPT randomized trial showed in 614 patients with moderate to severe secondary MR that mitraclip group resulted in a lower rate of hospitalization for HF and lower all-cause mortality within 24 months of follow-up than medical therapy alone (63).

In a subsequent editorial of the New England Journal of Medicine two outstanding opinion leaders in the field of MR (64) highlighted more than one possible reasons to explain the different findings

of the two trials. Clinical, bio-humoral and NYHA class profile of COAPT patients seemed to design a presence of more advanced, truly medical refractory HF caused by secondary MR; echocardiography indexes showed in COAPT respect to MITRA-FIR trial a greater mean effective regurgitant orifice area, indicating the presence of more severe mitral regurgitation, associated with smaller mean left ventricular end-diastolic volume. A larger proportion of COAPT trial patients received during interventional procedure more than one clip to reduce regurgitant volume and another interesting result derived from comparisons of the K-M curves in the two trials. The survival curves appeared approximately overlapping during 1 year follow-up in the two trials, after which time, the trial groups in the COAPT study diverged. This findig could suggest a temporal lag on enrollment process of patients in the two trials. Nevertheless taking together, important clinical messages derived from the two studies; secondary mitral regurgitation is a disease of the left ventricle, thus it is firstly mandatory managed the left ventricular dysfunction with optimal guideline-directed medical therapy and, when indicated, biventricular pacing before planning any type of intervention involving the mitral valve. Secondly, MITRAclip must to be performed in experienced centers with a high volume and degree of success in which a skilled heart team group is able to correctly select patients preoperatively; these two indubitable conditions could be the clinical key for translating the positive effect of clipping reduction of the MR severity in a decrease of death and hospitalization for HF.

Recently based on conflicting data from randomized trials and in an attempt to explain convincingly the different outcome conclusions (64), Grayburn et al. (65) conceptualized two different echocardiographic and haemodynamic models of secondary MR, according to the relationship between effective regurgitant orifice area (EROA) relative to left ventricular end-diastolic volume (65). The author demonstrated, basing on linear relationship between the EROA (calculated with Gorling formula) and LVEDV over a range of LV volumes, that in the presence of progression of LV dilatation with reduction in ejection fraction is necessary that cut off EROA changing accordingly for diagnosing a severe secondary MR; thus in the presence of advance severe dilated

LV dysfunction an EROA of >0.4 cm2 must to be necessary to qualify as severe MR. Conversely, if the LV size is normal or near normal, a EROA 0.2 cm2 or less may be sufficient to meet the regurgitant fraction criteria for severe MR. Based on this assumption the authors defined as disproportionately or proportionally severe secondary MR if Gorlin-formula for EROA prediction (in the presence of regurgitant fraction equal or more 50%) fit or not fit with echocardiographic findings (65). An editorial of G. Stone (66) focused on this interesting paper, summarized the difficulties and complexity of correct definition of severe secondary MR , and acknowledging the clinical value of this new echocardiographic definitions, once again, he confirmed the crucial role of careful clinical evaluation expertly performed, the fundamental role of detailed echocardiography interpreted by skilled cardiologists, the necessity of GDMT optimization, sound application of cardiac resynchronization therapy and coronary revascularization when indicated and finally he suggests to use COAPT-like patient criteria for MITRAclip selection strategy.

This novel percutaneous procedure is recently tested in oldest old patients and reported in real world registry (67). Elbadawi et al. demonstrated that MITRAclip in nonagenarians was as safe as that in younger patients with similar in-hospital outcomes (67).; similarly in a open-label prospective study composed by 493 patients with severe MR who were treated with clip in Dussendolf University Hospital (68), MITRAclip was feasible and safe with intermediate-term beneficial effects in selected nonagenarians comparable with younger patients. No differences was detected a 1 years follow-up in term of cardiovascular function, as demonstrated by New York Heart Association class improving in the majority of patients, irrespective of age; and the rate of HF rehospitalization after clipping did not differ among the groups (16% in the nonagenarians, 16.7% in the octogenarians, and 17.7% in the septuagenarians).

Mitral valve anuloplastic ring reduction: in the earliest years an interventional approach focused on reducing anulus diameter has been proposed (69). Several percutaneous devices have been developed to reproduce surgical anuloplasty based on two different anatomical approaches. Indirect anuloplasty, which utilizes the passage of device through the coronary sinus for arriving in a

proximity to the posterior and lateral mitral annulus, or direct annuloplasty that similarly to surgical procedure is based on use of cinching the mitral annulus with sutures or anchors. (69).

Among these, three techniques deserve to be mentioned, *Carillon mitral contour system* (70), *Mitralign system* (71), *Cardioband system* (69). *The Carillon Mitral Contour System* (Cardiac Dimension Inc., Kirkland, WA, USA) is an indirect annuloplasty system fixed-length double anchor device implanted in the coronary sinus around the mitral annulus with subsequent reduction of MR due to septal–lateral compression of the posterior. This device does not change tethering of the leaflets, and it does not alter the architecture of the leaflets so a subsequent MV interventions are possible. In a first European study (72) were registered significant complications related to insufficient MR reduction and compromise of coronary artery blood flow needing to remove the device before final deposition. In a TITAN II second study (73) 83 patients were enrolled with successful implantation in 66 patients that obtained a sustained MR reduction and functional capacity improvement. *The Mitralign system* is a set of devices approaching the posterior mitral annulus through the left ventricle for a direct annuloplasty system using radiofrequency energy to penetrate sutures for two pledgets into the mitral annulus tissue posterior and anterior to the commissure under transesophageal echocardiogram guide view. Surgical pledgets are delivered over the wires and anchored across the annulus. The pledgets are pulled together to decrease the annulus circumference and the achieved plication is locked in place. Once the entire procedure is completed at one location, the next wire pair can be placed at the other scallop location. In the Mitralign Percutaneous Annuloplasty First-in-Man Study (74), device was successfully implanted in 50 out of 71 patients with secondary MR. The 30 day mortality was 4.4%. Echocardiography demonstrated reduction of MR grade in 50% of patients 6 months after implantation, associated with reverse LV remodelling and improved functional status (74). *The Cardioband system (Edwards Lifesciences, Irvine, CA, USA)* is a catheter-delivered annular reduction system (75) that mimics the surgical approach, is a direct annuloplasty adjustable device that is implanted in the beating heart on the posterior annulus under fluoroscopic and

transoesophageal echocardiographic (TEE) guidance. It is anchored along the posterior annulus of the MV and is made of a contraction wire and polyester fabric covering and is anchored into position by a series of stainless steel anchors. The Cardioband is available in six lengths to cover a wide range of annulus circumference sizes, comparable to surgical annuloplasty devices. After anchoring, the Cardioband implant is contracted under fluoroscopic and echocardiographic guidance to achieve a targeted anatomic annulus constraint; the evolving Cardioband experience for tricuspid regurgitation is also in progress. In a multicentre study 31 patients (mean age 71 years; EuroSCORE II: 8.6 ± 5.9) with moderate to severe FMR, symptomatic heart failure, and depressed left ventricular function (were prospectively enrolled (76) was effective in reducing MR and was associated with improvement in heart failure symptoms and demonstrated a favorable safety profile with rehospitalization for HF occurred in 10 patients (32%) within 6 months and mortality rate was 9.6% (3/31 patients) at 6 months.

Percutaneous Mitral valve replacement-TMVR : over the past decade, several transcatheter MV repair technologies (TMVR) have proposed as alternative to surgical repair or replacement in patients at high or prohibitive surgical risk (77). The complex anatomy and significant high risk percutaneous approach to MR, it makes reason about several difficulties related to clinical application of novel TMVR devices. Nonetheless, different mechanical systems have been tested either in preclinical and human studies even if nowaday data are not particularly exciting in few older patients enrolled. These TMVR devices can be a suitable approach in the case of MITRAclip must to be considered as a suboptimal choice by the presence of severe leaflet calcification, small mitral orifice area or for the presence of degenerated surgical bioprosthetic disease (78). The first TMVR in a native valve was performed in 2012 in Denmark (79); unfortunately, the progress of this interventional procedure has been quite slower than that has happened with TAVI; as already underlined, the reasons are manifold; this is challenging because of the D and saddle-shaped MV geometry, the elastic nature of the annulus, the significant difficulties to anchor the prosthesis, the large variation in mitral annular sizes, and the high probability to create a LV outflow tract

obstruction. There are currently different biological, self-expanding prostheses that are under clinical development (80). The implantation TMVR is executed mostly through a transapical access and less frequently through trans-septal access for a broad spectrum of mitral valve diseases, including native valve mitral regurgitation, valve in valve in degenerated bioprosthetic valves, valve in annuloplasty ring, and finally valve in mitral annular calcification (81). Based on aforementioned options we can summarized the use of TMVR in two broad categories, for native mitral valves or for those valves before treated with surgical bioprosthetic valves, annuloplasty or with trans-catether aortic valves. In native valve treatment the main goal is to anchor stably the prosthesis in a D-shaped, non-calcified structure avoiding migration into the left ventricle, the onset of paravalvular leaks and displacement of the anterior mitral valve leaflet into the LVOT. Several anchoring mechanisms for stabilized the prosthetic valve are proposed by different TMVR devices, such as apical tether, annular winglets, native leaflet engagement or using radial force of the prosthetic valve designed as "champagne cork-like", mitral annular clamping, or with external dock (82). IN TMVR utilized as secondary procedure after failed surgical valve, annuloplasty or with severe annular calcification the presence of radiopaque landing zone in the mitral position often gives a workable procedural advantage for implantation, making easier the prediction of size dimensions and minimizing the risk of paravalvular leak. A recent (83) retrospective analysis of data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry, 903 high-risk patients (median Society of Thoracic Surgeons score 10%) underwent TMVR for failed surgical valve (n=680),

In previous annuloplasty (n=123), or severe annular calcification (n=100) with median age 75 yrs Median age was 30-day mortality was respectively 8.1%, 11.5%, 21.8% with p for trend p=0.003. Data for outcomes in TMVR in native valve analyzed in a unpublished (84) analysis of few clinical trials shows a 30-day mortality ranged from 6-14% in this setting).

Despite promising and excellent data in patients candidate to TMVR for prosthetic valve failure, this procedure remains associated with higher risk of periprocedural complications and increased

mortality. Thus the role of Heart Team patient's selection and multimodality imaging are crucial to optimize TMVR procedure; moreover, significant uncertainties remain regarding the durability of different devices and controversies about the type of anticoagulation and adjunctive therapies to be planned after implantation.

Figure 1

Secondary tricuspid valve regurgitation and percutaneous tricuspid valve repair: Tricuspid regurgitation (TR) is one of the most common manifestations of valvular heart disease and may affect 65–85% of the population(ref), with a yearly incidence of about 200,000 to 300,000 patients (85). Trace or mild TR may be detected in routinely echocardiography in healthy subject; conversely, moderate-to-severe TR is pathological and usually caused by leaflet abnormalities and/or annular dilatation. Tricuspid valve disease can be a consequence of primary damage of structural architecture due to rheumatic disease, degenerative process, congenital malformation, secondary infectious often associated to opioid drug abuse, traumatic or iatrogenic origin (86). Secondary (or functional) TR is the most prevalent tricuspid pathology, it is almost always associated right ventricular dilatation or dysfunction, (87). The majority of patients suffer of moderate-to severe TR as a consequence of left-sided valvular heart, particularly mitral but increasingly also aortic valve disease sometimes worsening by the presence of persistent/permanent atrial fibrillation with a progressive onset of secondary pulmonary hypertension (87). Right ventricular dilatation is the leading cause of secondary TR caused by increased afterload due to post-capillary pulmonary hypertension; more, RV systolic function is sensitive to increase afterload with high probability to fall in RV ejection fraction. The severity of secondary TR and RV dysfunction are partially reversible with therapies aimed to reduce post capillary pulmonary hypertension in the early phase of the disease but when RV enlargement becomes irreversible the evolution is unpredictable, and severe late TR is associated with reduced survival (88) independently by efficacy of drug or interventional therapies focused on left ventricular disease. The devious and silent characteristic of TR progression is often the reason for a delayed referral of the patients with end-stage biventricular heart failure associated with severe TR to Tertiary Hospitals to perform surgical and trans-catheter interventions on secondary TR with satisfactory outcomes. A Heart Team patient selection with a pre-operative detailed and multimodality evaluation of the grade and anatomical characteristics of TR is mandatory to reach short and long-term improvement in functional and survival outcomes (89). The echocardiography still remains the

cornerstone imaging for assessing the etiology and severity of TR, although the reliability and validity regarding the semi-quantitative, and quantitative severity grade of TR is suboptimal. The ESC/EACTS guidelines (90) recommend the use of three echocardiography indexes to assess the grade of RV dysfunction; the severity is defined by tricuspid annular plane systolic excursion-TAPSE <15 mm, tricuspid annular systolic velocity <11 cm/s and RV end-systolic area >20 cm2.

In a preoperative phase of trans-catheter correction of severe TR, computed tomographic (CT) imaging is becoming a fundamental imaging step thanks to the capacity in describing the details of TV complex geometry (91). This methodology can provide essential imaging information about TV morphology, anatomic relationships and possible impediments inside of right ventricular camera, as well as multiple measures and geometry details of landing zone essential for anchoring the device may be registered (91,92); lastly, the risk for right ventricular outflow tract obstruction and a correct assessment of vascular access and sizing of the inferior vena cava-right atrium junction plane may be assessed. Given the fundamental role of the correct measure of RV function, cardiac magnetic resonance imaging represents the gold standard for quantifying right ventricular volumes, regurgitant volume and fraction, mean and peak velocity or trans-valvular gradient (92). In the case of eccentric and/or multiple tricuspid regurgitant jet, invasive right atrial, ventricular and pulmonary pressure indexes have to be measured with right heart catheterization to avoid uncorrect Doppler-derived estimation. Current guidelines (ESC/EACTS and AHA/ACC) state that in secondary severe TR surgery approach is recommended for patients undergoing left-sided valve surgery, independently from symptoms (Class I) and it should also be not delayed when severe TR occurring after left-sided valve surgery (with or without original TV intervention) (Class IIa) in symptomatic patients and in those who are asymptomatic but with progressive RV dilatation or dysfunction (90). In the last years, on the wave of increasing use of mitral percutaneous valve repair or replacement procedures, new trans-catheter solutions for the treatment of TR are now

available with devices similar to MitraClip or Mitralign. The worldwide experience with these devices is episodic or confined to small series of patients with the aim to test the safety; because the short and long term efficacy is yet to be convincingly demonstrated. However this percutaneous approach might find the main clinical indication in the late TR following previous left-sided valve surgery in high-risk patients affected by severe comorbidity such as advanced renal and/or hepatic impairment, and severe RV dysfunction sometimes as compassionate therapy .

Transcatheter TV repair therapies: the pathophysiological mechanisms which underlie the secondary TR are annular dilation and leaflet tethering resulting in altered coaptation which accounts for 90% of the cases in adults (86). Thus, trans-catheter TV repair (clipping method or annuloplasty) devices may be an option for improving leaflet coaptation. Today, scientific literature reports few clinical experiences predominantly with leaflet/coaptation devices (Figure 2); Tricuspid MITRAclip, PASCAL system and FORMA spacer device (93). Tricuspid MitraClip (Abbott Vascular, Santa Clara, CA, USA) device is similar to delivery system utilized for MR during left side procedure. Normally two methologic approach are routinely used to achieve reduction of TR with the MitraClip system: Triple-Orifice Technique (TOT) provides that clips are anchored centrally between the septal and anterior tricuspid leaflet as well as the septal and posterior tricuspid leaflet; in the second approach,the Bicuspidization Technique (BT), more than one clip are placed between the septal and anterior tricuspid leaflet (94). Based on few data the BT is considered more feasible and nowadays this is performed more frequently (94). The MITRAclip procedures may be performed for isolated TR or combined with MR reduction with optimal rate of success. Even modest reduction in regurgitant grade seems to reach a significant improvement in exercise capacity and health related quality of life. Data from recent studies showed a positive effect of edge-to-edge repair of TV on RV reverse remodelling and outcomes (95).

The PASCAL Transcatheter Valve Repair System consists of a 10-mm central spacer, which reduces the regurgitant volume filling the orifice and attaching to the valve leaflets with two paddles and clasps that distribute the load across the surface area of the grasped leaflets (96). Two

episodic compassionate use of the device reported a significant reducing of torrential TR with improvement of NYHA functional class IV dyspnea, severe fatigue, ascites, and peripheral edema . However, further research to assess the safety, efficacy, and durability of this system is needed and ongoig trial-CLASP TR early Feasibility Study is started (97). The third device FORMA system (Edwards Lifesciences, Irvine, CA, USA) is a spacer device placed within the TV orifice and anchored into the RV myocardium (98). The holes within the spacer shaft allow the spacer to expand passively and act as a surface for valve leaflet coaptation, reducing the effective regurgitant orifice area (EROA). A first report of compassionate use experience with the FORMA system reported that in the 15-patients cohort there were no deaths, significant arrhythmias, device infections, or dislocations after 1 year follow-up with an increase in performance at 6-minute walking test and in the Kansas City Cardiomyopathy Questionnaire. The safety and efficacy of the FORMA system will be further evaluated in two ongoing studies. Recently Orban et al. (99) demonstrated in 119 patients that trans-catheter tricuspid MITRAclip or PASCAL device for isolated severe Tricuspid Regurgitation showed to reduce hospitalizations for HF

A careful patient selection, definition of optimal procedure timing and evaluation of long-term outcomes and device durability will be a challenge of future studies in the field of primary and secondary TR.

Figure 2

Third generation LVAD

Today, the need for mechanical cardiac support-MCS devices is become a therapeutic option more frequently evaluated than in the past; the reason resides in higher rate of survival of patients suffered by cardiogenic shock or affected by end-stage refractory HF. The development of left ventricular assist devices (LVADs) began in the 1970s as a final permanent option for patients affected by end-stage HF as bridge to transplantation (100). Now, thanks to significant technical improvements associated with better anticoagulant and anti-infective therapy, MCS therapy has become a viable therapeutic approach for destination therapy or, hopefully, as bridge to recovery (100).

In the early period of development, MCS devices were burdened by frequent, life-threatening adverse events such as sepsis, stroke, life-threatening bleeding or sudden pump failure (101). The technical revolution is related to overcome the pulse flow devices and the introduction of continuous flow ones (102) with subsequent reduction of adverse events. The innovation of continuous-flow LVADs permits to reduce the size of the pump and cable, and their less complex design was aimed to provide greater long-term mechanical reliability, leading to an improved usefulness in destination therapy (103). Recently the use of centrifugal magnetic levitation is become available and thank to this mechanical approach a further miniaturization of devices it is now possible. This new third generation of devices have produced a dramatic advancement of durability and less invasive approaches, smaller designs, and more safe energy sources, it will probably expand their indications and the eligible candidates for a MCS (Figure 3). Currently, the 2 most commonly implanted continuous flow MCS are ***Heart Mate II*** as axial flow device (104) and the ***HeartWare ventricular assist device*** is a smaller centrifugal pump implanted in the intrapericardial space (105). Both devices are FDA-approved either for patients awaiting cardiac transplantation and for those eligible to destination therapy. In 2014 an interesting multicentre post approval (PA) study (106) prospectively enrolled the first 247 consecutive patients candidate to implant HeartMAte II for destination therapy due to advanced HF according to INTERMACS

(Interagency Registry for Mechanically Assisted Circulatory Support) classification. In this study with the majority of patients aged more than 60 years the authors demonstrated a satisfactory survival at 1 and 2 year follow-up. In fact in comparison with TRIAL finding, registry patients showed satisfactory data, as demonstrated by Kaplan-Meier survival at 2 years that was 62% versus 58% of trial patients. According with different INTERMACS profile PA group survival at 1 and 2 years was 82 % and 69 6% for INTERMACS profiles 4 to 7 and 72 % and 60 % for profiles 1 to 3. Another significant finding was the extremely reduction in length of stay after surgery that was in the median of 6 days . As reported by the authors these results should further encourage cardiologists to discuss more often the option of MCS as destination therapy with patients in advanced heart failure and their patients; obviously without omitting the still highly significant adverse, sometimes fatal burden of events. HeartWare (HVAD) is a third-generation type of implantable LVAD able to produce a high flow rate of up to 10 L/min although it is composed by a small (50 mL) pump body, with a diameter of the drive line is quite thin, at 4.2 mm, and the weight of the pump itself is light at

160 g, while the outflow graft is only 10 mm. This small device weighs 1.1 kg with also two batteries. The impellor is levitated by a magnetic hydrodynamic suspended system, and operates at 1,800–4,000 rpm. The HVAD has received the CE mark based on good early results reported in Europe and USA. In the 2017 the result of ENDURANCE trial (107) has been published in New England Journal of Medicine, this multicenter randomized trial involving 446 patients who were assigned, in a 2:1 ratio, to the study (HVAD-centrifugal-flow) device or the control (axial-flow-HEARTMATE II) device with mean age 63 vs 66 years respectively and the majority of sample in INTERMACS class 2-4. The trial, involving patients with advanced heart failure who were ineligible for heart transplantation, showed that a small, intrapericardial, centrifugal-flow LVAD was found to be noninferior to an axial-flow LVAD with respect to survival free from disabling stroke or device removal for malfunction or failure. HVAD was associated with higher risks of

stroke, right heart failure, and sepsis, whereas use of the HEARTMATE II was associated with more frequent device malfunction or failure requiring surgical intervention.

Figure 3

CONCLUSION AND FUTURE PERSPECTIVES

Over the past few years, novel drug and device treatments for HF have addressed many challenging issues in the hope to ameliorate prognosis and further, with the aim to recruit a greater number of patients, even with advanced age, previously excluded from any therapeutic possibilities. Based on more and more experience, physicians have now numerous and valid therapeutic choices to manage complicated and high-risk cases, before referred only to palliative care. Today the panorama of patients affected by HF is mainly composed by older and very old patients with clinical complexity and severe non cardiac comorbidity in which the prognosis is often related to worsening of heart disease but also dragged by adverse effects of other chronic conditions. Furthermore, the necessity to evaluate the global functional capacity, the health related quality of life and the risk of disability is now a prioritization before any high technological interventions. Thus, clinicians have to modulate the therapeutic choices on these clinical domains which represent the main goals of care for patients affected by HF well beyond of survival per se. In this perspective, the role of multidisciplinary Heart Team is becoming crucial for tailoring the best pharmacological and interventional therapeutic algorithm in each patient and to program a continuum care in a post-acute phase of treatment. Finally in our opinion, the possibility to plan multicentre registries of several complex cases evaluated by Heart Team could become a very important source of real world data to further refine indications and contraindications of different highly technological therapeutic approach, today based often on randomized clinical trials that do not represent faithfully the current clinical practice population.

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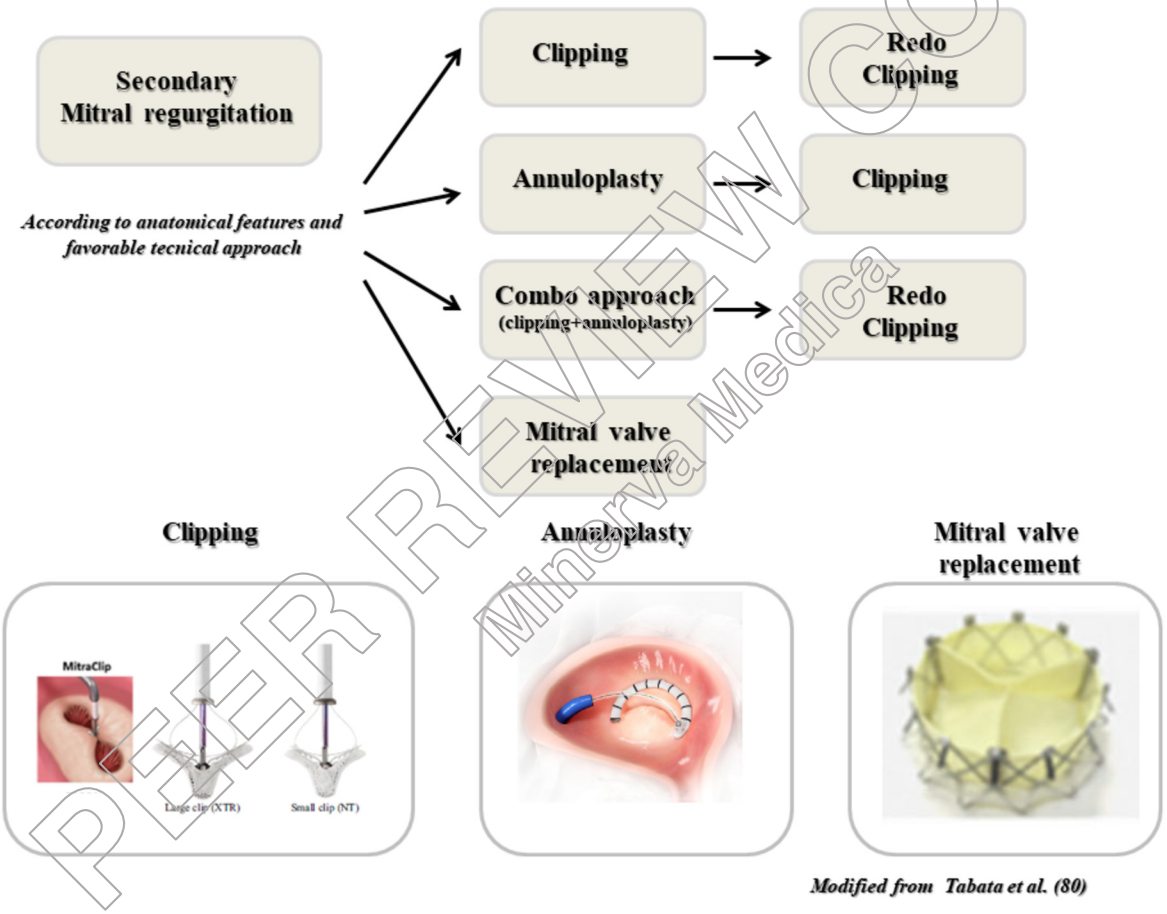
Table 1

Table 1. Representativeness of older patients in principle HF trials of ARNIs, SGLT2is and new potassium binder and results on outcomes and safety

	ARNI		SGLT2i			New potassium binder	
Trials (Type of HF) Comparator	PARADIGM-HF[10,13] (HFrEF) vs Enalapril	PARAGON-HF[23] (HFpEF) vs Valsartan	DAPA-HF[27,28] (HFrEF) vs Placebo	EMPEROR-R[29] (HFrEF) vs Placebo	SOLOIST-WHF[40] (Not specified**) vs Placebo	PEARL-HF[46] (Not specified#) vs Placebo	HARMONIZE[47##] (Not specified) vs Placebo
N° participants (Mean age, yrs)	8399 (63.8)	4796 (72.8)	4744 (66.4)	3730 (66.9)	1222 (69.5)	104 (68.0)	87 (69.1)
N° participants age ≥ 75yrs, %	18.6	45.9	24.2	Not reported*	Not reported***	Not reported	Not reported
Primary Outcome	Composite (CV death or first HF hospitaliz.) P <0.001, HR 0.80	Composite (HF hospitaliz. and CV death) P= 0.06,RR 0.87	Composite (worsening HF or CV death) P <0.001, HR 0.74	Composite (CV death or HF hospitaliz.) P <0.001,HR 0.75	Composite (CV deaths and HF hospitaliz./urgent visits P<0.001,HR 0.67	The mean change of serum K+ after 28 days P-value <0.001	Mean serum K+ comparison placebo vs treatment P-value <0.001
Primary outcome in older patients	Consistent across age subgroups P for interaction 0.94 HR 0.86	No age interaction (<75 yr vs ≥ 75 yr) RR 0.92	Consistent across age subgroups P for interaction 0.76 HR 0.68	Consistent across age subgroups (<65 yr vs ≥65 yr) HR 0.78	Consistent across age subgroups (<65 yr vs ≥65 yr) HR 0.62	Not specifically evaluated	Not specifically evaluated
Safety issues in older patients	Higher rate of symptomatic hypotension (not leading to discontinuation) 17.7% vs 11.9% in ARNI group P for interaction 0.95	Not specifically evaluated	Any serious AE (including death) increased with age but did not differ by treatment group in the ≥ 75 years patients P for interaction = 0.61	Not specifically evaluated	Not specifically evaluated	Not specifically evaluated	Not specifically evaluated

AE, adverse events; CV, cardiovascular; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFpEF/HFrEF, HF with preserved/reduced ejection fraction; HR, hazard ratio; RR, rate ratio; SGLT2i, sodium-glucose co-transporter inhibitor. *≥65 years = 62.1%; ** median left ventricular ejection fraction was 35%; **≥65 years = 70.2%; [#]mean left ventricular ejection fraction was 41%; [##]Here we reported only data about HF specific *post hoc* analisys.**



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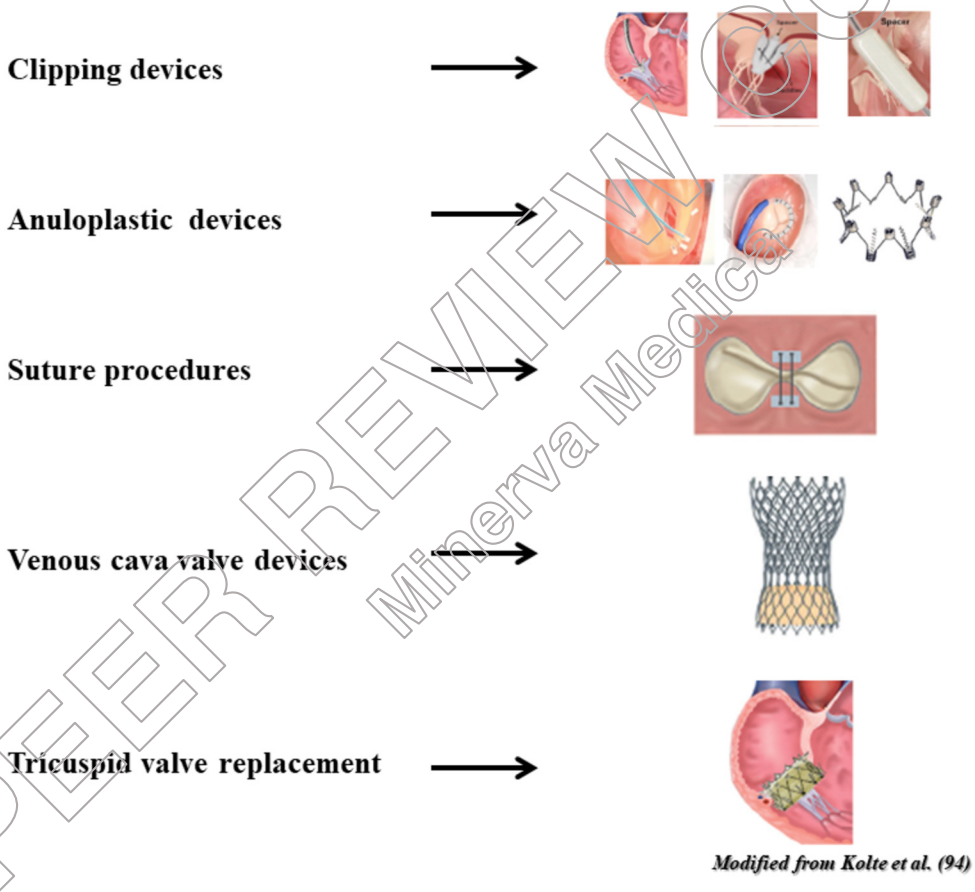

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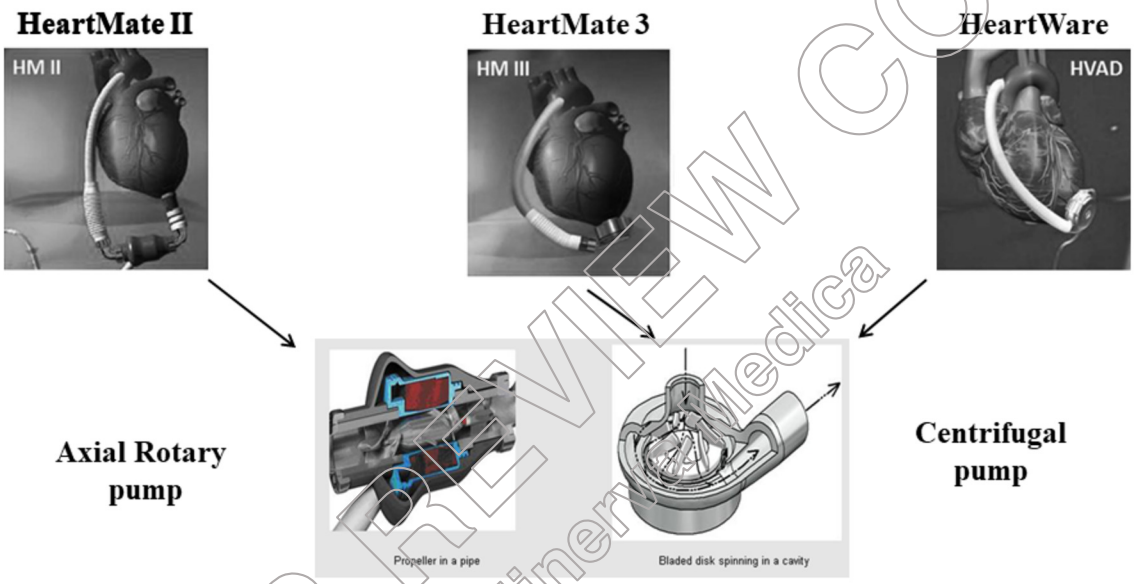

device	tipo	meccanismo	posizione	Peso gr	L/min	Velocità giri/min	terapia
HeartMate II	assiale	meccanico	Pre-peritoneale o addominale	350	4-8	8800-9200	Destination-T Bridge-trapianto
HeartWare	centrifuga	idrodinamico	Pericardico/ intratoracico	140	4-7	2500-2900	Destination-T Bridge-trapianto
HeartMate 3	centrifuga	magnetico	Pericardico/ intratoracico	240	4-6	5000-6000	Destination-T Bridge-trapianto

Modified from Moazami et al.(103) and Saeed et al. (108)