Review

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Ivabradine: a new frontier in the treatment of stable coronary artery disease and chronic heart failure

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Abstract

Ivabradine (IVA) is an inhibitor of the If channel, the main determinant of the pacemaker function of the sinus node. This pure heart rate-lowering agent possesses well-documented antianginal and anti-ischemic properties comparable to well-established antianginal agents, such as β-blockers and calcium channel blockers. IVA lowers heart rate (HR) without affecting contractility or vascular tone and it is licensed for HR control in chronic heart diseases. The heart rate reduction is beneficial in patients with coronary artery disease (CAD), chronic stable angina pectoris, and chronic heart failure (CHF). Published trials documented not only pharmacodynamic and pharmacokinetic properties but also acceptable tolerance and safety profile of IVA, compared to other currently used cardiovascular drugs, including betablockers. The aim of this review is to describe recent evidences with IVA an interesting medicament, able to lower HR by selective inhibition of the *If* current, and to describe its applications. ***Clin Ter 2020; 171 (5):e449-453. doi: 10.7417/CT.2020.2256***

Key words: *cardiovascular disease, chronic stable angina, chronic heart failure, heart rate, ivabradine*

Introduction

CAD and CHF belong to leading causes of death among patients with cardiovascular diseases. Therapeutical approaches do not always provide a significant improvement in the quality of life, a decrease in the frequency of CHF exacerbations and hospitalizations, and an improvement of the long-term prognosis. Selection of HR-slowing therapy in patients with CHF of ischemic genesis is often difficult due to the development of undesirable side effects of β-blockers, intolerance or contraindications for their use (1). In particular, not β1 selective β-blockers may cause bronchoconstriction in patients with chronic obstructive airway disease (2) and may have negative metabolic effects (3), including a reduction in insulin sensitivity.

A selective HR-lowering agent that does not produce these undesirable effects could thus be of therapeutic value (4).

HR is a powerful predictor of mortality in normal individuals and in patients with coronary events and heart failure (5,6), because its reduction decreases myocardial oxygen demand and improves endocardial blood supply. HR is the main determinant of myocardial oxygen consumption and energy utilization; furthermore, an increase in HR reduces the diastolic coronary perfusion time. An increase in HR as a consequence of increased sympathetic activity may trigger ischemic events (8). A wide number of epidemiological studies reported a strong independent association between elevated HR and major cardiovascular risk factors including atherosclerosis, ventricular arrhythmias, and left ventricular dysfunction: specifically, in CAD, elevated HR is an independent risk factor for major ischemic coronary events, cardiovascular mortality, and sudden cardiac death; in CHF, baseline HR is an independent risk factor of all-cause mortality, cardiovascular mortality, and hospitalization for CHF (9,10).

Numerous data in literature suggest that HR reduction during hospitalization or HR at discharge or in the vulnerable phase after it are more predictive of early-term events and may be therapeutic targets (11,12).

In this respect, IVA could be considered as a considerable option in patients with coronary stable angina (CSA) and CHF, because of its acceptable and favorable benefit-risk profile (13).

Characteristics of Ivabradine

IVA is a specific HR-lowering agent, with selective action on pacemaker activity in the sinoatrial node of the heart. It decreases HR and myocardial oxygen consumption at rest and during exercise (14-16). Its structure is similar to one of the first agents in this category of pharmacological compounds (zatebradine) but more specific and more reliable than zatebradine in selectively reducing HR (17). Both IVA and zatebradine are not able to influence the other currents involved in the genesis of action potentials in the sinus node cells: the specific action of ivabradine is the inhibition of the If current, which is a "mixed" conductance of Na+ and

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K+ ions. acts on a peculiar channel: the hyperpolarization activated-cyclic nucleotide (HCN)-gated channels, very similar to voltage-gated potassium channels (18).

The characteristic action of IVA consist in entering the open HCN channel; it is driven to its binding domain within the HCN channel by electrostatic forces generated by the depolarization process. The outward ion current pulls IVA to the site of interaction, while the repolarization produces an inward current able to determine a dissociation from the binding site. This unique characteristic of IVA is named current-dependence property (19). IVA is the first of a new class of HR-reducing agents without other direct cardiovascular effects (negative inotropic effect, blood pressure reduction) (20,21). It exhibited good tolerability and safety profile, and can be safely combined with other cardiovascular medicaments, such as β-blockers (22-24).

The HR-reducing effect of IVA is proportional to resting HR; extreme sinus bradycardia is uncommon. Although the QT interval is prolonged with the reduction in HR, no significant effect of IVA was found on ventricular repolarization duration (25), QT duration, QT dispersion, or maximum and minimum QT duration (26) with an adequate correction for HR. Consequently, IVA has no direct torsadogenic potential; however, this specific HR-reducing drug should not be administered with agents with QT-prolonging effects. Clinical trials evidenced that dose-dependent reversible visual side effects reported with IVA are not common at treatment doses up to 10 mg bid (27, 28).

Clinical Use of Ivabradine

IVA was firstly evaluated as an antianginal because of the expected anti-ischemic effect of its negative chronotropic properties, as was demonstrated in numerous early, multicenter, randomized studies. IVA (5.0, 7.5, and 10.0 mg bid) has been demonstrated to be non-inferior to atenolol (50 or 100 mg/day) in terms of antianginal and anti-ischemic efficacy in 939 patients with CSA in INITIATIVE (INternatIonal TrIAl on the Treatment of angina with IVabradinE versus atenolol) (29). In this study Tardif and coll. (29) found that the increase in exercise capacity was associated with a prolongation of exercise test duration. Another study, Associate (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibitor ivAbradine with a beTa-blockEr) explored the effect of IVA on top of atenolol 50 mg/day in 889 patients with CSA (28). IVA as monotherapy improved exercise tolerance, time to development of ischemia during exercise, and to reduce angina severity and nitrate usage, with benefits that were superior to placebo. When used concomitantly with betablockers, ivabradine displayed additional improvements these parameters (30): in combination with atenolol, IVA induced a significant increase in total exercise duration (primary efficacy criterion) and improvement in other exercise test criteria (time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression) compared with a placebo group receiving background therapy with atenolol. This study demonstrated that IVA can be added on top of β-blockers in CSA patients with insufficient HR reduction, in patients who remain symptomatic despite treatment with β-blockers (28), and in patients with refractory angina (31). The results of IVA in the treatment of CSA in patients with CAD have been confirmed in a broad patient population in everyday routine practice (REDUCTION Study) (32), independently of the severity of angina and the presence of comorbidities (33).

Another current indication of IVA in the international guidelines is CHF. The detrimental effects of elevated HR in both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) are well known. This is the basis for the use of IVA in the treatment of chronic HF as an agent that reduces HR without effects on inotropy, diastology, blood pressure, and vascular resistance. In SHIFT trial (Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial, which randomized 6,505 patients with New York Heart Association functional class II to IV symptoms, LVEF ≤35%, and sinus rates ≥70 beats/min to IVA versus placebo) the primary composite outcome of cardiovascular death for worsening HF was reduced by 18% in IVA group (HR: 0.82; 95% CI: 0.75 to 0.90), with a 26% reduction in hospitalizations. IVA was confirmed to be safe with infrequent, but statistically significant, side effects such as atrial fibrillation and symptomatic bradycardia (34,35).

HR reduction could also be an attractive therapeutic strategy HFpEF. Preclinical studies with IVA demonstrated a potential benefit in this condition, and led to small clinical studies that have had contradictory outcomes. Recently, in a randomized, double-blind, placebo-controlled trial of 179 patients with class II to III HF (LVEF ≥45%) and heart rate ≥70 beats/min, despite a reduction in HR of 13 beats/min, IVA did not improve any of the 3 coprimary endpoints (Doppler echocardiographic ratio of early diastolic mitral inflow velocity divided by mitral annular early diastolic velocity, distance on the 6-min walking test, and plasma N-terminal pro–B type natriuretic peptide), indicating a limited role in this population (30).

Impact of Ivabradine on Cardiovascular Morbidity

Measurement of HR represents an important component of the assessment of patients with CAD and CHF, and should be viewed in the same light as other risk factors, such as high blood pressure, cigarette smoking, cardiac dysfunction, and diabetes, all of which are associated with elevated HR. A high HR has direct detrimental effects not only on myocardial ischemia, but also on the progression of atherosclerosis, ventricular arrhythmias, and left ventricular function. The risk increases at values HR >60 bpm. IVA, a drug that slows HR though an effect on the If channels, can be used alone (when betablockers are contraindicated or not tolerated) or in combination with betablockers with an important impact on cardiovascular morbidity and mortality.

IVA has been demonstrated to improve cardiac outcomes in stable CAD and left ventricular systolic dysfunction in patients who have heart rates ≥70 bpm and in patients with stable angina. The BEAUTIfUL study demonstrated that the treatment with IVA (5.0 or 7.5 mg bid) in 11 thousands patients with stable CAD and left ventricular dysfunction (LVD) could lead to a 36% reduction in relative risk for fatal and nonfatal MI, a 30% reduction in the need for coronary

revascularization, and a 22% reduction in the hospitalization for fatal and nonfatal MI or unstable angina, in those with a baseline HR >70 bpm. This important research prospectively evaluated for the first time the effect of HR as a prognostic factor, by analyzing the effect of elevated HR on cardiovascular events in the placebo arm in this high-risk population of patients with CAD and LVD (36). Further analysis in the 1507 patients in BEAUTIfUL who had angina at baseline demonstrated that IVA improved the primary outcome (the composite of cardiovascular death, MI and hospitalization for heart failure) by 24% and MI alone by 42%, relative to placebo (37).

Similarly, the SHIfT study's secondary endpoints included cardiovascular mortality and hospitalization (38): IVA substantially and significantly improves outcomes in patients with CHF receiving the best possible evidence-based background treatment (39) and significantly reduced the primary composite endpoint of cardiovascular death or hospitalization for worsening heart failure by 18% (P<0.0001). The improvement in outcomes became apparent within 3 months of initiation of treatment, and benefits were maintained through the course of the trial in all prespecified subgroups: patients below or over 65 years of age, males and females, receiving or not betablockers at randomization, with heart failure of an ischemic or nonischemic etiology, NYHA class II or class III/IV, with or without diabetes, and with or without hypertension. Analysis of secondary endpoints showed a strong trend toward a 10% reduction in all-cause mortality (P=0.092), a significant reduction in death from heart failure by 26% (P=0.014), and significant reduction in hospitalization for heart failure by 26% (P<0·0001). In this study bradycardia leaded to study withdrawal in only 1% of the overall population, which is remarkable considering that 89% were receiving betablockers. These results support the importance of HR reduction with IVA for improvement of clinical outcomes in CHF (39).

The results of the BEAUTIfUL trial (24, 36, 37) shed new lights on the role of HR control in CVD and put the basis for the SIGNIfY trial (Study assessInG the morbidity-mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease), which enrolled patients with CAD and normal left ventricular function and resting HR ≥70 bpm. The primary endpoint took into consideration only CAD outcomes, i.e. cardiovascular mortality and hospitalization for MI. (40). Patients in the study received up to 10 mg twice daily, which is higher than the currently authorized maximum daily dose of 7.5 mg twice daily. The results from the trial suggest that these high doses of IVA have rather inconsistent effects on cardiovascular outcomes: there was no significant difference between the IVA group and the placebo group in the incidence of the primary end point (6.8% and 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; P=0.20). IVA was associated with a small but significant increase in the combined risk of CV death or nonfatal MI among patients with activity-limiting angina but not among those without activity-limiting angina. Among patients who had stable CAD without clinical HF, lowering heart rate with IVA doesn't reduce the risk of CV death or nonfatal MI (41).

In a very recent research (42), compared with placebo or standard care, IVA reduced HR compared with placebo or standard care (eight randomized clinical trials, 464 patients, weighted mean difference: –9.5 beats/min; 95% confidence interval: –13.3 to –5.8). Risk of bradycardia was not different between IVA and control (five randomized clinical trials, 434 patients; 95% confidence interval: 0.60–2.38).

Additionally, the use of IVA has recently been reported in limb girdle muscular dystrophy, in order to treat the associated cardiomyopathy (43). As advances in respiratory support have improved the outcomes of patients with muscular dystrophy; the prognostic significance of cardiac disease has increased: in this respect, IVA resulted to be well tolerated and reduced symptoms, morbidity and mortality in this cohort.

However, the effect on mortality in acute care remains unclear. Further clinical trials are required in order to detect changes in clinically relevant outcomes.

New Perspectives on the Use of Ivabradine

An interesting therapeutical strategy, recently gaining more attention in clinical practice, is the fixed combination in association with the betablocker metoprolol. In a recent prospective, multicenter, observational cohort study, the effectiveness and tolerability of the first fixed-dose combination (FDC) formulation of IVA and metoprolol was evaluated in stable angina pectoris: patients received this FDC for 4 months, in addition to cardiovascular standard therapy; HR, number of angina attacks, short-acting nitrate consumption, severity of symptoms and tolerability were documented (44). In this cohort of patients in their real-life setting (presenting with already intense anti-anginal pre-treatment at baseline) the FDC preparation was associated with a further reduction in HR by 10 bpm, a clinically relevant reduction of angina symptoms and nitrate consumption by more than 80%, an improved exercise capacity. Proportion of patients with ≥ 1 angina attacks/week decreased from 38 to 7%. The tolerability of the FDC was favorable with no unexpected safety signals during follow-up, thus increasing medication adherence and symptom control in clinical practice.

A beneficial effect of IVA on inappropriate sinus tachycardia has also been reported, with a significant reduction in the level of symptoms in investigated populations In a recent study, almost all patients with excessive sinus node automaticity were asymptomatic on treatment; in contrast, the majority of patients with autonomic dysregulation reported residual symptoms (45). As the remaining symptoms were observed despite effective heart rate reduction, these complaints could be attributed to dysautonomia. Another study investigated the effectiveness of early short-term IVA treatment in new-onset acute HF and concurrent sinus tachycardia in patients with inflammatory rheumatic disease (46). HR, left ventricular ejection fraction, biomarkers of HF and NYHA classification score were compared prior to and after IVA treatment. The mean resting HR decreased from 118.0±13.8 to 83.3±7.3 bpm; transthoracic echocardiography evidenced a significant improvement in the left ventricular ejection fraction after 2 weeks IVA prescription when compared with the baseline evaluation (51.2±8.4 vs. 38.0±9.0%); N-terminal proB-type natriuretic peptide decreased (4,900±3,672 vs. 16,806±16,130 pg/ml) with

an improvement in NYHA classification score (2.3±0.6 vs. 3.5±0.5) at 2 weeks. This suggested that early use IVA is safe in patients with new-onset acute HF and enhances the sinus rate reduction, which could improve heart function (46).

Conclusion

IVA points toward an important approach in the treatment of patients with CAD or CHF, the most common type of heart disease representing a global health problem with heavy economic costs (47-50), based upon the concept of exclusive HR reduction.

Together with life-style change and nutritional cardiovascular prevention (51-59), IVA can represent an appropriate pharmacological approach in order to reduce cardiovascular morbidity and mortality. Beyond simple HR reduction, IVA's benefits are related to its limited side effects: this characteristic makes it more acceptable to patients. Nevertheless, more research is needed in order to obtain more solid evidence about its use in clinical medical practice.

Conflict of interest: Authors declare no conflict of interest

References

1. Belenkov YN, Ilgisonis IS, Naymann YI, Privalova EA, Zhito AV. Kardiologiia. 2019; 59(10): 60–65
2. Tattersfield AE. Respiratory function in the elderly and the effects of beta blockade. Cardiovasc Drugs Ther 1991;4:1229–32
3. Baldini D, Beck R, Negro F, De Viti D. Assisted reproductive technologies and metabolic syndrome complications: medico-legal reappraisal. Clin Ter. 2019; 170(5):e364-e367
4. C. Perret-Guillaume, L. Joly, A. Benetos: Heart rate as a risk factor for cardiovascular disease. Prog Cardiovasc Dis 2009; 52:6-10
5. Gammone MA, Riccioni G, Massari F, et al. N. Beneficial effect of ivabradine against cardiovascular diseases. Front Biosci (Schol Ed) 2020; 12:161–172
6. Rosano GM, Vitale C, Volterrani M. Heart rate in ischemic heart disease. The innovation of ivabradine: more than pure heart rate reduction. Adv Ther 2010; 27:202-10
7. Kjekshus, L. Gullestad: Heart rate as a therapeutic target in heart failure. Eur Heart J 1999; 1:64–9
8. Gammone MA, Riccioni G, et al. Novel therapeutic strategies against cancer: marine-derived drugs may be the answer? Anticancer Agents Med Chem. 2016;16(12):1549-1557
9. Verrier RL, Tan A. Heart rate, autonomic markers, and cardiac mortality. Heart Rhythm 2009; 6:68-75
10. Fox K, Borer JS, Camm AJ, et al. Heart Rate Working Group. Resting heart rate in cardiovascular disease. J Am Coll Cardiol 2007; 50:823-30
11. DiFrancesco D. Cardiac pacemaker I_f, current and its inhibition by heart rate reducing agents. Curr Med Res Opin 2005; 21:1115-1122
12. Sciatti E, Vizzardi E, Bonadei I, et al. The role of heart rate and ivabradine in acute heart failure. Monaldi Arch Chest Dis. 2019; 89(3):10.4081
13. Alshammari TM. Ivabradine: do the Benefits Outweigh the Risks? J Cardiovasc Pharmacol Ther. 2016 [1074248416672008]
14. Riccioni G. Ivabradine: from molecular basis to clinical effectiveness. Adv Ther 2010; 27:160-7
15. Baruscotti M, Barbuti A, Bucchi A. The cardiac pacemaker current. J Mol Cell Cardiol 2010; 48:55-64
16. DiFrancesco D, Borer JS. The funny current: cellular basis for the control of heart rate. Drugs 2007; 67:15-24
17. Scicchitano P, Cortese F, Ricci G. Ivabradine, coronary artery disease, and heart failure: beyond rhythm control. Drug Des Devel Ther. 2014; 8:689–700
18. Bucchi A, Baruscotti M, DiFrancesco D. Current-dependent block of rabbit sino-atrial node I(f) channels by ivabradine. J Gen Physiol. 2002; 120(1):1-13
19. Scicchitano P, Carbonara S, Ricci G, et al. Molecules. 2012 Apr 5; 17(4):4225-35
20. Manz M, Reuter M, Lauck G, et al. A single dose of ivabradine, a novel If inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. Cardiology 2003; 100:149-55
21. De Ferrari GM, Mazzuero A, Agnesina L, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart Fail 2008; 10:550-5
22. Riccioni G. Focus on ivabradine: a new heart rate-controlling drug. Expert Rev Cardiovasc Ther 2009; 7:107-13
23. Gammone MA, Riccioni G, D'Orazio N. Impact of Ivabradine on Cardiovascular Morbidity. J Card Disease Res 2020; 11(1):4-8
24. Fox K, Ford I, Steg PG, et al. BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular dysfunction (BEAUTIFUL): a randomized, double-blind, placebo-controlled trial. Lancet 2008; 372:807-16
25. Savelieva I, Camm AJ. Novel If current inhibitor ivabradine: safety considerations. Adv Cardiol 2006; 43:79-96
26. Murat SN, Orcan S, Akdemir R, et al. Arrhythmic effects of ivabradine in patients with coronary artery disease. Clin Invest Med 2009; 32:322-6
27. Tardif JC. Ivabradine: I(f) inhibition in the management of stable angina pectoris and other cardiovascular diseases. Drugs Today 2008; 44:171-81
28. Tardif JC, Ponikowski T, Kahan T, for the ASSOCIATE Study investigators. Efficacy of If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4 month, randomized, placebo-controlled trial. Eur Heart J 2009; 26:2529-36
29. Tardif JC, Ford I, Tendera M, and INITIATIVE Investigators. Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 2005; 26:2529-36
30. Koruth JS, Lala A, Pinney S, et al. The Clinical Use of Ivabradine. J Am Coll Cardiol. 2017;70(14):1777–1784
31. Ripa C, Germano G, Caparra A,et al. Ivabradine use in refractory unstable angina: a case report. Int J Immunopathol Pharmacol 2009; 22:849-52
32. Koster R, Kaehler J, Meinertz T. REDUCTION Study Group. Treatment of stable angina pectoris by ivabradine in every day practice: the REDUCTION study. Am Heart J 2009; 158:51-7
33. Tendera M, Borer JS, Tardif JC. Efficacy of I(f) inhibition with ivabradine in different subpopulations with stable angina pectoris. Cardiology 2009; 114:116-25

34. Swedberg K, Komajda M, Böhm M, et al. SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376:875-885
35. Böhm M, Swedberg K, Komajda M, et al. SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010; 376: 886-894
36. Fox K, Ford I, Steg PG, et al. BEAUTIFUL investigators. Heart rate as a prognostic risk factors in patients with coronary artery disease and left-ventricular dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008; 372:817-21
37. Fox K, Ford I, Steg PG, et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur Heart J 2009; 30:2337-45
38. Swedberg K, Komajda M, Bohm M, et al. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail 2010;12:75-81
39. Swedberg K, Komajda M, Böhm M,et al. on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010; 376:875-85.
40. Ferrari R. A step further with ivabradine: SIGNIfY (Study assessInG the morbidity–mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease) Eur Heart J Suppl 2009;11:D19-D27
41. Fox K, Ford I, Steg PG, et al. SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014; 371(12):1091-9
42. Chen A, Elia N, Dunaiceva J, et al. Effect of ivabradine on major adverse cardiovascular events and mortality in critically ill patients: a systematic review and meta-analyses of randomised controlled trials with trial sequential analyses. Br J Anaesth. 2020; S0007-0912(20)30096-9
43. Rajendram R, AlDhahri F, Mahmood N, et al. The use of ivabradine in a patient with inappropriate sinus tachycardia and cardiomyopathy due to limb girdle muscular dystrophy type 2I. BMJ Case Rep. 2020; 13(1):e230647
44. Divchev D, Stöckl G; study investigators. Treatment of Stable Angina with a New Fixed-Dose Combination of Ivabradine and Metoprolol: Effectiveness and Tolerability in Routine Clinical Practice. Cardiol Ther. 2017; 6(2):239–249
45. Kaczmarek K, Klingenheben T, Poddebska I, et al. Baseline intrinsic heart rate and response to ivabradine treatment in patients with inappropriate sinus tachycardia. Ann Noninvasive Electrocardiol. 2019; e12709
46. Wu W, Zhang L, Zhao J, et al. Early short-term ivabradine treatment in new-onset acute systolic heart failure and sinus tachycardia patients with inflammatory rheumatic disease. Exp Ther Med. 2019;18(1):305–311
47. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442
48. Heart Disease and Stroke Statistics–2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119:21-181
49. Leal J, Luengo-Fernandez R, Gray A, et al. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006; 27:1610-9
50. Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. Eur Heart J 1999; 1:64-9
51. Gammone MA, Riccioni G, D'Orazio N. Carotenoids: Potential allies of cardiovascular health? Food Nutr. Res. 2015; 59: 26762
52. Gammone MA, Riccioni G, D'Orazio N. Marine carotenoids against oxidative stress: Effects on human health. Mar. Drugs 2015; 13:6226–6246
53. Gammone MA, Tettamanti G, Bergante S, et al. Prevention of cardiovascular diseases with carotenoids. Front. Biosci. (Schol. Ed.) 2017, 9, 165–171.
54. Gammone MA, Efthymakis K, Pluchinotta FR, et al. Impact of chocolate on the cardiovascular health. Front. Biosci. (Landmark Ed.) 2018; 23:852–864
55. Gammone MA, D'Orazio N.Anti-obesity activity of the marine carotenoid fucoxanthin. Mar Drugs. 2015 Apr 13; 13 (4):2196-214
56. Riccioni G, Gammone MA, Tettamanti G, et al. Resveratrol and anti-atherogenic effects. Int Journal of Food Sciences and Nutr. 2015
57. Gammone MA, Riccioni G, Parrinello G, et al. Omega-3 polyunsaturated fatty acids: Benefits and endpoints in sport. Nutrients 2019; 11(1): 46
58. Gammone MA, Danese A, D'Orazio N. Anti-Angiogenetic Agents from the Sea: A New Potential Preventive and Therapeutic Wave? Anticancer Agents Med Chem. 2020;10:2174
59. Riccioni G, Gammone MA, Currenti W, et al. Effectiveness and Safety of Dietetic Supplementation of a New Nutraceutical on Lipid Profile and Serum Inflammation Biomarkers in Hypercholesterolemic Patients. Molecules. 2018: 14;23(5)