Journal of the Egyptian Society of Parasitology, Vol. 54, No. 2, August 2024
J. Egypt. Soc. Parasitol. (JESP), 54(2), 2024: 313 - 318
Online: 2090-2549

VONOPRAZAN VERSUS PROTON PUMP INHIBITORS IN COMBINATION WITH ANTIBIOTICS AS A TRIPLE THERAPY FOR ERADICATION OF CLARITHROMYCIN RESISTANT STRAIN OF HELICOBACTER PYLORI

By
MOSTAFA A. ELFORS and AHMED M. NAGUIB
Department of Internal Medicine, Hepatology and GIT Unit, Faculty of Medicine, Ain Shams University, 11566 Cairo, Egypt
(Correspondence: mostafaalfors@med.asu.edu.eg, ORCID: 0009-0000-9578-8133; ahmed_naguib@med.asu.edu.eg ORCID: 0009-0008-8681-2857)

Abstract

Generally, the common etiology of gastritis infection with *Helicobacter pylori* (*H. pylori*) is increasing. Vonoprazan inhibits the activity of H+/K+ ATPases, with greater effect than PPIs on decreasing gastric acidity. This randomized controlled study was performed on two Egyptian patients groups: G1: 160 patients treated with Vonoprazan, Levofloxacin and Amoxicillin for two weeks, and G2: 160 pat-ients treated with Pantoprazole, Levofloxacin andAmoxicillin for two weeks. Testing fecal *H. pylori* Ag for all patients was done 8 weeks later after the completion of treatment course.

The results showed that 136 of 160(85%) patients were negative for *H. pylori* Ag in G1 compared to 112/160(70%) patients in G2 with the In intention to treat (ITT) analysis and per-protocol (PP) analysis, for eradication rates was in G1greater than in G2 (P = 0.004, 0.002), respectively.

Keywords: Vonoprazan, Proton pump inhibitors, *Helicobacter pylori*, Pantoprazole, Clarithromycin, levofloxacin, Amoxicillin, fecal *H. pylori* Ag, Intention to treat, per-protocol, resistant strain.

Introduction

Helicobacter pylori is a risk factor for development of peptic ulcer disease, gastric adenocarcinoma, and primary B cell lymphoma of stomach (Yang *et al,* 2009). *H. pylori* infection is considered to be the primary etiology of chronic gastritis with a carcinogenic effect on gastric mucosa (Maruyama *et al,* 2017). Long-standing inflammations in gastric mucosa led to peptic ulcers, atrophic gastritis, mucosa-associated lymphoid tissue lymphoma, other malignancies, and idiopathic thrombocytopenic purpura (Kiyotoki *et al,* 2020). For *H. pylori* diagnosed outside the peptic ulcer disease context, most authorities advocated eradication based on a 10% lifetime risk of developing peptic ulcer disease and a two to three times higher incidence of gastric adenocarcinoma (Chey *et al,* 2017). A major concern regarding long-term PPI therapy has been the suggestion that patients infected by *H. pylori* were at increased risk for the development of atrophic gastritis during long-term therapy with PPIs (Moayyedi *et al,* 2016), as *H. pylori* is a carcinogenic agent (Tsugawa *et al,* 2012).

A triple therapy protocol with PPIs, Amoxicillin (AMX), and Clarithromycin (CLR) was the first approach to eradicate *H. pylori*, commonly used **(**Gisbert and Calvet, 2011) Also, PPI-based therapy of eradication rate increased in the last decade, due to antibiotics decreased effectiveness and resistance **(**Liou *et al,* 2016). To improve the antibiotics efficacy for *H. pylori*-eradication, gastric pH must be 6 to 7 (Sachs *et al,* 2011)**.** But, *H. pylori* eradication failure was secondary to Clarithromycin resistance, and antibiotics resistance of combined drugs more doses for long treatment durations was indicated (Kiyotoki *et al,* 2020). Antimicrobial resistance of *H. pylori* can be identifed by culture and sensitivity, but presently, these tests aren't readily accessible on a large scale (Ierardi *et al,* 2013). If a patient received a Clarithromycin-containing regimen Levofloxacin salvage regimens or Bismuth quadruple therapy (BQT) as optimal management procedures (Shaikh and Fallone, 2016). The optimal salvage treatment must be determined based on localized antimicrobial resistance patterns and previous usage of antibiotics. If the individual has already had first-line BQT, the most effective therapeutic proto-

cols that included either clarithromycin or levofloxacin (Vaira and Vakil, 2001). The Salvage treatment options included the following: BQT for a duration of 14 days; Levofloxacin-triple therapy for a duration of 14 days; or a concomitant regimen duration of 10-14 days, but not to use with clarithromycin triple regimen as a salvage treatment (Chey *et al,* 2017)

Vonoprazan (VPZ) is a novel reversible K-competitive blocker that effectively inhibits acid secreation within gastric juice by H+/K+ ATPase, with a potency 350 times greater than that of Lansoprazole (LPZ), a commonly used PPI, in vitro studies causing gastric juice stability and immediate action (Echizen, 2015).

This study aimed to evaluate the efficiency of Vonoprazan in eradication of *Helicobacter pylori* of Clarithromycin®-resistant strain in *H. pylopri* patients.

Patients and Methods

Study design: The enrolled cases were inpatients and outpatient of Gastroenterology Departments, Ain Shams University Hospitals between October 2023 and April 2024.

Ethics approval: Trial registration FMA SU R288/2023: Efficacy of vonoprazan in eradication of *H. pylori* resistant strain, NCT0 6414707, by Faculty of Medicine, Ain Shams University (FMASU R288/2023). Each patient was given written concept after being informed about the study aim.

This randomized controlled trial was conducted on 320 Egyptian cases with dyspepsia due to *H. pylori* infection with Clarithromycin-resistant strains and randomly divided into two groups. G1 included 160 patients treated with Vonoprazan 20mg oral once/day, Levofloxacin 500mg oral once/day & AMX 1g oral twice/day for two weeks. G2 included 160 patients treated with Pantoprazole 40 mg oral twice/day, Levofloxacin 500mg oral once/day and Amoxicillin (AMX) 1g oral twice/day for two weeks.

Sample size was calculated by Med-Calc software version 22.009 packages for the biomedical study. Two-sided confidence level: 95%; power: 80% was in both groups with ratio 1:3. The eradication rate of Vonoprazan versus PPI among *H. pylori* cases was expected to be 91.5% versus 77.9% (Suzuki *et al,* 2015). Sample size was 109 patients per group, but to overcome the dropout rate, a total of 160 cases were in each group.

Inclusion criteria: All *H. pylori* cases suffered from Clarithromycin-resistance proved by a persistent fecal *H. pylori* Ag positive tests. All were followed up for 8 weeks post-treatment by fecal *H. pylori* Ag, and compliance failure or gastrointestinal bleeding.

Exclusion criteria: Drug allergy cases, with gastroenterology malignancy, on immune treatment, with inflammatory bowel diseases, malabsorption syndrome, and/or HIV ones.

Medical sheets were filled out on each. They were subjected to full physical and clinical assessments, and laboratory examination for CBC, ALT, AST, Serum creatinin, and fecal *H. pylori* Ag, and another stool samples were taken 8 weeks post-treatment to evaluate *H. pylori* eradication and by a pelvi-abdominal U/S was done.

Statistical analysis: Data were collected, coded on computers, and analyzed by SPSS Statis- tical Program for Analysis (USA, Chicago, IBM Inc., IL). Numerical variables were displayed as mean and standard deviation. Categorical parameters were displayed as frequencies. A two-tailed P value $\leq$ 0.05 was considered significant value.

Results

Patients were 200 males (62.5%), and 120 females (37.5%), distributed as 104 males (65%) and 56 females (35%) with an average age of 41.763±9.905 years in G1 and 96 males (60%) and 64 females (40%) with an average age of 42.706±10.710 years in G2. The missed were 8 instances in G1 and 12 instances in G2

Both groups as to CBC, liver enzymes, and serum creatinine didn't show sig-nificant variations. By correlating Hb levels with *H.pylori* Ag, a significant correlation existed among *H. pylori* Ag and Hb levels, with lo-

west Hb values in *H.pylori* Ag positive patients compared to higher *H.pylori* Ag values in negative ones (P< 0.001). *H. pylori* Ag results after therapy showed a significant difference (P= 0.004).

The eradication rate using intention to treat analysis (ITT), full analysis study (FAS), and per-protocol study (PP) showed that a substantial variation existed among the both groups as regard ITT and PP, with higher rates of eradication in G1 versus G2 (P= 0.004 & 0.002 respec- tively).

Details were given in tables (1, 2, 3 & 4) and figures (1, 2, & 3)

Table 1: Comparison between groups according to CBC (n= 320)

Variations		G1	G2	T- test	P-value
Hb (gm./dl)	Range	9-16.4	8.5-16.3	1.567	0.118
	Mean ±SD	12.813±2.082	12.447±2.093		
PLTs x10^3/cmm	Range	178-442	149-449	1.666	0.097
	Mean ±SD	302.12±78.566	286.900±84.754		
WBCs x10^3/cmm	Range	3.8-8.7	3.9-10.4	-0.756	0.450
	Mean ±SD	6.233±1.395	6.355±1.503		
AST(IU/L)	Range	16-43	11-52	-1.641	0.102
	Mean ±SD	29.319±7.561	30.875±9.314		
ALT(IU/L)	Range	22-47	16-49	-1.001	0.318
	Mean ±SD	32.725±7.230	33.575±7.946		
S. Creat (mg/dl)	Range	0.5-1.3	0.6-1.4	-1.042	0.298
	Mean ±SD	0.958±0.252	0.985±0.219		

Table 2: Correlation between *H. pylori* Ag & Hb leves

Item	*H. p.* Ag negative	*H. p.* Ag positive	T-Test	
	Mean± SD	Mean± SD	t	P-value
Hb (gm/dl)	12.930±2.009	11.423±2.148	4.859	<0.001*

*P≤ 0.05

Table 3: Comparison between groups according to *H. p.* Ag post-treatment (n= 320)

H. p. Ag	G1		G2		Chi-Square	
	No.	%	No.	%	X^2	P-value
Missed	8	5.00	12	7.50	10.815	0.004*
Negative	136	85.00	112	70.00		
Positive	16	10.00	36	22.50		

*P≤ 0.05.

Table 4: Comparison between groups as to eradication rate analysis (95% C.I).

H.P Ag	G1		G2		P-value	
	ITT	PP	ITT	PP	ITT	PP
%	85	89.47	70	75.68	0.004*	0.002*
95% C.I	(71-100)	(75-100)	(58-84)	(62-91)		

*Significant. ITT, Intention to treat. PP; Per-protocol

Discussion

Helicobacter pylori is the most common human bacterial infection globally, infecting most of the world's population. However, antibiotic used for *H. pylori* eradication, the recommended antibiotic type varies from one to country according to *H. pylori* resistance pattern, such as Egypt, may have different patterns than others (Metwally *et al,* 2022). Hassanein *et al.* (2023) in Alexandria added that swimmers must be aware of getting different microbes as *H. pylori*, together with *Giardia* spp., *Blastocystis* spp., or *Cryptosoridium* spp., which can live together in human body.

Clarithromycin resistance has notably escalated over time, leading to decline in efficacy of frequently used combination of PPIs, AMX, & CLR for *H. pylori* eradication (Fallone *et al,* 2016). In Europe and the USA, effectiveness of PPI-based triple treatment decreased infection to fewer compared to 80%, and it is important to optimize antimicrobial agents on *H. pylori* increases with high gastric acidity. Optimal antibact- erial action of some maintaining control over the pH levels in the stomach might potentially enhance the success eradicating rate of *H. pylori* (Chey *et al,* 2022).

Sue *et al.* (2018) in Japan carried out prospective randomized trial to evaluate the efficacy of VPZ-based and PPI-based seven-day

triple therapy, using AMX and Sitafloxacin as a 3rd line medication, for *H. pylori* eradication after failures with CLR-based and Metronidazole-based regimens. They used a regimen contained VPZ 20mg or a combination of PPI & AMX 750mg & Sitafloxacin 100mg twice/ day for a week as measured by VAS or PPI-AS. They reported that the VPZ group had rates of eradication of 75.8% (95% CI, 57.7-88.9%) for ITT and 83.3% (95% CI, 65.3-94.4%) for PP as compared to PPI group with rates of eradication of 53.3% (95% CI, 34.3–71.7%) for ITT and 57.1% (95% CI, 37.2–75.5%) for PP. They added that in the VAS one, eradication rates were higher compared to those in PPI-AS group in the PP analysis (P= 0.043). Nevertheless, the ITT analyses didn't show significant variations (P= 0.071).

Chey *et al.* (2022) in France carried out a randomized clinical trial with extensive analysis of a multicenter discovered the *H. pylori* eradication rates by VPZ-triple therapy were 80.8% (273/380), but with Lansoprazole triple therapy 68.5% (226/330). They concluded that both vonoprazan-based regimens were superior to proton pump inhibitor-based triple therapy in clarithromycin-resistant strains and in all studied population.

Fallone *et al.* (2019) in Canada mentioned that increasing resistance to antibiotics globaly has adverse effects on the standard therapies effectiveness to eradicate *H. pylori* infection, and reviewed guidelines developed by expert groups in Europe, Canada, and the United States for the *H pylori* treatment. They concluded that the options under investigation included substituting vonoprazan for proton pump inhibitors, adding probiotics, and vaccine development. Narrow-spectrum antibiotics and new therapeutic targets must be identified based on genomic, proteomic, with *H. pylori* metabolomic analyses.

Islam *et al.* (2024) reported some patients with coexistence of drug resistant- and sensitive-isolates (drug-heteroR/S-patients), and that more than 60% of patients were drug-heteroR/S to all four drugs, indicating extensive heterogeneity. They concluded that two mutations in PBP1A, G591K and A480V, as well as analyzed these in recombinants to directly demonstrate their association with AMX resistance.

Okubo *et al.* (2020) in Japan reported that clarithromycin (CAM)-resistant *H. pylori* was prevalent in one-third of patients in the Tokyo metropolitan area. They added Vonoprazan (VPZ)-based triple therapy was highly effective and well-tolerated irrespective of CAM susceptibility. Thus, it could be a valuable first-line treatment regimen for *H. pylori* infection. Liu *et al.* (2024) in USA, found that eradication rate of vonoprazan-based bismuth-containing quadruple therapy (VBQT) was highest above 90% followed by vonoprazan-amoxicillin-clarithromycin (VAC) & vonoprazan-amoxicillin (VA). VA was as effective as VAC and superior to PPI-based therapies with favora-ble safety, highlighting the potential of VA therapy as a promising alternative to traditional PPI-based therapies. The VPZ-based triple or quadruple therapies was more effective than PPI-based therapies. They concluded that more studies are needed to establish optimal treatment regimen mainly in western countries.

Ju *et al.* (2024) in China found that a low-dose amoxicillin (VLA) therapy showed comparable efficacy and safety to VHA one, along with regional differences.

In the present study, Pantoprazole 40mg oral twice daily as a part of triple therapy with 8 missed or dropped-out cases in G1 and 12 missed cases in G2 due to non-compliance with treatment and incomplete follow-up, eradication rate was higher in VPZ-based therapy versus PPI-based one by ITT analysis (85% vs. 70% P= 0.004; 95% CI 71-100 versus 58-84%) and in PP analysis (89.47 versus 75.68% P. = 0.002; 95% CI 75-100 versus 62-91 %).

In this study, a substantial correlation was among *H. pylori* Ag and Hb levels, showed low Hb values in *H. pylori* Ag positive patients and higher values were in ***H****. pylori* Ag negative ones (P<0.001) needed more study.

Acknowledgements

The authors are grateful to Head and Staff Members of the Internal Medicine, Hepatology, and Gastroenterology Unit for kind allowing and facilitating this study.

Conclusions

Efficacy of VPZ, given orally 20mg at a daily dose in combined with antibiotics as a triple treatment, surpassed PPI when combined with antibiotics for eradicating *H. pylori* resistant strains.

Vonoprazan combined with antibiotics gave a higher eradication rate than PPIs.

Authors' declarations: The authors reported that they neither have any competing of interests nor revived any funds. They equally contributed in theoretical and clinical study, wrote, revised the manuscript and approved its publication.

Recommendation

H. pylori infections must be treated with at least two different antibiotics at once

References

Chey, WD, Leontiadis, GI, Howden, CW, Moss, SF, 2017: ACG Clinical guideline: Treatment of *Helicobacter pylori* infection. Amer. J. Gastroenterol. 112, 2:212-39.

Chey, WD, Mégraud, F, Laine, L, *et al,* 2022: Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: Randomized clinical trial. Gastroenterology 163, 3:doi:https://doi.org/10.1053/j.gastro.2022.05.055

Echizen, H, 2015: The first-in-class potassium-competitive acid blocker, vonoprazan fumarate: Pharmacokinetic and pharmacodynamic considerations. Clin. Pharmacokinet. 55, 4:409-18.

Fallone, CA, Chiba, N, van Zanten, SV *et al,* 2016: The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. Gastroenterology 15, 1:51-69.e14.

Fallone, CA, Moss, S, Malfertheiner, P, 2019: Reconciliation of recent *Helicobacter pylori* treatment guidelines in a time of increasing resistance to antibiotics. Gastroenterology 157, 1:44-53.

Gisbert, JP, Calvet, X, **2011**: Review article: Effectiveness of standard triple therapy for *Helicobacter pylori* has not changed over the last decade, but it is not good enough. Alimen. Pharmacol. Therapeut. 34, 11/12:1255-68.

Hassanein, F, Masoud, IM, Awwad, ZM, Abdel-Salam, H, Salem, M, *et al,* 2023: Microbial bowel infections-induced biochemical and biological abnormalities and their effects on young Egyptian swimmers. Sci. Rep. 13, 1:4597. doi: 10.1038/s41598-023-31708-3.

Ierardi, E, Giorgio, F, Losurdo, G, Di Leo, A, Principi, M, 2013: How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography? World J. Gastroenterol. 19:8168-80.

Islam, J, Yano, Y, Okamoto, A, Matsuda, R, Shiraishi, M, *et al,* 2024: Evidence of *Helicobacter pylori* heterogeneity in human stomachs by susceptibility testing and characterization of mutations in drug-resistant isolates. Scientific Reports Published Online 27 May 2024.

Liu, L, Shi, H, Shi, Y, Wang, A, Guo, N, *et al,* 2024: Vonoprazan-based therapies versus PPI-based therapies in patients with *H. pylori* infection: Systematic review and meta-analyses of randomized controlled trials *Helicobacter*. May-Jun29, 3:e13094. doi: 10.1111/hel.13094.

Ju, KP, Kong, QZ, Li, YY, Li, Y, 2024: Low-dose or high-dose amoxicillin in vonoprazan-based dual therapy for Helicobacter pylori eradication? A systematic review and meta-analysis. *Helicobacter.* Jan-Feb;29, 1:e13054. doi: 10.1111/hel.13054.

Kiyotoki, S, Nishikawa, J, Sakaida, I, 2020: Efficacy of Vonoprazan for *Helicobacter pylori* eradication. Inter. Med. 59, 2:153-61.

Liou, JM, Wu, MS, Lin, JT, 2016: Treatment of *Helicobacter pylori* infection: Where are we now?. J. Gastroenterol. Hepatol. 31, 12:1918-26.

Maruyama, M, Tanaka, N, Kubota, D, *et al,* 2017: Vonoprazan-based regimen is more useful than PPI-based one as first-line *Helicobacter pylori* eradication: A randomized controlled trial. Canad. J. Gastroenterol. Hepatol. 1-7. https: // doi.org/ 10.1155/ 2017/4385161

Metwally, M**, Ragab, R, Abdel Hamid, HS, Emara, N, Elkholy, H, 2022:** *Helicobacter pylori* antibiotic resistance in Egypt: A Single-center study. Infect. Drug Resist. 15:5905-5913.

Moayyedi, P, Bardhan, C, Young, L, *et al,* 2001: *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. Gastroenterology 121:1120-8.

Okubo, H, Akiyama, J, Masao Kobayakawa, *et al,* 2020: Vonoprazan-based triple therapy is

effective for *Helicobacter pylori* eradication irrespective of clarithromycin susceptibility. J. Gastroenterol. 55, 11:1054-61.

Sachs, G, Scott, DR, Wen, Y, 2011: Gastric infection by *Helicobacter pylori*. Curr. Gastroenterol. Reports 13, 6:540-6.

Sakurai, Y, Nishimura, A, Kennedy, G, *et al,* 2015: Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (Vonoprazan) doses in healthy male Japanese/non-Japanese subjects. Clin. Translat. Gastroenterol. 6, 6:e94. https://doi.org/10.1038/ctg. 2015. 18.

Shaikh, T, Fallone, CA, 2016: Effectiveness of second through sixth line salvage *Helicobacter pylori* treatment: bismuth quadruple therapy is almost always a reasonable choice. Can. J. Gastroenterol. Hepatol. doi: 10.1155/7321574.

Sue, S, Shibata, W, Sasaki, T, *et al,* 2018: Randomized trial of vonoprazan based versus proton-pump inhibitor-based third-line triple therapy with sitafloxacin for *Helicobacter pylori.* J. Gastroenterol. Hepatol. 34, 4:686-92.

Suzuki, S, Gotoda, T, Kusano, C, *et al,* 2016: The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day PPI-based low-dose clarithromycin triple therapy. Am. J. Gastroenterol. 111, 7:949-56.

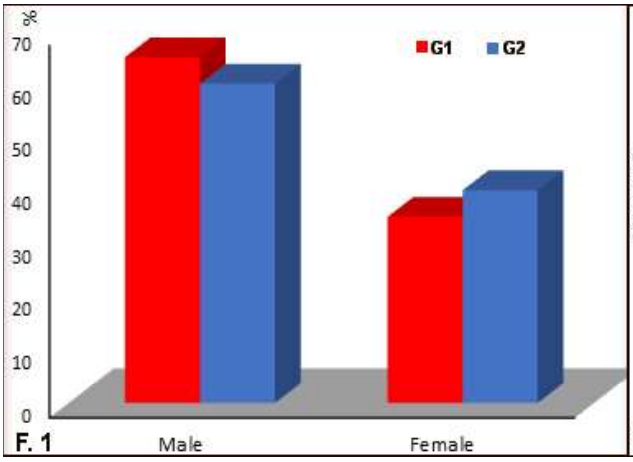
Tsugawa, H, Suzuki, H, Saya, H, *et al,* 2012: Reactive oxygen species-induced autophagic degradation of *Helicobacter pylori* CagA is specifically suppressed in cancer stem-like cells. Cell Host Microbe 12, 6:764-77.

Vaira, D, Vakil, N, 2001: Blood, urine, stool, breath, money, and *Helicobacter pylori.* Gut. 48:287-9.

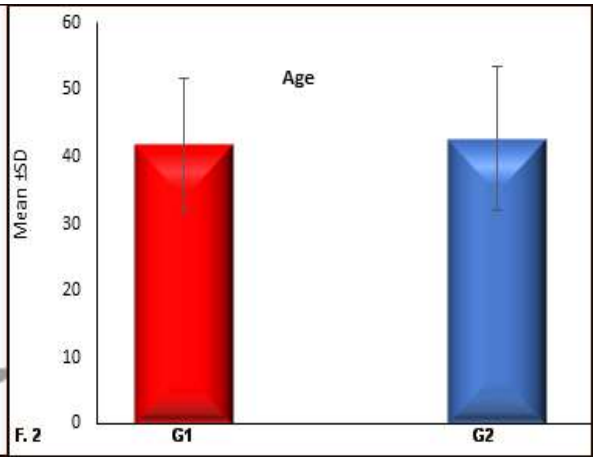
Yang, HB, Sheu, BS, Wang, ST, *et al,* 2009: *H. pylori* eradication prevents the progression of gastric intestinal metaplasia in reflux esophagitis patients using long-term esomeprazole. Am. J. Gastroenterol 2009; 104:1642.

Explanation of figures

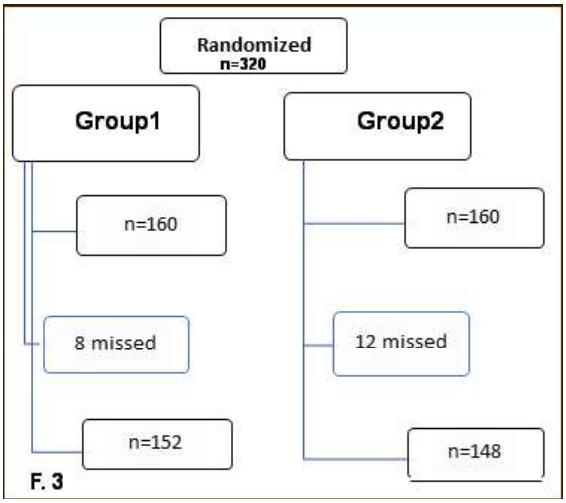
Fig. 1; Samples distribution according to sex in G1 (n= 160) and G2 (n= 160).
Fig. 2: Comparison between groups according to ages in years (n= 320)
Fig. 3: Flow chart of among participants, ITT; Intention to treat. PP; Per-Protocol.



F. 1



F. 2



F. 3