Exploring the Role of Gut Microbiota in Antibiotic Resistance: Mechanismsand Mitigation Strategies

Tehmina Bashir[1], Ashique Hussain[2], Rizwan Ali Shah[3], Asad Perveiz[4], Asadullah Dero[5], Saqib Shabbir[6]

[1]Government College University Lahore
[2,3,4,5,6]Jinnah College of Nursing Sohail University Karachi

Corresponding author: [1]Tehmina Bashir

Abstract

Gut microbiota profile is an essential part of the human body physiology and is associated with the high carriage of ARGs. This review focuses on the intricate relationship between gut microbiome and antibiotic resistant bacteria with special reference to the several ways that bacteria get antibiotic resistance genes, such as horizontal gene transfer and mobile genetic elements. Antibiotics come into bacteria and alter the composition and structure of microbiota by inducing dysbiosis and creating a persistent resistome that perpetuates the occurrence of resistance. On these lines, several approaches are proposed to overcome this problem, and they include the administration of probiotics and prebiotics to rebalance the beneficial micro flora, the control of antibiotics usage, the application of newer concepts such as phage therapy, FMT and alterations in the diet pattern. Further, strategies such as innovation of new antibiotics and additional agents capable of counteracting the resistance mechanisms also holds some possible solutions. The review underscores a call for heightened collaboration of various branches of medicine and academia as well as further research to curb the emerging menace of antibiotic resistance and to maintain the effectiveness of antibiotics in the treatment of bacterial infections.

Introduction

The gut microbiota refers to the trillions of microorganisms living in the human gastrointestinal tract whose function include aiding in digestion, synthesis of vitamins and defense against pathogenic organisms (Guarner & Malagelada, 2003). However, it has also been associated with extensive spread of antibiotic resistance, which is a major issue of concern in the entire world. Furthermore, it is also vital to look into the relationship that exists between the gut microbiota and antibiotic resistance so as to come up with the relevant interventions. Some of the newer findings about microbiome depict that host, microbiota and antibiotics are not static elements and hence the problem requires an entrenched solution (Blaser, 2009).

The Role of Gut Microbiota in Antibiotic Resistance

1. Composition and Function of Gut Microbiota

These are bacteria, archaea, viruses and fungi of which bacteria are the most abundant (Sekirov et al., 2010). Another bacterium category that has a significant number of sequences is Firmicuttes, Bacteroidetes, Actinobacteria and Proteobacteria. These microorganisms play a central role in the metabolic activity of the human body including carbohydrate metabolism where they are involved in the fermentation of non-susceptible carbohydrates, synthesis of short-chain fatty acids and immune-regulation (Turnbaugh et al., 2007). Metabolic status and immune function are the typical proof of the necessity of the gut microbiota for the host organism's health. Imbalances in this fragile symbiotic relationship results to dysbiosis which is linked with various diseases such as inflammatory bowel disease, obesity and metabolic syndrome (Kamada et al., 2013).

2. Antibiotic resistance in Gut microbiota

The, gut microbiota can thus harbor antibiotic resistance genes (ARGs) that bacteria use to neutralise or counteract the action of antibiotics (Van Schaik, 2015). These genes can be chromosomally integrated or incorporated through horizontal gene transfer (HGT) procedures including transformation, transduction and conjugation as stated by Smillie et al., 2011. It is for this reason that microbial load in the gut is high, and therefore the opportunity to spread resistance genes is high. This process is made worse by the action of antibiotics as those bacteria with resistance genes have higher chances of survival as compared to those without the ability to produce these genes (Martínez et al., 2015). Therefore, the gut microbiota can be considered not only as a source and a vector of the ARG distribution, which is indeed a very challenging factor for public health (Sommer et al., 2009).

Mechanisms of Resistance Acquisition and Transfer

1. Horizontal Gene Transfer (HGT)

HGT is considered as one of the major mode through which bacteria acquire resistance genes. Conjugation is the movement of plasmids from one bacterium to another via a physical contact and this process is usually facilitated by the structure known as pili (Thomas & Nielsen, 2005). Transformation is the ability of a bacterial bacterium to acquire genes from the surrounding environment that is free while transduction is the action of bacteriophages transferring genes among bacteria (Chen et al., 2005). Such processes allow ARGs to be swiftly transferred between various bacterial species or even between the generi and play a crucial role in the development of antibiotic resistance. It has been proved in experiments that the gut bacteria can receive resistance genes from both symbiotic and pathogenic bacteria suggesting that the microbial communities in the gut are closely intertwined (Forsberg et al., 2012).

2. Mobile Genetic Elements (MGEs)

These include the plasmids, the transposons, and the integrons, which were established as MGEs that affect the distribution of ARGs. It has been identified that plasmids can harbor more than one resistance gene and can mobilize it across various genera of bacteria (Carattoli, 2013). Transposons are capable of mobilizing genes both within and between DNA molecules whereas integrons acquire and drive the expression of gene cassettes including those involved in antibiotic resistance (Stokes & Gillings, 2011). Borrowing from biologists, these entities are portable in the sense that it makes the dissemination of the resistance genes faster and far reaching thus making it difficult to slow or contain the spread of antibiotic resistance. The existence of MGEs in gut bacteria, therefore, raises concerns on the part they play in the spread of ARGs, and the need to come up with the right measures to curb this issue (Partridge et al., 2018).

3. Selective Press by use of Antibiotics

In particular, the application of antibiotics puts pressure on microbial communities and as a result increases the number of resistant strains (Levy & Marshall, 2004). Antibiotics also have the potential of compromising the natural bacterial flora in the gut; this decreases the ability to support friendly bacteria and at the same time increases the ability of resistant bacteria to grow (Dethlefsen et al., 2008). This is explained as the "resistome", whereby anyone and anything that can harbor resistance genes is considered within the microbiota (Wright, 2007). Fortunately, the resistome has functions that play a vital role in maintaining and transferring ARGs in bacteria, hence the continuity of antibiotic resistance. It therefore is important to know how the resistome behaves and how it reacts to the influence of antibiotics to inform the best strategies to counter resistance (Perry & Wright, 2013).

Impact of Antibiotics on Gut Microbiota

1. Disruption of Microbial Communities

Antibiotic treatment has the potential to affect microbiota in the gut in a very profound manner. Jernberg et al., 2010 have investigated that the common antibiotics such as amoxicillin and ciprofloxacin decrease microbial richness and allow the growth of resistant

strains. These alterations may remain stable for an extended period even after discontinue of antibiotic treatment and subsequently help to maintain the pool of resistance genes (Jakobsson et al., 2010). The disruption of microbial communities does not only enhances the occurrence of antibiotic resistant bacteria but also distorts the favorable functions of microbiota making a detrimental effect to the host health (Modi et al., 2014).

2. Resilience and Recovery

Although, gut microbiota exhibits a great resilience to the assault by antibiotics, the recovery process from antibiotic disruption is generally insufficient and less than optimal, and some of these changes perhaps are irrevocable (Dethlefsen & Relman, 2011). Prolonged use of antibiotics in a person's lifetime will lead to compounded effects, whereby the ARGs and resistant bacteria will be amplified in the human body (Sommer & Dantas, 2011). Both duration of treatment with the antibiotic and type of the antibiotic also play a certain role in regulating the gut microbiota as well as the diet and lifestyle of the population (Relman, 2012). Knowledge of these factors is crucial if interventions to improve microbiota re-establishment and thus minimize the effects of antibiotics on resistance are to be implemented.

3. Long-Term Consequences

The effects of antibiotic induced alterations in microbial associated community are profound in the long run. For instance, disruption of the microbiota leads to dysbiosis and it is linked with such problems as IBD, obesity and even mental health disorders (Bercik et al., 2011). The fact that ARGs reside in gut microbiota also constantly poses a threat to public health as these genes can be transferred to pathogens and cause hard to treat infections (Penders et al., 2013). Such alterations can last indefinitely, and therefore large, long-term investigations are required to assess the effects of antibiotics on microbiota and to design the ways of minimizing the effect on human health (Blaser & Falkow, 2009).

Mitigation Strategies

1. Probiotics and Prebiotics

While probiotics refer to the living microorganisms that have health benefits or can be consumed for health benefits, prebiotics refers to the non-digestible food constituents particularly the dietary fibers that influence the growth of beneficial bacteria (Gibson et al., 2017). It is supposed that both can positively influence the balance of microbial composition in the gut and decrease the quantity of the resistant strains. Some of the probiotics which have been known to prevent the growth of resistant bacteria and also decrease the content of ARGs in the gut include Lactobacillus, Bifidobacterium among others according to McFarland (2015). For example, the Lactobacillus and Bifidobacterium can improve gut integrity and inhibit the pathogenic and resistant bacteria (Veiga et al., 2010). It has also been noted that Dietary Fibre ingredients like inulin and fructo-oligosaccharides can selectively enhance the growth of such clients further confirming the ability to restore the right microbiota (Bindels et al., 2015).

2. Antibiotic Stewardship

Antibiotic stewardship programmes are basically geared towards improving the appropriate utilization of antibiotics in fighting resistance. Some of them are, prescribing antibiotics if they are necessary, choosing amongst those available, focusing on susceptibility test results and shortening the course of the treatment (Dellit et al., 2007).

It is indicated that such programs can lower selective pressure and retain effectiveness of the existing antibiotics. The effectiveness of such programs in healthcare setting has been demonstrated to reduce. Thus, the rate of antibiotic-resistant infections and the status of the patient can be reduced, as well as enhance the effectiveness of treatment (Dyar et al., 2017). Other strategies of antibiotic stewardship include community health promotion and education as a way of reaching out to the public to ensure that they understand on how to use antibiotics responsibly (Ventola, 2015).

3. Phage Therapy

Phage therapy means that bacteriophages are applied to work on the bacteria specifically. The use of phage as an alternative to traditional antibiotics is that they can be engineered to target antibiotic-resistant bacteria (Abedon et al., 2011). It has efficiency in decreasing bacterial load and prevalence of resistance genes in the gut as revealed by Loc-Carrillo and Abedon, (2011). They are precise, hence, minimizing the chances of having unwanted effects on the useful bacteria, they can be used together with anti-biots to amplify the therapy potency (Oechslin, 2018). However, there are obstacles such as regulatory,that comprise the ability of phage therapy to become successful and the problem of patient-to-patient variation (Kutter et al., 2010).

4. Fecal Microbiota Transplantation (FMT)

FMT is the process of taking fecal matter from a healthy individual and delivering it to a client with the intention of rectifying the status of his/her gut flora. Fecal microbiota transplantation has added value in the management of recurrent C. Difficulties infections and sees a promising way to lower ARGs in the gut (van Nood et al., 2013). It can aid in restoration of balance of microbiota balance and decrease the number of multidrug resistant varieties (Smits et al., 2013). Currently, research is still underway in expansion of FMT in handling everyone regarding the antibiotic resistance and other gut health problems. The quality of FMT, safety, and complications have been known to be enhanced by strict protocols in the conduct of the procedure as well as the screening of the source of the stool (Cammarota et al., 2014).

5. Dietary Interventions

The diet is an important determinant of the variety of gut microbes. Some of the strategies, including change in diet with emphasis on high fiber diets, reduction in intake of processed foods, and consumption of fermented foods may be useful in enhancing the ratio of the healthy microbiota and possibly confining the incidence of antibiotic resistant bacteria (Singh et al., 2017). High fibre diets, especially, were followed by an increase in microbial diversity and the number of bacteria that could dominate resistant strains (De Filippo et al., 2010). Here, yogurt and kimchi can be identified as examples of the fermented foods that contain live cultures and may help to act on the gut and minimize the negative effects of antibiotics on the microbiota (Marco et al., 2017).

6. Novel Antibiotics and Adjuvants

Continued studies are being conducted on the discovery of new antibiotics and adjuvants that may overcome or counter the mechanisms of resistance. Those antibiotics can either be of the same class as the adjuvants or different, and they work by reducing the likelihood of resistance or by improving the immune response (Brown, 2013). The use of adjuvants together with antibiotics could hence form a new approach to dealing with resistant infections, and thereby decreasing the selective favor on the gut microbiome (Laxminarayan et al., 2013). The emergence of new antibiotics, consisting in identifying the action of novel molecules on separate bacterial reactions or on special bacterial formations also offers an outlook on the issue of antibiotic resistance (Bush & Bradford, 2016).

Conclusion

The research also reveals that antibiotics drive the development and extension of a resistant new gut microbiota. The nature of Resistance acquisition and reclining, the role played by antibiotic and the interactions on microbial population needs to be understood effectively for preventing the development of plenty of Resistances. Interventions like, the use of probiotics, antibiotic stewardship, phage therapy, fecal microbiota transplantation, dietary management, and introduction of new antibiotics are some of the possible ways of solving the crisis of antibiotic resistance or at least preserving antibiotic efficacy in the future. Further studies and solutions must be developed if this multifaceted and rapidly developing issue needs to be solved. The measures applied towards counteracting the dangers of antibiotic resistance have to be complex, utilizing the input of researchers, health care providers, policy makers and the public.

References

Abedon, S. T., Kuhl, S. J., Blasdel, B. G., & Kutter, E. M. (2011). Phage treatment of human infections. Bacteriophage, 1(2), 66-85.

Bercik, P., Collins, S. M., & Verdu, E. F. (2011). Microbes and the gut-brain axis.

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., & Collins, S. M. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology, *141*(2), 599-609.

Bindels, L. B., Delzenne, N. M., Cani, P. D., & Walter, J. (2015). Towards a more comprehensive concept for prebiotics. Nature Reviews Gastroenterology & Hepatology,12(5), 303-310.

Bindels, L. B., Delzenne, N. M., Cani, P. D., & Walter, J. (2015). Towards a more comprehensive concept for prebiotics. Nature Reviews Gastroenterology & Hepatology, *12*(5), 303-310.

Blaser, M. J. (2016). Antibiotic use and its consequences for the normal microbiome.

Blaser, M. J., & Falkow, S. (2009). What are the consequences of the disappearing human microbiota? Nature reviews Microbiology, 7(12), 887-894.

Brown, E. D. (2013). Is the gain act a turning point in new antibiotic discovery? CanadianJournal of Microbiology, 61(9), 697-698.

Bush, K., & Bradford, P. A. (2016). β-Lactams and β-Lactamase Inhibitors: An Overview.

Cammarota, G., Ianiro, G., & Gasbarrini, A. (2014). Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. Journal of Clinical Gastroenterology, 48(8), 693-702.

Cammarota, G., Ianiro, G., & Gasbarrini, A. (2014). Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. Journal of Clinical Gastroenterology, 48(8), 693-702.

Carattoli, A. (2013). Plasmids and the spread of resistance. International Journal of Medical Microbiology, 303(6-7), 298-304.

Chen, I., Christie, P. J., & Dubnau, D. (2005). The ins and outs of DNA transfer in bacteria.

Chen, Z. Y., He, C. Y., & Kay, M. A. (2005). Improved production and purification of minicircle DNA vector free of plasmid bacterial sequences and capable of persistent transgene expression in vivo. Human Gene Therapy, 16(1), 126-131.

De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J. B., Massart, S., & Lionetti,

P. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proceedings of the National Academy of Sciences, 107(33), 14691-14696.

Dellit, T. H., Owens, R. C., McGowan, J. E., Gerding, D. N., Weinstein, R. A., Burke, J. P., & Hooton, T. M. (2007). Infectious diseases society of America and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clinical Infectious Diseases, 44(2), 159-177.

Dellit, T. H., Owens, R. C., McGowan, J. E., Gerding, D. N., Weinstein, R. A., Burke, J. P., ... & Hooton, T. M. (2007). Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clinical Infectious Diseases, *44*(2), 159-177.

Dethlefsen, L., & Relman, D. A. (2011). Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proceedings of the National Academy of Sciences*, 108(Supplement 1), 4554-4561.

Dethlefsen, L., Huse, S., Sogin, M. L., & Relman, D. A. (2008). The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biology, 6(11), e280.

Dyar, O. J., Huttner, B., Schouten, J., & Pulcini, C. (2017). What is antimicrobial stewardship? Clinical Microbiology and Infection, 23(11),793-798.

Dyar, O. J., Huttner, B., Schouten, J., & Pulcini, C. (2017). What is antimicrobial stewardship?. Clinical Microbiology and Infection, *23*(11), 793-798.

Forsberg, K. J., Reyes, A., Wang, B., Selleck, E. M., Sommer, M. O., & Dantas, G. (2012). The shared antibiotic resistome of soil bacteria and human pathogens. Science, 337(6098), 1107-1111.

Forsberg, K. J., Reyes, A., Wang, B., Selleck, E. M., Sommer, M. O., & Dantas, G. (2012). The shared antibiotic resistome of soil bacteria and human pathogens. Science, *337*(6098), 1107-1111.

Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S. J., & Reid, G. (2017). The International Scientific Association for Probiotics and Prebiotics (ISAPP)

Guarner, F., & Malagelada, J. R. (2003). Gut flora in health and disease. The Lancet,361(9356), 512-519.

Jakobsson, H. E., Jernberg, C., Andersson, A. F., Sjölund-Karlsson, M., Jansson, J. K., & Engstrand, L. (2010). Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS One, 5(3), e9836.

Jakobsson, H. E., Jernberg, C., Andersson, A. F., Sjölund-Karlsson, M., Jansson, J. K., & Engstrand, L. (2010). Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS one, 5(3), e9836.

Jernberg, C., Lofmark, S., Edlund, C., & Jansson, J. K. (2010). Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology, 156(11), 3216-3223.

Jernberg, C., Löfmark, S., Edlund, C., & Jansson, J. K. (2010). Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology, 156(11), 3216-3223.

Kamada, N., Chen, G. Y., Inohara, N., & Núñez, G. (2013). Control of pathogens andpathobionts by the gut microbiota. Nature Immunology, 14(7), 685-690.

Kutter, E., De Vos, D., Gvasalia, G., Alavidze, Z., Gogokhia, L., Kuhl, S., & Abedon, S. T.(2010). Phage therapy in clinical practice: treatment of human infections. Current Pharmaceutical Biotechnology, 11(1), 69-86.

Kutter, E., De Vos, D., Gvasalia, G., Alavidze, Z., Gogokhia, L., Kuhl, S., & Abedon, S. T. (2010). Phage therapy in clinical practice: treatment of human infections. *Current* Pharmaceutical Biotechnology, 11(1), 69-86.

Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., & Cars, O. (2013). Antibiotic resistance the need for global solutions. The Lancet Infectious Diseases, 13(12), 1057-1098.

Laxminarayan, R., Matsoso, P., Pant, S., Brower, C., Rottingen, J. A., Klugman, K., & Davies,

Levy, S. B., & Marshall, B. (2004). Antibacterial resistance worldwide: causes, challengesand responses. Nature Medicine, 10(12), S122-S129.

Loc-Carrillo, C., & Abedon, S. T. (2011). Pros and cons of phage therapy. Bacteriophage,1(2), 111-114.

Marco, M. L., Heeney, D., Binda, S., Cifelli, C. J., Cotter, P. D., Foligne, B., & Hutkins, R.(2017). Health benefits of fermented foods: microbiota and beyond. Current Opinion inBiotechnology, 44, 94-102.

McFarland, L. V. (2015). Probiotics for the primary and secondary prevention of C. difficile infections: a meta-analysis and systematic review. Antibiotics, 4(2), 160-178.

Modi, S. R., Collins, J. J., & Relman, D. A. (2014). Antibiotics and the gut microbiota. The Journal of Clinical Investigation, 124(10), 4212-4218.

Oechslin, F. (2018). Resistance development to bacteriophages occurring during bacteriophage therapy. Viruses, 10(7), 351.

Partridge, S. R., Kwong, S. M., Firth, N., & Jensen, S. O. (2018). Mobile genetic elements associated with antimicrobial resistance. Clinical Microbiology Reviews, 31(4), 10-1128.

Penders, J., Gerhold, K., Stobberingh, E. E., Thijs, C., Zimmermann, K., Lau, S., & Hamelmann, E. (2013). Establishment of the intestinal microbiota and its role for atopic dermatitis in early childhood. Journal of Allergy and Clinical Immunology, 132(3), 601-607.

Perry, Julie A., and Gerard D. Wright. "The antibiotic resistance "mobilome": searching for the link between environment and clinic." Frontiers in Microbiology, 4 (2013): 138.

Relman, D. A. (2012). The human microbiome: ecosystem resilience and health. Nutrition Reviews, 70(suppl_1), S2-S9.

Sekirov, I., Russell, S. L., Antunes, L. C. M., & Finlay, B. B. (2010). Gut microbiota in health and disease. Physiological Reviews.

Singh, A., Sharma, S., & Singh, B. (2017). Effect of germination time and temperature on the functionality and protein solubility of sorghum flour. Journal of cereal science, 76, 131-139.

Smillie, C. S., Smith, M. B., Friedman, J., Cordero, O. X., David, L. A., & Alm, E. J. (2011). Ecology drives a global network of gene exchange connecting the human microbiome. Nature, 480(7376), 241-244.

Smits, L. P., Bouter, K. E., De Vos, W. M., Borody, T. J., & Nieuwdorp, M. (2013). Therapeutic potential of fecal microbiota transplantation. Gastroenterology, 145(5), 946-953.

Sommer, M. O., & Dantas, G. (2011). Antibiotics and the resistant microbiome. Current Opinion in Microbiology, 14(5), 556-563.

Sommer, M. O., Dantas, G., & Church, G. M. (2009). Functional characterization of the antibiotic resistance reservoir in the human microflora. Science, *325*(5944), 1128-1131.

Stokes, H. W., & Gillings, M. R. (2011). Gene flow, mobile genetic elements and the recruitment of antibiotic resistance genes into Gram-negative pathogens. FEMS Microbiology reviews, 35(5), 790-819.

Thomas, C. M., & Nielsen, K. M. (2005). Mechanisms of, and barriers to, horizontal gene transfer between bacteria. Nature Reviews Microbiology, 3(9), 711-721.

Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C. M., Knight, R., & Gordon, J. I. (2007). The human microbiome project. Nature, 449(7164), 804-810.

Van Nood, E., Vrieze, A., Nieuwdorp, M., Fuentes, S., Zoetendal, E. G., de Vos, W. M., & Keller, J. J. (2013). Duodenal infusion of donor feces for recurrent Clostridium difficile. New England Journal of Medicine, 368(5), 407-415.

Van Schaik, W. (2015). The human gut resistome. Philosophical transactions of the Royal society B: Biological Sciences, 370(1670), 20140087.

Veiga, P., Gallini, C. A., Beal, C., Michaud, M., Delaney, M. L., DuBois, A., & Garrett, W. S. (2010). Bifidobacterium animalis subsp. lactis fermented milk product reduces inflammation by altering a niche for colitogenic microbes. Proceedings of the National Academy of Sciences, 107(42), 18132-18137.

Ventola, C. L. (2015). The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and Therapeutics, 40(4), 277.

Wright, R. S., Anderson, J. L., Adams, C. D., Bridges, C. R., Casey, D. E., Ettinger, S. M., & Zidar, J. P. (2011). 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology, 57(19), e215-e367.