Reviewer #1

This is an very review which presents updated information regarding the association of CAD with genetic factors. The 2 major problems are: 1) the very large extent of the text 2) the fact that in the current form it is doubtful whether the average clinician will be attracted to read it. I propose, to reduce the extent of the text by 50% and eliminate some very specific information in order to make it friendlier to the reader. Otherwise, it can split and presented in 2 consecutive issues.

Genetics of CAD and MI is one of the most extensively studied subject in disease genetics. The intention of this systemic review is to provide interested readers and the scientific community with an extensive, up-to-date summary of current knowledge and progress. We deeply appreciate the reviewer's concern of length of the article and the constructive proposal of splitting the article to 2 consecutive issues for the Journal. Thanks to the advantage of online publishing format with *World Journal of Cardiology*, it would be feasible and acceptable to publish the review in one document, as its' entirety, which we believe, would provide interested readers the convenience to access all the related information.

Minor Comments 1) there are several grammar and punctuation mistakes throughout the text which should be addressed e.g. last line of first paragraph (introduction), instead of "in predict" please write in "predicting", etc.

The article has undergone extensive English language editing by American Journal Experts editorial team. This editing has eliminated grammar and punctuation mistakes throughout the text and has dramatically improved phrasing and overall language accuracy. The "in predict" has been changed to "for predicting" as suggested with details below.

Original sentence: "The development of genetic risk score from CAD genetic risk factors and its initial success in predict life-long risk of CAD is also discussed."

New Sentence: "The development of a genetic risk score based on genetic risk factors related to CAD and its initial success for predicting the life-long risk of CAD is also discussed."

2) in the section "III-2, Monogenic lipid disorders" it is written " Heterozygous LDLR mutation carriers, … suffer CAD/MI at the age of 30 years" This is not true. They have a high risk of development premature CAD but they do not suffer CAD/MI at the age of 30 years.

We agree with the reviewer's comment. The sentence has been revised. It reads now as "Carriers of heterozygous LDLR mutations, demonstrating a frequency of 1/500 in the general population, display a 2-fold increase in low-density lipoprotein cholesterol (LDL-C) levels from birth and may at risk to suffer CAD and MI at 30s years of age."

Reviewer #2

This is an extensive narrative review on genetic factors in coronary heart disease (CAD). I have the following comments - The great amount of data presented could generate confusion in the non-specialist reader. In fact this great deal of information should be presented with a more critical approach indicating the genetical alterations that have major significance. - Authors should be more explicit throughout the text in differentiating consolidated knowledge from sporadic results.

The reviewer is absolutely correct. The evidence of its' role of mutations of a specific gene are various. Many of the novel gene discoveries are published in the last two years. Additional validation with more pedigree data and data from general population would be crucial to further establish the role of genes in CAD and MI. In additional to our statements differentiating gene discoveries with limited data from consolidated knowledge, we have added further statements indicating the requirement of further validation or population studies, to those sections describing rare or novel mutations in related to CAD and MI. We hope the reviewer found it improves the clarities of the level of evidence for each genes mentioned.

- It would be helpful for the reader to reformulate Table 3 adopting the same order used in the text: genetic variance for CAD / AMI; or regulating lipid metabolism subdivided into those increasing LDL, lowering HDL or increasing triglycerides.

It is a great suggestion. We have made the changes to Table 3 accordingly.

- It is also very important to graduate the solidity of evidence for protective factors.

Overall, there were very limited studies addressing protective factors against CAD and MI. We have specifically pointed out in the manuscript (Page 19, para 3).

- I also comment that major importance should be given to those genetic variants that have been found to be directly related with CAD/AMI. Those related to lipid disorders are in some way less important. As we anyway will measure, in patients predisposed to CAD, lipid values in the laboratory. - I will add that as you deal with genetic factors related to lipids, why should you not include those related to hypertension?

We have emphasized monogenic CAD and MI causal genes and their mutations. Monogenic genes involved in the lipid metabolism often directly lead to premature CAD and MI with significant inheritability. Although HTN is a known risk factor for CAD and MI, familiar or genetic hypertension was not well documented to directly be associated with atherosclerotic CAD. This is applicable to other risk factors. Therefore, concerning of genetics of CAD and MI, monogenic etiology of dyslipidemia becomes unique and provides more directly causal relationship between gene mutations, certain types of dyslipidemia and premature CAD and MI.

- Chapter 4 is somewhat deceiving: Authors should propose one or more simplified schemes for diagnostic applicarions, on the background of their experience.

We assumed that the reviewer referred "Chapter 4" to the section, "**IV, Genetic risk score to predict the risk of CAD and MI**" in our manuscript. The ultimate goal of study CAD and MI genetics is to provide preventive and therapeutic strategies for these diseases. It is now possible to apply genetics information to predict disease in

early stage of life. Atherosclerotic CAD is commonly a multi-decade process. If genetics information eventually allows us to predict the disease with adequate accuracy, it will be beneficial to guide prevention. Therefore, we believe that this topic is an integrative component of CAD genetics field. There are many challenging issues remained un-resolved as discussed in the manuscript. We have revised this section to improve its clarity.

- Another point to stress could be epigenetics. What do we know about modifications incuded by environmental factors or traditional risk factors on activity of the involved genes?

We agree that epigenetics play important role in the development of CAD and MI. It is also closely interacting with genetic factors. It would be worthy of summarizing this extensive topic in a separate article. We are afraid that it is beyond the scope of this review to cover this important topic. We did point out that "e) considering the epigenomic regulation of gene expression" as one of the five possible sources of the missing heritability of CAD and MI (Section III-4, A. Searching for unexplained heritability in page 18).

- I also suggest to reduce the amount of graphic material. For instance Figure 3 and Table 2 could be suppressed and only described in the text.

We have now eliminated Table 2.

Minor comments: Some revision of the english is necessary and there are also a number of mis-spellings.

The article has undergone extensive English language editing by American Journal Experts editorial team. This editing has eliminated grammar and punctuation mistakes throughout the text and has dramatically improved phrasing and overall language accuracy.

Finally, check wheter the references are written according to the style of the journal.

The references have been re-formatted by following WJC's style.