Top Ten Things to Know
Recommendation on Design, Execution, and Reporting of Animal Atherosclerosis Studies

1. Atherosclerosis is a major cause of morbidity and mortality in many populations that contributes to coronary artery disease, stroke, and peripheral vascular diseases.

2. The natural history of atherosclerosis can take decades to develop as seemingly small molecular changes compound into overt clinical manifestations in the artery wall.

3. Imaging modalities have evolved to provide reasonably precise measurements of atherosclerotic lesion dimensions, but these methods have a limited ability to provide characterizations of these lesions. Similarly, human vascular tissues can only be obtained during surgery or at autopsy, so animal models have been used for decades to better understand the development of atherosclerosis.

4. Several species have been routinely used in cardiovascular disease studies, including mice, rabbits, pigs, non-human primates, and other species. Due to their different anatomies, physiologies, lifespans, and lipoprotein and lesions characteristics, there are different benefits and limitations to designing experiments with each of the animal models. This Scientific Statement summarizes the key considerations when selecting an animal model appropriate for the research question.

5. **Mice** are the most commonly used animal model in atherosclerosis studies and offer several advantages including relatively low cost and ease of maintenance and breeding, genetic and transgenic pliability, and the rapid formation of atherosclerosis. However, atherosclerosis differs in mice in several ways including HDL subsets, apolipoprotein E isoforms, expression of cholesterol ester transfer protein (CETP) and other key molecular and physiologic differences.

6. **Rabbits** were the original animal model for atherosclerosis studies in 1913 and there are currently 2 main rabbit models used in atherosclerosis studies (New Zealand White and Watanabe hereditary hypercholesterolemic rabbits). Similar to mice, rabbits have some molecular and physiologic differences which limit their ability to accurately model the human condition; however, they offer some advantages over mice including larger size for imaging, intervention, and pharmaceutical testing.

7. **Pigs** represent a model of atherosclerosis that has more similarity in terms of anatomy, physiology, lipoprotein profile, and site of lesion formation to humans. Whereas mice and rabbits can be induced to develop atherosclerotic lesions relatively quickly and at a more modest cost, pigs are large enough to study hemodynamic changes in arteries and endothelial dysfunction.

8. **Non-human primates** are the closest humanoid model of atherosclerosis based on comparison of anatomy, physiology, lipoprotein profile, and site of lesion formation. Similar to humans, non-human primates have a predominance of non-HDL lipoproteins and express human-like HDL subclasses. While studies on non-human primates are costly and their atherosclerotic lesions could take years to develop, non-human primates are the most comparable model to mimic atherosclerosis in humans.

9. Studies can be designed to analyze several comorbidities in animal models, including diabetes, renal failure, high blood pressure, and obesity. Studies can also be designed to control for or test for factors such as sex, genetics, diet, duration, and other factors. Additionally, there are many methodologies available for analyzing the development of atherosclerosis including serum and lipoprotein analysis, tissue staining and analysis, and imaging studies.

10. To provide insight into the human disease, animal studies must be rigorously designed, conducted, and interpreted as a step towards extrapolating the results to humans. This Statement was developed to provide a framework for designing studies that will contribute to the understanding of cardiovascular disease and development of new and effective therapies.
