

## ATHENS CARDIOLOGY UPDATE 2010

# Coronary Artery Disease, Nicotine Addiction, and Depression: The Tragic Triad

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A great number of diseases are directly related to active smoking. In the recent years more and more malignant neoplasms were causally related to active smoking.<sup>1</sup> Lung cancer is the “leader” of smoking related neoplasm’s and the 3<sup>rd</sup> cause of death in high income countries,<sup>2</sup> followed by cancer of the oral cavity/pharynx, laryngeal, esophageal, stomach, pancreatic, kidney, bladder, cervical cancer, leukemia and other malignant neoplasm’s. Among other diseases, cardiovascular (coronary heart disease, peripheral vascular disease cerebrovascular disease and abdominal aortic aneurysm) and respiratory diseases (chronic obstructive pulmonary disease-COPD, pneumonia) are also causally related to cigarette smoking. According to World Health Organization (WHO) 5 out of 6 leading causes of death world wide (*Ischemic heart disease, cerebrovascular disease, HIV/AIDS, COPD, lower respiratory infections trachea, bronchus, lung cancers*) are smoke related. WHO claims that under the baseline scenario, total tobacco-attributable deaths will rise from 5.4 million in 2005 to 6.4 million in 2015 and 8.3 million in 2030. Projected deaths for 2030 range from 7.4 million in the optimistic scenario to 9.7 million in the pessimistic scenario. According to their baseline projection, smoking will kill 50% more people in 2015 than HIV/AIDS, and will be responsible for 10% of all deaths globally<sup>2</sup>.

**KEY WORDS:** *smoking; cardiovascular disease depression*

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## SMOKING AND CARDIOVASCULAR DISEASE

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Cardiovascular diseases are the first cause of death independently of income state and existing evidence is more than sufficient to establish a causal relationship between each of them and cigarette smoking<sup>1</sup>.

### SMOKING AND CORONARY ARTERY DISEASE (CAD)

The role of smoking in ischemic heart disease includes endothelial dysfunction, increased hematologic thrombogenicity, enhanced inflammatory response and oxidative modification.<sup>3</sup> Tissue factor (TF) is highly expressed in atherosclerotic plaques and may play a role in thrombosis. Current smokers have significantly higher levels of circulating TF activity than nonsmokers<sup>4</sup>. Smoking impairs endothelial vasodilator function since flow-dependent dilation is significantly blunted in current smokers compared with nonsmokers and long-term cigarette smoking is associated with impaired endothelium-dependent coronary vasodilatation regardless of the presence or absence of coronary atherosclerotic lesions.<sup>5</sup>

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Young smokers are characterized by epicardial coronary endothelial dysfunction, elevated white blood cell (WBC) counts and increased levels of inflammatory biomark-

ers and oxidative stress<sup>6</sup>. Elevated WBC counts are associated with greater coronary heart disease mortality<sup>7</sup>. Smoking leads to increased oxidative modification of important biologic molecules *in vivo*<sup>8</sup> and reduces nitric oxide (NO) biosynthesis<sup>9</sup>. It's no wonder that smoking increases CAD mortality<sup>10</sup> and rate of progression<sup>11</sup>, multiplies risk factor for CAD along with hypertension and hypercholesterolemia<sup>12</sup>, increases the risk of angina<sup>13</sup>, of sudden cardiac death<sup>14</sup>, of acute nonfatal myocardial infarction (MI)<sup>15</sup> and of Q-wave MI after percutaneous coronary revascularization<sup>16</sup>.

*In summary:*

- Smoking plays a role in the development of CAD via:
  - Endothelial dysfunction
  - Increased thrombogenicity
  - Elevated WBC counts
  - Increased oxidative stress
  - Reduced NO biosynthesis
- Smoking acts as a multiplicative risk factor for development of CAD
- Smoking is associated with an increased
  - Rate of progression of CAD
  - Risk of angina
  - Risk of acute myocardial infarction
  - Risk of sudden cardiac death
  - Risk of Q-wave myocardial infarction after percutaneous coronary revascularization.

**SMOKING AND PERIPHERAL VASCULAR DISEASE (PVD):**

PVD affects approximately 20% of adults older than age 55<sup>17</sup>. Approximately half of patients with PVD are asymptomatic<sup>18</sup> and 5% to 10% of them will progress to symptomatic PVD over 5 years<sup>19</sup>. Patients with symptomatic PVD are at higher risk for other cardiovascular disease and mortality<sup>20</sup>. Current smokers develop asymptomatic PVD 2,8 times more often than nonsmokers and ex-smokers 1,6 times respectively.<sup>20</sup> The rate of development of intermittent claudication (IC) is approximately 4 times as great in current smokers as in nonsmokers (OR 4.1[2.3-7.9]) and risk tends to increase with the intensity of smoking. The 5-year mortality for patients with IC who continue to smoke is 40% to 50%<sup>20,21</sup>. For smokers, the risk of PVD is greater than the risk of CAD.<sup>22</sup> Smoking is the most important risk factor for the progression PVD and symptoms occur approximately a decade earlier in smokers than nonsmokers while smokers with PVD have twice the amputation rate of nonsmokers<sup>23</sup>. Continued smoking after lower limb bypass surgery results in a threefold increased risk of graft failure. Smoking cessation, even if instigated after the operation, restores graft patency towards the patency of never smokers.<sup>24</sup> Smoking is also associated with increased mortality after vascular surgery.<sup>25</sup>

*In summary:*

- Smoking is associated with an increased risk of
  - Asymptomatic PVD
  - Intermittent claudication
  - Progression of PVD
  - Amputation due to complications of PVD
  - Femoral-popliteal bypass graft failure
  - Mortality after vascular surgery
- Symptoms of PVD occur approximately a decade earlier in smokers than in nonsmokers
- Current smokers are at greater risk for developing PVD than coronary artery disease.

**SMOKING AND ABDOMINAL AORTIC ANEURYSM (AAA)**

The association between smoking and aortic aneurysm is substantially stronger than the association between smoking and coronary or cerebrovascular disease. Current smokers develop AAA 3 times more often than CAD and 4,7 times than cerebrovascular disease<sup>26</sup>. Smoking is an independent and remains the most important avoidable risk factor for AAA, with level of exposure (cigarettes/day) being more significant than duration<sup>27</sup>. In fact the progression of aortic atherosclerosis is directly associated to the number of cigarettes smoked per day<sup>28</sup>. Smoking also accelerates AAA expansion while other factors including lipids and blood pressure are not associated with AAA growth<sup>29</sup>.

*In conclusion:*

- Current smokers have a higher risk of developing an AAA than either coronary artery disease or cerebrovascular disease
- Smoking is associated with an increased risk of
  - Formation of AAA
  - Progression of aortic atherosclerosis
  - Expansion of AAA

**SMOKING AND STROKE:**

Smoking contributes to 12% to 14% of all stroke deaths. Smoking also potentiates the effects of other stroke risk factors and increases stroke risk acutely, effecting the thrombus formation and chronically, increasing the burden of atherosclerotic disease<sup>30</sup>. Both active smoking and environmental tobacco smoke exposure are associated with increased progression of carotid atherosclerosis<sup>31</sup>. The number of cigarettes smoked per day is associated positively with the risk of stroke in women. Compared with the women who had never smoked, those who smoked 1 to 14 cigarettes per day had an age-adjusted relative risk of 2.2 (95 percent confidence interval, 1.5 to 3.3), whereas those who smoked 25 or more cigarettes per day had a relative risk of 3.7 (95 percent confidence interval, 2.7 to 5.1). For women in this latter group, the relative risk of subarachnoid haemorrhage was 9.8 (95 percent confidence

interval, 5.3 to 17.9), as compared with those who had never smoked<sup>32</sup>. Cigarette smoking increases the risk of total hemorrhagic stroke in women (both intracerebral and subarachnoid) and this is also positively associated with the amount of cigarettes smoked per day<sup>33</sup>. Smoking also increases the mortality rate from stroke in men<sup>34</sup>.

*In conclusion:*

- Smoking contributes to 12% to 14% of all stroke deaths
- Increases the risk of
  - Progression of carotid atherosclerosis
  - Ischemic stroke
  - Hemorrhagic stroke
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- Increases stroke-related mortality.

**CARDIOVASCULAR DISEASE  
AND ENVIRONMENTAL TOBACCO SMOKE**

Environmental tobacco smoke effects cardiovascular system in several ways. Environmental tobacco smoke increases the risk of heart disease among non smokers by 30%<sup>35</sup>, increases arterial stiffness, oxidative stress, inflammation, atherosclerosis and infarct size while changing platelet and endothelial function, heart rate variability and energy metabolism<sup>36</sup>. Passive smoking may activate thromboxane A<sub>2</sub> release from the platelets, contributing to the development of hemostatic imbalance<sup>37</sup>, and significantly reduces mean coronary flow velocity reserve in nonsmokers thus causing endothelial dysfunction of the coronary circulation<sup>38</sup>. Exposure to environmental tobacco smoke increases the risk of non-fatal acute myocardial infarction in a graded manner<sup>15</sup>. A public ordinance reducing exposure to second hand smoke in Pueblo city, Colorado, was associated with a decrease in acute myocardial infarction hospitalizations<sup>39</sup>.

*In conclusion:*

- Exposure to environmental tobacco smoke increases risk of
  - Heart disease, by 30%
  - Acute myocardial infarction (MI)
- Environmental tobacco smoke affects multiple factors associated with the development of coronary artery disease, including
  - Platelet activation
  - Vascular endothelial dysfunction.

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**CARDIOVASCULAR BENEFITS  
OF SMOKING CESSATION**

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The benefits of non-smoking and smoking cessation in healthy individuals and cardiac patients are beyond controversy<sup>40</sup>. Abstention from smoking for a period of only 2 weeks

induces a significant decrease in the rate of fibrinogen synthesis by the liver, with a concomitant reduction in the plasma fibrinogen concentration<sup>41</sup>, while 8 weeks of smoking reduction results in clinically significant improvements in established cardiovascular risk factors (including fibrinogen, white blood cell count and the high-density/low-density lipoprotein-HDL/ LDL ratio). These improvements are even greater after an additional period of abstinence from smoking<sup>42</sup>. Smoking cessation also improves arterial stiffness as assessed by the augmentation index, owing mainly to increasing the small artery compliance, which is known to be an early index of endothelial damage<sup>43</sup>. Quitting smoke leads to a decreased platelet volume and increased susceptibility of platelets to antiaggregatory prostaglandin E1<sup>44</sup>, while only two weeks of smoking cessation can ameliorate the enhanced platelet aggregability and intraplatelet redox imbalance in long-term smokers, possibly by decreasing oxidative stress<sup>45</sup>. Cessation of cigarette smoking is associated with a reduction in arrhythmic death for patients with post-myocardial infarction and left ventricular dysfunction<sup>46</sup> and a reduced risk of acute myocardial infarction<sup>15</sup>, while the risk for recurrent cardiac arrest is lower among those who quit smoking than among continuing smokers<sup>47</sup>. Patients who continue to smoke after a successful percutaneous coronary revascularization are at greater risk for Q-wave infarction and death than smoke quitters, so the cessation of smoking either before or after percutaneous revascularization is beneficial<sup>16</sup>. Patients who continue to smoke after coronary artery bypass graft surgery have a greater risk of death than those who stop smoking and also they undergo repeat revascularization procedures more frequently<sup>48</sup>. Smoke cessation also lowers the risk of PVD<sup>49</sup> and stroke<sup>50</sup>.

In conclusion the cardiovascular benefits of smoking cessation can be divided into:

**LONG-TERM BENEFITS**

- Reduced risk of
  - Stroke
  - Repeat CABG
  - Recurrent coronary events after MI
  - Arrhythmic death after MI
  - Secondary CVD events
  - Revascularization procedure after CABG
- Reduced
  - Mortality after CABG
  - Mortality after PTCA
  - Levels of inflammatory markers associated with progression of CVD (C-reactive protein, WBC, and fibrinogen)

**SHORT-TERM BENEFITS**

- ↓ fibrinogen concentration
- ↓ rate of fibrinogen synthesis

- ↓ WBCs
- Improved HDL/LDL ratio
- ↓ risk of stroke
- ↑ HDL; decreased LDL
- ↓ arterial pressure
- ↓ HR
- Improved arterial compliance
- ↓ risk of arrhythmic death after MI
- ↓ platelet volume
- Enhanced platelet cAMP response to stimulation of ADP with prostaglandin E1
- ↓ smoking-induced platelet aggregability.

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#### DEPRESSION, SMOKING AND CARDIOVASCULAR DISEASE

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Smokers with psychiatric disorders consume more cigarettes. Namely the Odds Ratio for smokers and major depression is 3.2. Also psychiatric patients who smoke have:

- Higher incidence of illicit drug use.
- Poorer treatment compliance
- Lower Global Assessment Functioning (GAF) score

The relationship between cardiovascular disease and depression poses a lot of interesting questions. Preliminary studies have shown the following:

- Depression increases the risk of coronary artery disease by 1.5 – 2 times in otherwise physically healthy individuals.<sup>51</sup>
  - Patients with early-onset depression are at a significantly increased risk for developing cardiovascular disease (CVD) after correcting for cardiovascular risk factors. This effect occurs even in the absence of a diagnosis of major depression.<sup>52</sup>
  - Patients with treatment-resistant depression (failure to respond to a single trial of antidepressant) after an acute coronary syndrome are at even greater cardiovascular risk.<sup>53</sup>
  - Patients with CVD such as myocardial infarction, stroke, heart failure, and atrial fibrillation are at increased risk of developing depression and, when depression develops, cardiovascular risk is exacerbated further.<sup>51,54</sup>
- As for the use of drugs research has shown that:
- The use of antidepressants does not appear to mitigate cardiovascular risk associated with depression, despite altering one or more of the physiological abnormalities linking CVD to depression such as increased inflammatory cytokines, a decreased circulation of endothelial progenitor cells,
  - and a deficiency in nitric oxide availability.<sup>55-57</sup>
  - The combination of an SSRI and n-3 fatty acids reduce mood-associated cardiovascular risk.<sup>58</sup>

- In patients surviving their first hospitalization for heart failure the use of both TCAs and SSRIs is associated with an increased risk of total and cardiovascular-related mortality.<sup>59</sup>
- Co-administration of an SSRI and a beta-adrenergic blocking agent is associated with an increased risk of total and cardiovascular-related mortality.

Further clinical study needs to be done in order to determine the optimum antidepressant strategy in patients with heart failure.

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