Antioxidants Use in Human Cardiovascular Disease – Where Are We?

64

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Contents

Abstract

Despite good basic science evidence for the benefit of antioxidants, clinical trials show little benefit from oral supplements containing one or several antioxidants. This chapter details the clinical trials and discusses possible reasons for the failure of oral antioxidant supplements. This analysis does not rule out a potential benefit from oral antioxidants in food, given the large benefits seen with the Mediterranean diet.

Introduction

In people with atherosclerotic cardiovascular disease or at high risk for atherosclerotic cardiovascular disease, there is excellent basic and clinical data for benefit with avoiding smoking, the Mediterranean diet (de Lorgeril et al. 1999; Estruch et al. 2013), aerobic exercise (Lee et al. 2012), treating hypertension (Beckett et al. 2008), low-dose aspirin (Baigent et al. 2009), and lipid-lowering therapy

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(Collins et al. 2002b; Coronary Drug Project Research Group 1975; Rubins et al. 1999). There is very promising basic science data supporting a role for antioxidants in preventing atherosclerosis (e.g., Touyz and Schiffrin 2004); however, the clinical trials for oral supplements containing one or several antioxidants have been very disappointing. In this chapter, I will review the clinical trial results with various oral antioxidants and the possible reasons for the divergent results.

Clinical Trials of Antioxidant Supplements

Beta-carotene, 60–200-mg daily, was studied in four large primary and four large secondary prevention trials (Vivekananthan et al. 2003). Six trials individually showed no benefit and two trials individually showed significantly increased mortality. Meta-analysis showed a significant absolute risk increase for total mortality of 0.4 % ($p = 0.003$, $n = 138{,}113$ people), predicting a number needed to harm (NNH) of 250.

Vitamin E, 300–800 units daily, was studied in two large primary and five large secondary prevention trials (Vivekananthan et al. 2003). No trial individually showed an effect on mortality. Meta-analysis showed a nonsignificant absolute risk increase for total mortality of 0.2 % ($p = 0.42$, $n = 81{,}788$ people), predicting a NNH of 500. One of the secondary prevention trials (CHAOS) showed a significant reduction in myocardial infarction (absolute risk decrease 2.6 %, $p = 0.01$, number needed to treat (NNT) of 38); however, when combined by meta-analysis of all of the trials, there was no effect on myocardial infarction (absolute risk unchanged, $p = 0.93$, (Stephen et al. 1996)).

A combination of Vitamin E 600 mg, Vitamin C 250 mg, and 20 mg beta-carotene in the Heart Protection Trial had no effect significant on mortality, myocardial infarction, or stroke (20,536 people, (Collins et al. 2002a)).

A recent large and detailed meta-analysis of 50 trials showed no benefit of oral vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, beta-carotene, folic acid, or selenium compared to placebo (Myung et al. 2013).

Clinical Trials of Synthetic Antioxidants

The potent oral antioxidant probucol was studied in two small trials. In the FAST trial, 500-mg probucol reduced carotid intimal medial thickness and reduced the combined endpoint of cardiovascular death, myocardial infarction, and revascularization ($p < 0.05$, $n = 246$ people, (Sawayama et al. 2002)). However, in the PQRST trial, 500-mg probucol did not slow progression of femoral intimal medial thickness ($n = 276$ people, (Walldius et al. 1994)). Probucol was removed from the US market because it increased the QTc interval.

The potent oral antioxidant succinobucol 300-mg daily was studied in the ARISE trial (Tardif et al. 2008). There was no effect on the primary endpoint of cardiovascular death, cardiac arrest, myocardial infarction, stroke, angina, and

revascularization ($p = 0.96$). In this trial, there were divergent effects on the endpoints: Succinobucol significantly reduced cardiovascular death, cardiac arrest, myocardial infarction, and stroke (absolute risk decrease 1.5 %, $p = 0.028$, $n = 6{,}144$ people), predicting an NNT of 67. Succinobucol significantly increased angina and revascularization. Succinobucol was not marketed.

Clinical Trials of the Mediterranean Diet

The Mediterranean diet in the Lyon trial (de Lorgeril et al. 1999) showed a very large absolute risk reduction in myocardial infarction and cardiovascular death in the first year: 5.2 % in the first year and 1.6 % in the subsequent year (Rembold 2007). This predicts a first year NNT of 19 and a subsequent yearly NNT of 63 (4 year NNT of 10). This occurred despite a relatively small reduction in LDL cholesterol from 176 to 162 mg dl^{-1}. It is likely that some of the reduction in myocardial infarction/cardiovascular death in the Lyon trial resulted from the change in dietary fats from saturated and omega 6 to omega 3 and 9 fats (de Lorgeril et al. 1999).

The larger PREDIMED trial showed a 30 % relative risk reduction in myocardial infarction, stroke, and cardiovascular death with a Mediterranean diet supplemented with extra virgin olive oil or nuts compared to the control diet (Estruch et al. 2013). The benefit was better with stroke than with the other outcomes in this trial. A substudy of the PREDIMED trial found that ferric-reducing antioxidant potential (FRAP) was significantly higher in the groups treated with the Mediterranean diet supplemented with extra virgin olive oil or nuts compared to the control diet (Zamora-Ros et al. 2013). This suggests that some of the clinical benefits seen in the PREDIMED trial might have been caused by either: (1) increased antioxidants found in the Mediterranean diet or (2) effect of the Mediterranean diet enhancing endogenous antioxidants.

Why Were the Basic Science Studies Positive and Clinical Trials of Supplements and Synthetic Antioxidants Negative?

1. It is possible that the route of administration is important. Perhaps the gastrointestinal tract alters antioxidants. This would explain positive studies in tissue culture and with intravenous antioxidants in animals.
2. It is possible that there may be drug heterogeneity (e.g., type of vitamin E) or stability issues in clinical trials.
3. It is possible that dosing was incorrect. Roberts et al. found in humans that only daily doses of >1,600 mg of vitamin E (RRR-alpha tocopherol) significantly reduced plasma F2 isoprostane levels (Roberts et al. 2007). Perhaps the 300–800-mg dose of vitamin E studied in the above clinical trials was inadequate.

4. It is possible that the duration of antioxidant therapy needs to be longer and/or start earlier in the atherosclerotic process.
5. It is possible that other atherosclerosis treatments, e.g., lipid lowering and/or aspirin, provide enough benefits so that the effects of antioxidants are not seen. This argument is similar to that found in the PEACE and HOPE trials (Braunwald et al. 2004). Both studied the role of ACE inhibitors in normotensive people with coronary disease. The earlier HOPE trial showed a large benefit from ACE inhibitors in people poorly treated with statins and aspirin. The subsequent PEACE trial found no benefit with ACE inhibitors compared to placebo in people who were mostly treated with statins and aspirin. Interestingly, the placebo and ACE inhibitor event rate in the PEACE trial was ~50 % lower than the ACE inhibitor treated arm of the HOPE trial, suggesting that the benefit of lipid lowering and/or aspirin in the PEACE trial overwhelmed the benefit of the ACE inhibitor in the HOPE trial (Braunwald et al. 2004).
6. It is clear that endogenous antioxidants are important. In humans, naturally occurring higher levels of bilirubin, an endogenous antioxidant, were associated with lower total mortality (Horsfall et al. 2011). In high-fat diet fed LDLR -/- mice, there were fewer endogenous antioxidants (lower superoxide dismutase, lower catalase, lower GPX-1, lower GPX-4, NADPH dehydrogenase quinone 1, and lower upstream mediators of antioxidants including FOXO1 and FOXO4). These mice also had more oxidative stress (higher plasma F2a isoprostane and higher vascular superoxide) and more aortic atherosclerosis (Collins et al. 2009). Perhaps, endogenous antioxidants are more important than exogenous antioxidants.
7. Exogenous antioxidants could potentially reduce endogenous antioxidants, thereby inhibiting their action. While I am not aware of data supporting this contention, there are data supporting the opposite: Oral oxidants do enhance endogenous antioxidants. Coffee drinking in humans increased urinary oxidant hydrogen peroxide 3–10 fold (Hiramoto et al. 2002; Long and Halliwell 2000). Theoretically, these data would suggest that coffee drinking should be pro-oxidant and therefore harmful. However, recent meta-analyses show no effect of coffee intake on cardiovascular disease (Sofi et al. 2007) and possibly a protective effect on dementia (Santos et al. 2010). Oxidants could increase endogenous antioxidants via the protein Nfr2 (Leiser and Miller 2010). A possible scenario is that administration of a mild pro-oxidant could induce endogenous antioxidant production which are cardio- and/or vasculoprotective.
8. Finally, it could be possible that a complex mixture of antioxidants, like those present in the Mediterranean diet (Zamora-Ros et al. 2013), is more effective than single or simple mixture of antioxidants present in supplements. Alternatively, the Mediterranean diet per se could increase endogenous antioxidants.

These data suggest that we do not have data supporting oral administration of single or several antioxidant supplements at present. However, these data do not rule out a possible benefit from antioxidants in food, given the large benefits seen with the Mediterranean diet, which includes food-based antioxidants, high levels of omega 3 and 9 fatty acids, and low levels of omega 6 and saturated fats.

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