Volume 1, Number 1, August 2013
ISSN: 2309-0901
http://cardioprogress.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

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Printed in Russia

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Volume 1, Number 1, August 2013

Contents

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Rafael G. Oganov
President, Cardioprogress Foundation
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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

EDITORIAL

Demographic trends in the Russian Federation: the impact of cardiovascular disease

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Summary
Cardiovascular disease (CVD) is the leading cause of death in the Russian population followed by cancers and external causes. At the present time, CVD is responsible for 56.8% of all deaths in the Russian Federation. Over the past 30 years, trends in CVD mortality in Russia have undergone political, social and economic transformations characterized by rapid and sharp fluctuations in mortality rates, which were most pronounced in the working-age population. A similar situation occurred in mortality rates from external causes and, to a lesser extent, in mortality rates from cancers. Improvements in the economic situation and population prosperity since 2003 have lead to improvements in living standards and quality of medical care. This has resulted in a steady reduction in CVD, external causes, and cancer mortality; and, an increase in life expectancy.

Keywords
Non-communicable disease, cardiovascular disease, cancers, external causes, mortality, life-expectancy.

From the beginning of the 20^{th} Century non-communicable diseases (NCD) were the major cause of death in high- and medium-income countries. Today the same tendency is detected in many low-income countries. The leading NCDs include cardiovascular diseases (CVD), malignant neoplasms, and respiratory tract diseases. These are followed by infectious diseases, maternal and perinatal mortality, and diseases of malnutrition. The third position involves external causes (traumas, intoxication, accidents) [1]. Fifty seven million deaths were registered in 2008, of which 36.1 million (63.1%) died of NCD. Seventy eight percent (n=28.2 million) of deaths, associated with NCD, happened in medium- and low-income countries [2].

NCD (CVD, malignant neoplasms and external causes) are also in the top position of total mortality in the Russian Federation. CVD (n=1,137,000; 56.8% of all deaths), malignant neoplasms (n=295,000; 14.7%) and external causes (n=225,000; 11.2%) lead

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Table 1. **Mortality associated with major NCD and external causes in 2009**

Age 0 – ≥85 years	**Men**						**Women**					
	All-causes (Total mortality)	**DCS**			**Malignant neoplasms**	**External causes**	**All causes (total mortality)**	**DCS**			**Malignant neoplasms**	**External causes**
		Total	**IHD**	**CerVD**				**Total**	**IHD**	**CerVD**		
Quantity	1.42 mln.	513.5 thous.	156.9 thous.	143.8 thous.	156.9 thous.	173.1 thous.	962 thous.	623.1 thous.	306.2 thous.	228.7 thous.	136.7 thous.	51.5 thous.
Per 100,000 people European Standard	1769.2	921.8	268.0	267.8	268.0	246.3	869.9	524.5	265.4	189.5	133.9	59.3
Per 100,000 people New World Standard	1414.5	704.8	205.7	202.3	205.7	225.7	677.0	391.8	189.8	140.9	104.8	54.2
Age 25 – 64 years	**Men**						**Women**					
	All causes (total mortality)	**DCS**			**Malignant neoplasms**	**External causes**	**All causes (total mortality)**	**DCS**			**Malignant neoplasms**	**External causes**
		Total	**IHD**	**CerVD**				**Total**	**IHD**	**CerVD**		
Quantity	529 thous.	198.8 thous.	106.9 thous.	40.2 thous.	72.7 thous	132.6 thous.	209 thous.	75.0 thous.	32.1 thous.	22.1 thous.	52.6 thous.	31.2 thous.
Per 100,000 people European Standard	1477.0	573.3	330.2	118.6	212.7	350.5	483.5	173.0	79.2	51.0	120.6	72.9
Per 100,000 people New World Standard	1340.0	496.6	265.2	100.8	180.0	344.9	435.3	149.1	62.4	43.3	105.3	71.3

Note: DCS (ICD* — 11:115-147), IHD (ICD 11:121–129), CerVD (ICD — 11:133-141), malignant neoplasms (ICD — 11:56-89), external causes (ICD —11:239-274).
* The International Classification of Diseases

to 83% of total mortality in 2009. This value among men was 81% and among women — 84% (Table 1) [3]. Ischemic heart disease (IHD) and cerebrovascular disease (CerVD) are the major contributive factors to death from CVD; mortality from IHD and CVD is equal to 82.3% of all deaths among women and to 85.8% of all deaths among men. It must be noted, that absolute death cases, associated with all forms of CVD, is higher among men, than among women. The same tendency is detected during separate evaluation of IHD and CerVD contribution to mortality.

Mortality in the most active working age (25–64 years) contributed to 36.8% of total mortality in population: 24% of people died from CVD, 43% — from malignant neoplasms, 73% — from external causes. Analogous values among men were 39%, 46% and

Table 2. **Trend of mortality associated with major NCD and external causes among male population (age 25–64 years) of the Russian Federation, 1980–2009**

Causes of death	**1980**	**1981**	**1982**	**1983**	**1984**	**1985**	**1986**	**1987**	**1988**	**1989**
Total	1401.9	1374.1	1338.9	1353.1	1402.8	1290.7	1086.3	1083.0	1103.7	1167.8
DCS	467.9	453.1	449.9	460.6	481.0	453.1	404.0	409.8	406.3	418.9
Malignant neoplasms	265.7	266.2	270.8	272.1	274.7	276.4	278.6	280.0	284.7	284.6
External causes	417.9	413.2	390.4	387.4	404.1	333.8	231.1	226.9	250.3	296.6
Causes of death	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**
Total	1228.6	1251.3	1416.7	1804.8	2052.7	1921.8	1718.5	1548.0	1497.1	1673.4
DCS	442.5	445.0	489.6	634.9	751.6	687.6	619.9	562.6	547.6	618.4
Malignant neoplasms	288.1	287.4	286.8	293.6	291.8	280.3	266.8	258.1	253.7	254.9
External causes	320.5	342.1	435.0	588.3	656.5	574.2	499.5	436.7	429.1	467.5
Causes of death	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Total	1806.2	1862.0	1939.3	1981.7	1932.7	1941.0	1728.4	1598.2	1572.3	1477.0
DCS	657.8	701.0	745.4	773.0	756.7	762.8	673.7	614.8	610.6	573.3
Malignant neoplasms	252.6	242.8	238.5	233.1	229.6	224.5	217.2	213.7	212.5	212.7
External causes	511.1	535.0	550.9	545.6	529.7	512.7	450.5	411.1	385.4	350.5

Note: Mortality was calculated per 100,000 people of defined age group and standardized in accordance with European standard

Table 3. **Trend of mortality associated with major NCD and external causes among female population (age 25–64 years) of the Russian Federation, 1980–2009**

Causes of death	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Total	480.7	470.3	459.0	469.6	481.7	463.2	410.1	403.8	403.4	409.6
DCS	183.9	178.7	174.4	181.3	189.3	182.0	161.3	159.3	156.2	155.8
Malignant neoplasms	132.0	131.7	132.5	133.7	131.4	131.4	131.7	131.2	130.5	130.8
External causes	85.0	80.9	78.2	79.0	82.6	73.1	52.3	49.8	52.6	58.5
Causes of death	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**
Total	421.6	428.6	466.0	571.5	641.8	604.9	550.4	509.6	490.5	535.0
DCS	159.8	162.2	176.0	224.2	258.4	236.5	215.6	198.4	189.4	210.0
Malignant neoplasms	131.7	131.9	132.7	133.6	137.3	134.7	132.1	130.9	129.4	131.8
External causes	63.0	66.5	84.6	119.7	134.8	118.7	102.9	90.7	88.2	98.3
Causes of death	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Total	564.0	585.6	611.2	625.1	610.5	610.8	552.9	512.0	506.5	483.5
DCS	224.4	233.6	245.2	252.1	240.7	241.9	212.7	187.9	187.3	173.0
Malignant neoplasms	129.6	129.1	126.7	126.4	126.7	123.4	121.3	121.1	120.7	120.6
External causes	104.2	110.5	115.7	115.2	111.9	105.3	93.7	83.9	78.3	72.9

Note: Mortality was calculated per 100,000 people of defined age group and standardized in accordance with European standard

77% and among women — 12%, 38% and 61%, respectively. The total mortality structure of 25–64-year old population has the following view: CVD contribute to 37.6%, malignant neoplasms — to 13.7%, external causes — to 25% of all death cases among men; values among women are equal to 35.9%, 25% and 14.9%, respectively. In this age group, the total contribution of IHD and CerVD mortality from CVD in men was 74%, in women — 72%.

Table 2 (men) and Table 3 (women) show mortality trend in the most active working age population from CVD, malignant neoplasms and external causes during last three decades (1980–2009) [4]. It was shown earlier that the period of political, social and economic transformations in Russia was characterized by rapid and sharp increase and decrease of mortality, which were the most pronounced in working-age population [5–7]. Comparative analysis of mortality rates can be divided into 3 periods: the first one (1980-1989) — period of relative political and economic stability, the second (1990–1999) — period of political and economic transformations (dissolution of the USSR, reforms, economic crisis) and the third (2000–2009) — period of adaptation to new political and economic transformations (reforms). It must be noted that during all thirty years total mortality and mortality from CVD and malignant neoplasms among men were 2–3 times higher and from external causes — 3–4 times higher than among women. Odds of total mortality, CVD and external causes' mortality had a mild trend to decrease in the first period, but such minimal values of mortality were not attained during two subsequent periods. There was a slight increase of mortality from malignant neoplasms among men at the end of the first period; values of mortality among women were stable during all the first period. The first half of the second period (1990–1994) was characterized by sharp increase of mortality among men as well as among women: total mortality increased on 67% and 52%, CVD mortality — on 70% and 62%, mortality from external causes — more than 2 times, respectively. Mortality from malignant neoplasms among men and women was almost stable during all second period. At the second half of the second period (1994–1999) there was detected a gradual decline of mortality (total mortality, CVD mortality and mortality from external causes) among men and women. Nevertheless mortality remained higher than in the beginning of transformation period. A decrease in mortality from malignant neoplasms was detected among men in the second half of the second period; almost no changes were visualized among women. The third period (2000–2009) can be also divided into two intervals: the interval of increase in total, CVD and mortality from external causes (2000–2003); and the interval of slight (after 2003 year) and then (from the beginning of the 2006 year) more prominent decrease of total, CVD and mortality from external causes among men and women. In spite of mortality decrease it must be noted, that by 2009 values of total, CVD and mortality from external causes among men as well as women were higher than in 1989. At the same time there was detected a reduction of mortality from malignancies among men and women during all follow-up period.

Population dynamics repeats the trends in mortality in the country. The first period of relevant political and economic stability was characterized by the 5 million increase of the male population (from 64 million

Table 4. **Dynamics of the male population of the Russian Federation in 1980 to 2009**

Age groups (years)	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
0–4	5,421	5,464	5,536	5,667	5,808	5,913	6,024	6,135	6,157	6,058
5–14	9,809	9,920	10,072	10,248	10,419	10,569	10,699	10,833	11,027	11,233
25–64	32,252	32,869	33,527	34,191	34,858	35,553	36,252	36,894	37,410	37,770
≥65+	3,813	3,797	3,745	3,722	3,708	3,656	3,619	3,617	3,657	3,769
0 – ≥85	63,813	64,231	64,700	65,246	65,807	66,359	67,003	67,720	68,391	68,904
	1990	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**
0–4	5,877	5,407	5,214	4,766	4,370	4,048	3,765	3,550	3,431	3,310
5–14	11,397	11,655	11,747	11,901	11,950	11,957	11,814	11,538	11,097	10,490
25–64	37,985	37,943	37,866	37,620	37,420	37,299	37,226	37,248	37,364	37,332
≥65	3,947	4,343	4,502	4,827	5,107	5,336	5,512	5,646	5,712	5,687
0 – ≥85	69,266	69,522	69,565	69,530	69,455	69,388	69,159	68,926	68,717	68,051
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
0–4	3,232	3,238	3,239	3,298	3,400	3,566	3,659	3,767	3,888	4,018
5–14	9,986	9,492	8,832	8,328	7,801	7,468	7,124	6,911	6,848	6,870
25–64	37,358	37,373	36,951	36,732	36,517	36,621	36,645	36,912	37,456	38,085
≥65	5,708	5,816	5,959	6,106	6,250	6,370	6,404	6,330	6,110	5,848
0 – ≥85	67,678	67,533	67,114	66,720	66,267	66,383	66,006	65,783	65,679	65,641

people to 69 million people due to child and working age population (Table 4). Distinguishing feature of two subsequent decades (1990–2009) was a decrease of male population size by 3.5 million people; male population size was equal to 65 million people in 2009. Total decrease was mainly associated with decrease of child population: at the age of 0–4 years — by 2 million people (34%), at the age of 5–14 years — by 4,364 million people (40%).

It must be noted, that the decrease of male population (early childhood — 0–4 years) was registered until 2003, when a gradual increase of child population started. A the same time this period was characterized by a growth of aged population (≥65 years) by 2 million people, while the working age population almost did not change. Population dynamics among women was similar to population dynamics among men. Female population growth by 4 million people (from 74,671 million to 78,426 million) was detected in 1980–1989. It was driven by an increase of child and working age population (Table 5). Two subsequent decades of transfomations and adaptation to transformations were characterized by a decrease of female population due to decrease of child population at the age of 0–4 years (by 2 million people; 35%) and at the age of 5–14 years (by 4,364 million people; 40%). Female population was estemated as 76,269 million people in 2009. The decrease of female population at the age of 0–4 years also continued until 2003. Then gradual growth of this age grade population was detected. It should be pointed out that this period was also characterized by an increse of female population

Table 5. **Dynamics of the female population of the Russian Federation in 1980 to 2009**

Age groups	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
0–4	5,242	5,278	5,342	5,463	5,600	5,703	5,812	5,918	5,933	5,828
5–14	9,508	9,601	9,734	9,893	10,061	10,226	10,370	10,509	10,700	10,899
25–64	37,610	38,072	38,634	39,170	39,663	40,209	40,749	41,169	41,411	41,471
≥65	10,327	10,356	10,290	10,279	10,286	10,222	10,186	10,223	10,341	10,577
0 – ≥85	74,671	74,990	75,364	75,810	76,253	76,672	77,155	77,664	78,103	78,426
	1990	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**
0–4	5,639	5,169	4,978	4,535	4,147	3,839	3,573	3,370	3,259	3,142
5–14	11,050	11,290	11,376	11,511	11,563	11,519	11,362	11,081	10,638	10,037
25–64	41,418	41,146	41,022	40,746	40,506	40,343	40,278	40,309	40,447	40,460
≥65	10,892	11,407	11,580	11,894	12,146	12,363	12,523	12,626	12,649	12,522
0 – ≥85	78,649	78,756	78,748	78,619	78,488	78,386	78,214	78,012	77,816	77,118
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
0–4	3,063	3,066	3,080	3,135	3,228	3,386	3,471	3,569	3,682	3,806
5–14	9,543	9,063	8,447	7,960	7,450	7,138	6,809	6,605	6,540	6,553
25–64	40,615	40,794	40,945	40,776	40,594	40,786	40,872	41,214	41,897	42,690
≥65	12,481	12,592	12,692	12,919	13,178	13,410	13,510	13,441	13,134	12,746
0 – ≥85	76,822	76,853	76,996	76,733	76,423	76,731	76,481	76,332	76,277	76,269

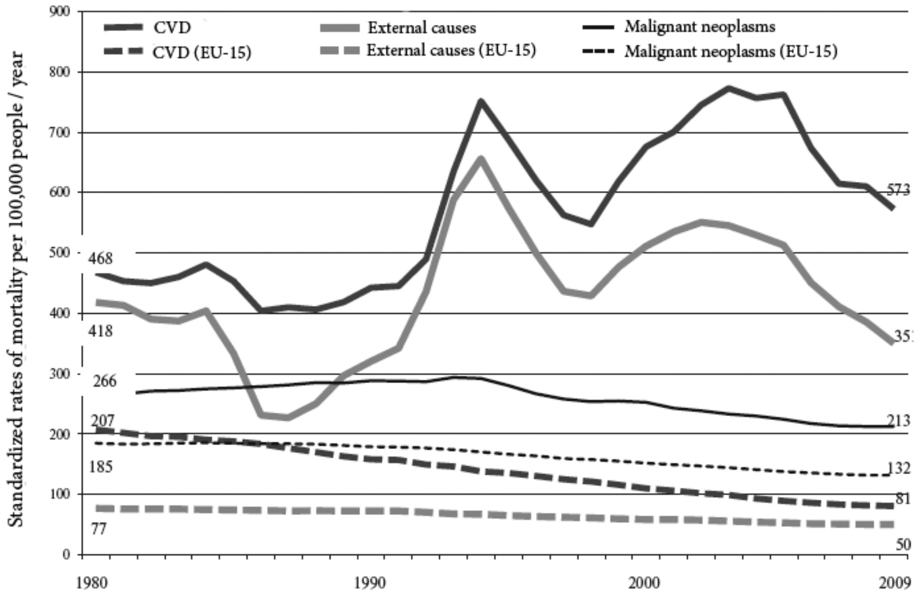

Figure 1. Trend in mortality from major NCDs and external causes among male population of the Russian Federation and 15 European countries (EU-15) in 1980–2009. Age — 25-64 years

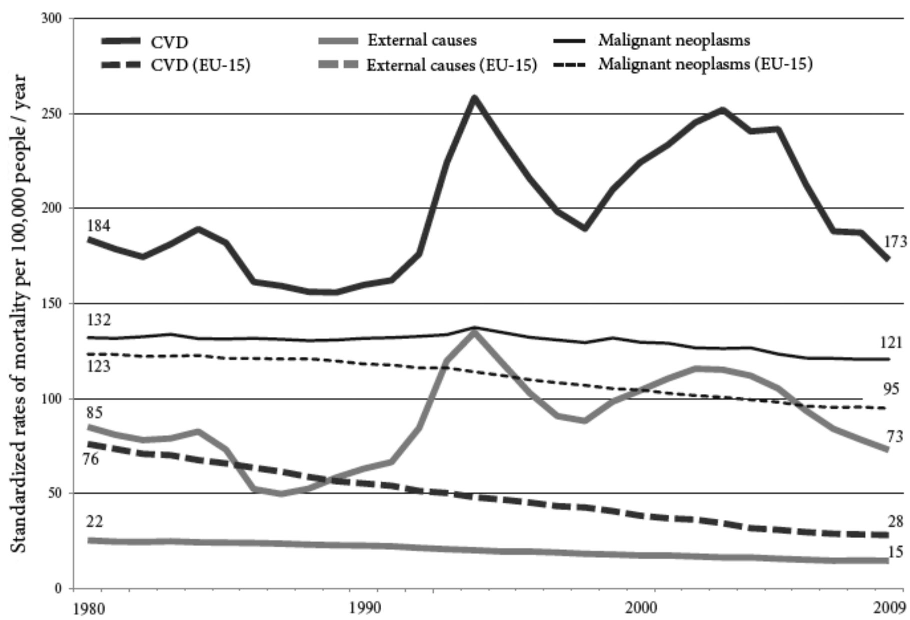

Figure 2. Trend in mortality from major NCDs and external causes among female population of the Russian Federation and 15 European countries in 1980–2009. Age — 25–64 years

at the age of ≥65 years by 2.2 millon people and of female working age poplation by 1.2 million people, which did not match with the demographic situation among men.

The present demographic situation in Russia stems from not only low birth rate, but also from high rates of premature death from NCD (mainly from CVD) among working age population. In the face of above mentioned information it is supposed that demographic situation can be improved by realization of effective, long term national programs aimed at birth rate escalation as well as reduction of NCD incidence (mainly CVD incidence). Primary prevention must be a priority, as improvement of diagnostic and treatment measures alone can only lead to an increase in CVD prevalence due to advances in disease detection. Improvement of diagnosis and treatment of increasing number of patients will only lead to raising expenditures on healthcare.

Early publications have shown that in spite of existing similar mortality structure in Russia and other economically developed countries, including European countries, U.S. and Japan, standardized rates of mortality associated with NCD and external causes are different, especially when comparing working age population [6,7]. Mortality trends in Russia and economically developed countries are also different. Thus during mentioned 30-year period scientists detected gradual decrease of mortality, associated with CVD, external causes and malignancies, among working age male (Figure 1) and female (Figure 2) population of 15 economically developed countries, which entered European Union (EU-15). At the same time mortality from CVD and external causes was characterized by marked rises and falls in Russia, especially during the

Table 6. **The dynamics of life expectancy at birth in the population of the Russian Federation, and 15 European countries (EU-15), 1980 to 2009**

Sex	1980		1990		2000		2009	
	Russia	EU-15	Russia	EU-15	Russia	EU-15	Russia	EU-15*
Male	61.5	70.6	63.3	73.1	58.4	75.8	61.8	77.2
Female	73.1	77.3	73.9	79.8	71.9	81.8	74.2	82.6

Note: *Information was obtained in 2008. The economic and fiscal consequences of ageing, with special focus on health and long term care. Bartosz Przywara European Commission, DG ECFIN Ageing and Haemophilia-EHC Roundtable of Stakeholders. Brussels, 23 February 2010. Sources: http://www.demographic-research.org/volumes/Vol.20/8/doi:10.4054/DemRes.2009.20.8.

period of political and economic transformations. As a result, differences in mortality of working age (26–54 years) male and female population became more pronounced between the Russian Federation and EU-15, when comparing data obtained in 1980 and in 2009. Differences in mortality from CVD and external causes among male population are characterized by 2–7-fold and 5-7-fold increase (Figure 1) and among female population — by 2–6-fold and 4–5-fold increase (Figure 2), respectively.

Mortality trends reflect changes of population size as well as life expectancy (LE). Table 6 reflects the LE dynamics among male and female population of Russian Federation and EU-15 during 30-year period. The first period (1989–1990) was characterized by an increase of LE among male and female population of the Russian Federation. Then there was a marked decrease of LE (by 5 years among men and by 2 years among women) in the second period (1990–2000). The third period was marked by an increase of LE by 3.4 years among male population and by 2.3 years among female population. Nevertheless male LE had not yet reached the level in 1990, when political and economic transformations happened. LE in EU-15 on the contrary was characterized by a constant increase during the observation period. It reached 77.2 years for male population and 82.6 years for female population in 2009 and exceeded comparable values, determined in 1980, by 6.6 years among men and by 5.3 years among women. As a result marked differences in LE formed between the Russian Federation and EU-15 during a 30-year period. LE dissemblance elevated from 9.1 in 1980 to 15.4 in 2009 between male populations and from 4.2 to 8.4 years between female populations, respectively.

Conclusion

In the beginning of the 21st Century NCD, mainly CVD, remain the major cause of death in high- and medium-income countries. The same situation is observed in Russia, where CVD is the leading cause of mortality. Nevertheless mortality trends and standardized values per 100,000 people in Russia differ from analogous values in economically developed countries, including countries of Western Europe. It is generally recognized nowadays that high prevalence of CVD is associated with living habits and risk factors, including smoking, unhealthy diet, low physical activity, alcohol consumption. These factors contribute to high prevalence of hypertension, hypercholesterolemia, diabetes mellitus and obesity in population, which in turn promote the development and progression of main forms of CVD. Marked fluctuations of mortality from CVD and external causes in the period of social and economic transformations in Russia were probably associated with psychosocial factors, because no increase of other risk factors was detected during that period. There were distinguished seven major risk factors of premature mortality in the Russian Federation: high blood pressure (BP) (35.5%), hypercholesterolemia (23%), smoking (17.1%), unhealthy diet, including the lack of fruit and vegetable consumption (12.9%), obesity (12.5%), alcohol abuse (11.9%) and low physical activity (9%) [8]. These risk factors are also the main cause of physical disability among working age population: alcohol abuse (16.5%), high BP (16.3%), smoking (13.4%), hypercholesterolemia (12.3%), obesity (8.5%), unhealthy diet, including the lack of fruit and vegetable consumption (7.9%), low physical activity (4.6%) [8].

Taking the above mentioned into consideration it must be noted that preventive measures should be aimed primarily on improvement of lifestyle and lowering of relevant risk factors prevalence. Scientists from different countries have detected, that this measures can result in 44-60% reduction of CVD-associated mortality [9]. Contribution of treatment in the reduction of mortality, associated with CVD, is also high (23-47%), so improvement of treatment quality must be taken into account. Constant mortality reduction, LE increase and population growth in foreign countries is a result of growth in prosperity as well as implementation of primary and secondary preventive measures that lead to reduction of risk factors prevalence and enhancement of treatment efficiency [9,10]. In accordance with the one of the first analysis of CVD mortality in the Russian Federation, «a sustained reduction of CVD-associated mortality is unachievable until improvement of economic situation and population prosperity» [5]. Improvements of economic situation and population prosperity were registered in the end of 2003. They certainly had an impact on lifestyle and quality of medical care, so further reduction of CVD-associated mortality and increase of LE is expected.

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

REVIEW PAPER

Evidence based cardiovascular risk assessment

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Summary

In order to best identify persons at risk for cardiovascular disease (CVD), it is important to understand the guidelines for CVD risk assessment and evidence-based methods for evaluation of risk in asymptomatic individuals. In this report, we will 1) review the role and limitations of global risk assessment, 2) review the evidence and recommendations for biomarkers in CVD risk assessment, and 3) review the evidence and recommendations for subclinical disease evaluation / imaging in CVD risk assessment.

Keywords

Screening, atherosclerosis, prevention, risk assessment

In 1961, Dr. William B. Kannel from the Framingham Heart Study introduced the concept of cardiovascular risk factors from some of the early longitudinal data showing the importance of elevated cholesterol, blood pressure (BP), and smoking in relation to future coronary heart disease (CHD) risk [1]. The concepts of multivariable and global risk assessment, based on estimating risk from the combination of several risk factors (Figure 1) developed over succeeding decades cumulating in the development of the Framingham Risk Scores, as well as other risk scores used in other parts of the world, including the Systematic COronary Risk Evaluation (SCORE) algorithms in Europe [2–4], which all differ according to the endpoint used, length of follow-up, and risk factors included. The U.S. National Cholesterol Education Program was one of the first groups to recommend use of global risk assessment scoring specifically for persons at suggested intermediate risk based on the presence of 2 or more risk factors [5]. For example, one can apply different risk scoring systems to a given case study, a 67-year old woman, nonsmoker, with total cholesterol of 210 mg/dL, systolic BP of 138 mm Hg, and high-density lipoprotein (HDL) cholesterol of 42 mg/dL. She also has a triglyceride level of 201 mg/dL, waist circumference of 36 inches, and fasting glucose of 109 mg/dL which do not factor into these risk scores, but show that she has all five metabolic syndrome risk factors. Depending on what risk score is used, one gets dramatically different results, ranging from only 1–2% of the European SCORE algorithm for fatal CVD is used, to 3% if the 10-year CHD Framingham risk score is used [6], 10% if the Framingham 10-year total CVD risk score is used, to

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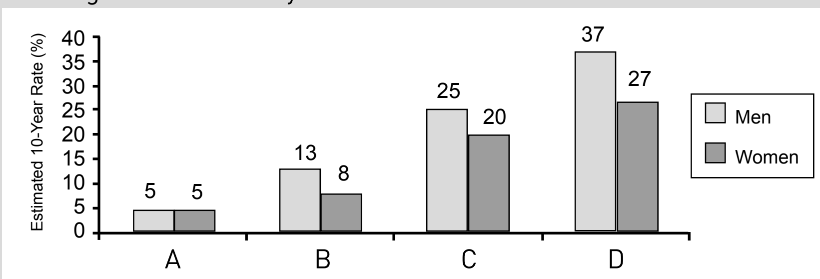
Estimated 10-Years CHD Risk in 55-Year-old Adults According to Levels of Various Risk Factors

Framingham Heart Study



	A	B	C	D
Blood Pressure (mm Hg)	120/80	140/90	140/90	140/90
Total Cholesterol (mg/dL)	200	240	240	240
HDL Cholesterol (mg/dL)	50	50	40	40
Diabetes	No	No	Yes	Yes
Cigarettes	No	No	No	Yes

mm Hg – millimeters of mercury
mg/dL – milligrams per deciller of blood

Source: Circulation 1998;97:1837-1847

Figure 1. Multivariable CHD risk assessment

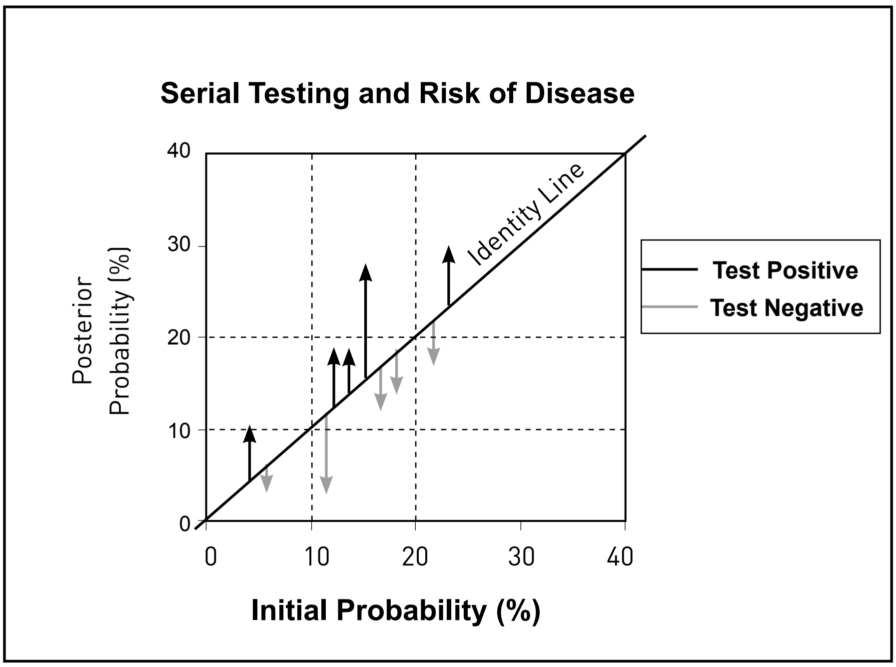


Figure 2. Reclassification of risk by a screening test

39% if lifetime risk is estimated. Many persons who suffer CVD events are not at high risk; in fact, 56% or 87 million persons in the U.S. have low short-term but high lifetime risk [7] and lifetime risk for total CVD is approximately 60% in men and 50% in women [8]. One can suggest possibly considering use of a short-term (e.g., 10-year) risk score initially, and in those at low or intermediate risk, then applying a lifetime risk estimation to decide who should be treated. Persons initially at high risk by the short-term score or lifetime risk score would be treated, whereas those at lower risk by both short-term and lifetime risk scoring would receive lifestyle management.

Global risk scoring algorithms are therefore only moderate accurate for identifying those who will eventually suffer a major coronary event. There are a number of criteria that are required for a good screening test for evaluation of CVD risk. These criteria include sensitivity in identifying those who have the condition of interest, providing reproducible results, detecting those where early intervention is likely to have a beneficial impact, and being able to provide incremental value to risk predicted by office-based risk assessment (e.g., risk scores) [9]. One example of how a screening test may work is that it can be applied to those initially at intermediate (e.g., 10–20%) risk and if positive, would stratify that person to a higher risk category, and if negative would stratify them to a lower risk category (Figure 2). A new metric for clinical utility, the net reclassification

Applying Classification of Recommendation and Level of Evidence

Class I	Class IIa	Class IIb	Class III
Benefit >>> Risk	Benefit >> Risk Additional studies with focused objectives needed	Benefit ≥ Risk Additional studies with broad objectives needed; Additional registry data would be helpful	Risk ≥ Benefit No Additional studies needed
Procedure or theatment SHOULD be performend or administered	IT IS REASONABLE to perform procedure or administer treatment	Procedure or treatment MY BE CONSIDERED	Procedure or treatment SHOULD NOT be performed or Administered SINCE IT IS NOT HELPFUL AND MY BE HARMFUL

Level of Evidence	**A: Multiple randomized controlled trials** **B: Single trial, non-randomized studies** **C: Expert opinion**

Figure 3. American Heart Association / American College of Cardiology Classification of Recommendations and Levels of Evidence

index, is defined as the net proportion of persons who are correctly reclassified from the new test, or the sum of 1) cases whose risk is stratified upward (correct) by the test being positive minus the cases where risk is stratified downward (incorrect) and 2) controls whose risk is stratified downward (correct) minus those who are stratified upward (incorrect) [10].

In 2010, the *American College of Cardiology Foundation* (ACCF) / *American Heart Association* (AHA) guidelines for CVD risk assessment in asymptomatic adults were published and form the basis for the recommendations and screening tests discussed in this report [2]. They graded a large number of screening tests according to the strength of recommendation or size of effect (Class I being strongest, III being weakest) and level of evidence (A being strongest and C being weakest) (Figure 3).

Inflammatory factors and other biomarkers

Numerous prospective studies have documented high sensitivity C-reactive protein as an independent risk factor for CVD events with approximately a two to four-fold greater risk associated with being in the highest vs. lowest quartile [11]. These studies, as well as the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) clinical trial involving rosuvastatin given to persons with normal low-density lipoprotein (LDL) cholesterol but elevated high-sensitivity C-reactive protein (hs-CRP) resulting in significant CVD event reduction, have led to the hs-CRP recommendations from the *ACCF / AHA* statement and the *National Lipid Association* expert panel. They do recommend (Class IIa or IIb, level of evidence B) hs-CRP assessment in men aged 50 years or over or women aged 60 years and over not on lipid-lowering therapy but with an LDL cholesterol <130 mg/dL, as well as younger intermediate risk persons. Measurement, however, is not recommended in higher or lower risk persons [2].

Elevated levels of lipoprotein associated phospholipase A2 (LpPla2) are also shown from a large meta-analysis to confer excess risk of CVD events, and to provide additive value in combination with hs-CRP for identification of higher risk persons [12]. The guideline panels did give LpPla2 a class IIb level of evidence B recommendation for measurement in those at intermediate risk [2].

B-type natriuretic peptides or BNP have also been shown to be positively associated with CVD risk both in persons with and without existing CVD from large meta-analyses [13], but only very modest improvements in discrimination as measured by the C-statistic have been noted, and the *ACCF/AHA* panel did not recommend (Class III) its measurement for CHD risk assessment in asymptomatic adults [2].

It is possible that a multimarker approach utilizing biomarkers representing complementary, but different pathologies may be practical in the future and numerous groups are trying to identify the "cocktail" of biomarkers that will serve to significantly enhance risk reclassification. For example, such a combination of biomarkers might involve inflammation, myocyte necrosis, hemodynamic stress, accelerated atherosclerosis, and vascular damage. An example from the Framingham Heart Study utilizing five distinct biomarkers (BNP, C-reactive protein, urine albumin / creatinine, homocysteine, and renin) shows an index consisting of the biomarkers to be independently associated with risk of CVD events; however, only a very modest improvement in C-statistic was observed [14].

While somewhat obvious, but poorly documented in the medical history, a premature family history of CHD is strongly associated with future risk and a careful evaluation of family history in all first degree relatives is recommended; however, genomic screening, despite its popularity, as failed to be proven to provide incremental predictive utility for CVD events over standard risk assessment and is not recommended. Modest recommendations, however, are made for the assessment of HbA1c in persons without diabetes, as well as urinary albumin excretion, especially in those with hypertension or diabetes [2].

Subclinical CVD assessment methods

Screening tools have been developed for evaluating subclinical CVD in just about every part of the body, ranging from carotid ultrasound to aortic and carotid magnetic resonance imaging (MRI), coronary calcium screening by computed tomography (CT), ankle brachial index for peripheral artery disease, and brachial artery reactivity and radial tonometric techniques for assessing endothelial function. We will review the principal screening modalities (namely carotid ultrasound, ankle-brachial index, and coronary calcification screening) that have the greatest evidence base for cardiovascular risk assessment.

Carotid ultrasonography. Probably the most established method for examining subclinical atherosclerosis is carotid B-mode ultrasound (Figure 4). It is noninvasive without radiation and of moderate cost and there are numerous clinical trials that have used this as a surrogate endpoint for examining effects of therapeutic interventions such as lipid-lowering on retarding progression of atherosclerosis. While the accuracy of assessments of carotid intima-media thicknesses (IMT) depends on the operator, easier more automated devices are being developed which will make its assessment more standardized and applicable to the office-based practitioner. The *ACCF/ AHA* guidelines give IMT measurement a class IIa level of evidence B recommendation in asymptomatic intermediate risk persons [2]. Increased carotid IMT has long been shown to be associated with greater

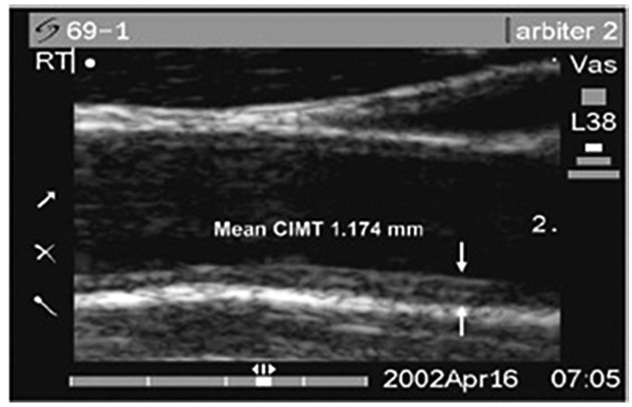


Figure 4. Example of carotid B-mode ultrasonography for assessment of carotid intimal media thickness

CVD event risk, such as shown by the Cardiovascular Health Study in the elderly, where among those in the 5th quintile for carotid IMT, one quarter had suffered a MI or stroke within 7 years [15]. More recently, the Atherosclerosis Risk in Communities study demonstrated the combined importance of both carotid IMT as well as carotid plaques for prediction of CHD events; at each level of carotid IMT, there was added prediction offered by the presence of carotid plaques [16]. The combination of both was able to reclassify 23% of individuals over traditional risk factors.

Ankle brachial index. Measurement of subclinical peripheral arterial disease can help identify persons more likely to have vascular disease in other areas as well as increased CVD risk. Ankle brachial index (ABI) measurement involves a simple Doppler tool and is completely noninvasive, with the ratio of the higher of the systolic BP measures from each ankle forming the numerator for the left and right ABI and the higher of the systolic BP measures taken in each arm being the denominator. An ABI < 0.9 is diagnostic of peripheral arterial disease. Studies such as the Cardiovascular Health Study have shown the lower the ABI the worse the survival, with <80% of subjects alive after 6 years among those with an ABI < 0.9 [17]. The more recently reported ABI Collaboration showed that compared to a reference group of 1.1–1.2, those with an ABI <1.0 were at significantly higher risk of total mortality, even those in the borderline 0.9-<1.0 range, there was nearly a two-fold increase in the risk of mortality [18]. From this study, 19% of men and 38% of women were reclassified in their risk category from the addition of ABI.

Coronary artery calcium. Coronary artery calcium (CAC) measured by computed tomography (Figure 5) has established itself as a potent subclinical disease predictor of future CVD events. The extent of CAC correlates with overall atherosclerotic burden,

Figure 5. Example of coronary calcium evaluation by computed tomogrphy

although the greatest CAC deposits may not necessarily be present where the tightest stenosis are located and not all atherosclerotic lesions necessary contain CAC. While numerous "commercial" scanning cohorts have shown a direct relation between CAC scores and future CHD events, the Multiethnic Study of Atherosclerosis (MESA) was the first population-based prospective study to demonstrate this with successively higher rates of CHD events associated with greater CAC scores [19]. Those with a CAC score >300 compared to 0 had nearly a 7-fold greater risk of major CHD events and 10-fold greater risk of any CHD events. Moreover, incremental discrimination from higher C-statistics were noted in the four major ethnic groups included in MESA over and above standard risk factors. Overall, 23% of persons with events were reclassified as high risk and 13% without events reclassified as low risk [20]. More recently, we demonstrated CAC scoring to stratify risk in those with metabolic syndrome and diabetes; there was a 10-fold or greater gradient in risk from those without CAC to those with CAC scores of 400 or greater, thus demonstrating that diabetes is not a CHD risk equivalent but is associated with significant heterogeneity in risk (Figure 6) [21]. More than one-third of our cohort with diabetes had CAC scores of 0 and CHD risk was lower than many persons without diabetes or metabolic syndrome; thus, this raises question regarding whether diabetes is in fact a CHD risk equivalent. The *ACCF/AHA* statement has noted with a Class IIa level of evidence B recommendation that measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk, as well as at low to intermediate risk based on 6-10% (class IIb), but not in those at low risk. However, those with diabetes aged >40 are also appropriate for CAC measurement (Class IIa level of evidence B) (2). Progression of CAC has also recently been demonstrated to be independently associated with future CHD event risk [22]; however, guidelines thus far have not endorsed repeat CAC scanning for stratification of risk or treatment [23].

The identification of CAC has also been shown to be related in an observational study to be related to the subject's greater likelihood of practicing preventive behaviors, such as starting aspirin or cholesterol medicine, losing weight, and seeing a doctor, with the extent of calcification also shown to be related to the likelihood of certain behaviors [24]. More recently, in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) prospective randomized trial, where over 2,000 asymptomatic subjects were randomized 2:1 to calcium scanning or not to scanning, those who received scanning showed no increase in their Framingham risk score 4 years later, compared to an increase in the risk score seen among those not received scanning [25]. Also, in a very recent report, the greater the lifestyle score (number of healthy lifestyle behaviors), the less the incidence or progression of CAC seen from serial CAC scanning in MESA [26].

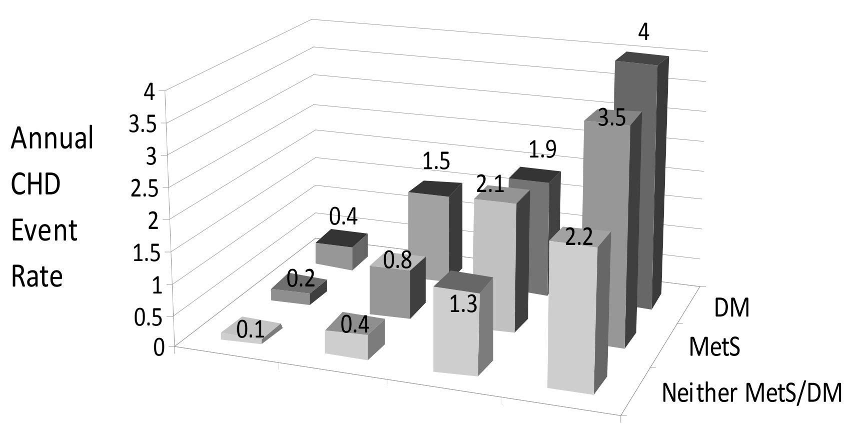


Figure 6. Stratification of CHD risk by coronary calcium levels in persons with and without metabolic syndrome and diabetes. Adapted from Malik et al. [21]

Some have argued that CAC testing might increase the utilization of other testing, but this has not been proven. In fact, the Eisner Study of subjects randomized to CAC testing or no testing showed no significant difference in the incidence of downstream testing over 4 years of follow-up [25]. In addition, the radiation dose from CAC scanning has been shown to be similar to that of a mammogram or a long distance air flight.

Further, CAC scanning can help identify those most likely to have a positive nuclear myocardial perfusion test; the likelihood of such a test being positive is quite low unless CAC scores exceed 400 [27]. Among those with diabetes or metabolic syndrome, a threshold CAC score of 100 is seen to identify those with an increased likelihood of a positive nuclear study [28]. Thus, CAC scanning may serve as a useful gatekeeper for identifying those most likely to benefit from nuclear myocardial perfusion testing.

There has also been interest in whether CAC testing can help identify those who may or may not benefit from statin therapy. In the Jupiter eligible population from MESA (e.g., LDL cholesterol <130, hs-CRP > 2, and no diabetes mellitus) it was shown that only 25% of subjects had a CAC >100 and when the Jupiter relative risk reduction was applied to the CHD event rates observed in this group, it would take only 24 persons treated with a statin to prevent one event; however, in the 27% with CAC 1-100, the number need to treat (NNT) was 94 and in the remainder with CAC=0, the NNT was 549 [29].

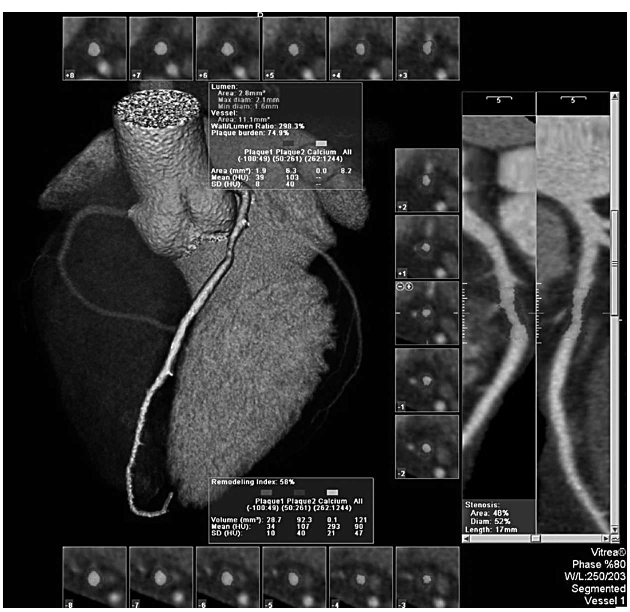


Figure 7. 3D vessel probe of the Left Main and left anterior descending (LAD) coronary artery from CT angiography. Curved Multi-planar Reconstruction (MPR) images are automatically rendered and quantify this LAD lesion at 48% diameter stenosis. SUREPlaque software is used to determine plaque burden and a vessel remodeling index at this lesion. Images courtesy of Courtesy of Toshiba America Medical Systems and Vital Images SUREPlaque and University of California Irvine, Cardiac CT Center.

When all the noninvasive screening modalities are examined together in MESA, a recent report shows CAC to be by far the strongest predictor and is associated with the greatest incremental value improvement by the C-statistic over Framingham Risk Score [30].

CT angiography and non-calcified plaque. CT angiography has paved the way for identification of non-calcified and vulnerable plaque characteristics (Figure 7) which quantification that compares well to that of intravascular ultrasound [31]; however, due to the radiation and contrast enhancement required, the *ACCF/AHA* recommendations still do not indicate it for CVD risk assessment in asymptomatic adults [2]. Nevertheless, the number of diseased vessels from CT angiography has been shown to be a strong predictor of prognosis [32], although information provided by CT angiography does not appear to add further information to prediction of CHD events over that of CAC [33].

Summary

The *ACCF/AHA* statement has made recommendations for screening certain populations with different imaging modalities and biomarkers. Most key imaging modalities have been recommended for CVD risk assessment in intermediate risk persons. It is important that screening tests be able to provide added clinical utility over global risk assessment and that screening be able to help identify persons most likely to benefit from more intensive therapy. However, it is not known whether screening for subclinical atherosclerosis will eventually result in improved clinical benefit. There will be newer guidelines for CVD risk assessment released in the near future by the U.S. National Institutes of Health in collaboration with U.S. cardiology professional societies.

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

Heart rate and nicotine: a chronic problem

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Summary
Elevated resting heart rate is an independent risk factor for developing cardiovascular disease and increases the risk of adverse outcomes in patients with established cardiovascular disease. Heart rate elevated over time is particularly deleterious to health. Tobacco use has been widely reported to affect heart rate, due principally to the acute positive chronotropic effect of its key component, nicotine. This review explores the proposition that chronic nicotine consumption equates to chronic elevated heart rate.

Keywords
Heart rate, nicotine, tobacco, smoking, electronic cigarettes, smokeless cigarettes

Introduction

Heart rate is a fundamental measure of cardiac function, and is of prognostic and therapeutic significance for both cardiovascular and general health. Over the past 30 years, evidence has emerged to show elevated resting heart rate to be an independent risk factor for developing cardiovascular disease in the general population [1,2,3], which may be comparable in importance as a risk factor to smoking or hypertension [4].

Elevated resting heart rate is a prognostic indicator for several cardiac and non-cardiac disorders [5,6]. It is associated with an increased risk of further cardiac events and adverse outcomes in patients with established cardiovascular disease [7,8], and is an important risk marker for cardiovascular and all-cause mortality [9]. There is a strong independent association between elevated resting heart rate and Sudden Cardiac Death, including in studies of apparently healthy men and women [10].

Heart rate features in an ever-increasing number of national and international clinical guidelines, both within cardiology and beyond. Current cardiovascular disease prevention guidelines identify heart rate as an independent cardiovascular risk factor but refrain from identifying heart rate as an intervention target for primary prevention given the lack of outcomes data [11]. In preventive strategies, therefore, heart rate remains a marker of risk rather than a target for treatment. In secondary prevention and rehabilitation, elevated heart rate is a well established target for intervention, with management strategies involving lifestyle advice and prescribed medications.

With heart rate holding such a prominent position in cardiovascular health, any factors which serve to

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raise heart rate above a normal, healthy and appropriate level should cause concern and prompt intervention. This review looks at the impact of nicotine in raising heart rate acutely and chronically and discusses the clinical implications of this relationship.

Chronic Effects of Long-term Elevated Resting Heart Rate

There is plausible physiological evidence to support the hypothesis that maintaining a low resting heart rate over a lifetime can increase longevity [12,13]. In support of this premise, epidemiological data on the long-term follow-up of healthy individuals have demonstrated that there is an independent association between chronic elevated heart rate and cardiovascular mortality and morbidity. Two large observational studies have demonstrated an increased risk of cardiac events in individuals whose resting heart rate has increased over time [14,15]. Although, a decreased risk of CVD in individuals whose heart rate has decreased over time was only demonstrated in one of these studies [14].

In the Framingham study (n = 5,070), there was a 30-year follow-up of healthy men and women. Although the increase in the overall mortality as a consequence of elevated resting heart rate was more marked among men, it was also found to be significant among women and in both younger and older individuals [16]. In another American study (n = 5,995), healthy subjects aged 25–74 years were followed for between 6 and 13 years. Elevated resting heart rate was found to be an independent risk factor for coronary artery disease (CAD) incidence or death among white and black men and women [17].

An elevated resting heart rate that develops or persists over a five year treatment period predicted greater likelihood of subsequent cardiovascular or all-cause mortality, independent of treatment modality, blood pressure lowering, and other variables [18]. In a sub-analysis of the LIFE (Losartan Intervention For Endpoint) study (n = 9,193), researchers discovered that a heart rate of 84 beats per minute (bpm) or greater, that either developed after initiation of treatment for hypertension or persisted during the study's average five-year follow-up, was linked to a 55% greater risk of cardiovascular death and a 79% greater risk of death from all causes. Although the participants had hypertension, researchers adjusted for this and other cardiovascular risk factors (including age, gender, race, diabetes, smoking, and history of heart disease) and found a strong association between persistent elevated heart rate and risk of death. Even incremental increases in heart rate were associated with increased risk of death. For example, every 10 bpm increase from baseline resting heart rate was associated with a 16% increased risk of death from cardiovascular disease and a 25% greater risk of all-cause mortality.

Tobacco use and cardiovascular disease

Tobacco products are made entirely or partly of leaf tobacco. These products are most commonly consumed through combustion, in which tobacco leaves are burned at high temperatures and the resulting smoke is inhaled (cigarettes, cigars, pipes). Tobacco may also be consumed via smokeless methods such as chewing, sucking, or snuffing. Tobacco is the single most preventable cause of death in the world today and is responsible for about one-in-ten deaths worldwide, equating to an estimated 5 million deaths each year [19].

Tobacco products are used by 1.1 billion people, representing up to one-third of the adult population [19]. The *World Health Organization* (WHO) only collects data on smoked tobacco and smoking has been studied more extensively than any other form of consumption. Rates of smoking have levelled off or declined in developed countries, but tobacco consumption continues to rise in developing countries [20]. According to data from 71 countries compiled by the *World Lung Foundation* and *American Cancer Society*, China is the world's largest overall consumer of cigarettes, accounting for 38% of the world market, followed by Russia with 6.5% and then the U.S. with 5%. However, Russia is in fourth place in terms of annual per capita consumption at 2,786 cigarettes per person (with China at 1,711, U.S. at 1,028, and U.K. at 750) [21].

Tobacco use is a major risk factor for several chronic diseases, including cancer, lung diseases, and cardiovascular diseases. Life expectancy is reduced in long-term smokers, with estimates ranging from 10 to 17.9 fewer years than non-smokers [22,23]. About one-half of long-term male smokers will die of illness due to smoking [23]. Male and female smokers lose an average of 13.2 and 14.5 years of life, respectively [24].

The harmful effects of tobacco consumption principally derive from three mechanisms. Firstly, thousands of different compounds are generated in tobacco smoke, many of which comprise chemical and radioactive carcinogens. There are over 45 known or suspected chemical carcinogens in cigarette smoke. These carcinogens can bind irreversibly to a cell's nuclear DNA, which may either kill the cell or cause a genetic mutation [25]. If the mutation inhibits programmed cell death, the cell can survive to become a cancer cell.

Secondly, significant cardiovascular effects result from tobacco use. Inhalation of tobacco smoke causes several immediate responses. Within one minute, the heart rate begins to rise, increasing by as much as 30% during the first 10 minutes of smoking. Carbon monoxide in tobacco smoke exerts a negative effect on the heart by reducing the blood's ability to carry oxygen. Both of these conditions can become permanent with prolonged use of cigarettes. Smoking also increases blood pressure, vasoconstriction, and weakens blood vessels. Incidence of impotence is approximately 85% higher in male smokers compared to non-smokers and is a key factor causing erectile dysfunction. These effects increase the risk of smokers experiencing endothelial dysfunction and developing various forms of arteriosclerosis. Smoking increases blood cholesterol levels, negatively impacts on the ratio of high-density lipoprotein to low-density lipoprotein, raises the levels of fibrinogen, and increases platelet production. Indeed, cigarette smoking affects many aspects of atherogenesis and the spectrum of disease from atherosclerosis to angina and ultimately to acute coronary syndrome (ACS) has been extensively studied and reviewed [26].

The third mechanism by which tobacco use exerts a harmful effect is via the highly addictive alkaloid nicotine, which acts as a stimulant and can cause physical and psychological dependency.

Nicotine

Nicotine is a potent parasympathomimetic alkaloid found in the nightshade (Solanaceae) family of plants. It acts as a nicotinic acetylcholine receptor agonist, enhancing acetylcholine neurotransmission in the basal forebrain. It is produced in the roots and accumulates in the leaves of the plants. Nicotine is particularly prevalent in tobacco plants (Nicotiana), where is constitutes approximately 0.6–3.0% of the dry weight of tobacco leaves. Nicotine is present in various edible plants, including tomatoes, potatoes, aubergines, and peppers, with a mean daily dietary nicotine intake of approximately 1.4 μg/day in European and North American populations. By comparison, an average cigarette delivers 1–3 mg of absorbed nicotine and the typical pack-per-day smoker absorbs 20–40 mg of nicotine each day [27].

Transdermal nicotine patches are available in several different doses, and deliver between 5–22 mg of nicotine over a 16- or 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers. Nicotine lozenges and nicotine chewing gum are available in both 2 mg and 4 mg strengths. None of these nicotine replacement products deliver nicotine in the same quantity or as quickly as tobacco cigarettes. There is currently much debate over how much nicotine is delivered via an «electronic cigarette» with estimates varying widely, in part due to the variable efficacy and consistency of nicotine delivery within and between products. In electronic cigarettes that vaporize nicotine effectively, the amount inhaled from 15 puffs is lower compared with smoking a conventional cigarette, but some experienced users may be able to achieve cigarette-like increases in blood nicotine concentration (>10 ng/mL in 5 min) [28].

Nicotine is considered harmful to health, with the principal negative health effects deriving from two characteristics. Firstly, nicotine acts as a stimulant in mammals and this stimulant effect is likely to be a major contributing factor to the dependence-forming properties of tobacco use. Although the amount of nicotine inhaled with tobacco smoke is quite small, as most of the substance is destroyed by the heat, it is still sufficient to cause physical and/or psychological dependence. Nicotine addiction is one of the hardest addictions to break, with some studies suggesting that nicotine is more addictive than cannabis, caffeine, ethanol, cocaine and heroin when considering both somatic and psychological dependence. There is also the formation of harmane, a monoamine oxidase inhibitor (MAOI), from the acetaldehyde in cigarette smoke, which seems to play an important role in nicotine addiction, probably by facilitating dopamine release in the nucleus accumbens in response to nicotine stimuli. Evidence has shown that smoking tobacco increases the release of dopamine in the mesolimbic dopamine system, specifically in the mesolimbic pathway, the same neuro-reward circuit activated by drugs of abuse such as heroin and cocaine. This suggests nicotine consumption has a pleasurable effect that triggers positive reinforcement. It is worth noting that nicotine, although frequently implicated in producing tobacco addiction, is not significantly addictive when administered alone. The addictive potential manifests with the production of the MAOI harmane, which causes sensitization of the locomotor response, a measure of addictive potential [29].

Secondly, nicotine is a potent activator of the sympathetic nervous system and stimulates the body to produce adrenaline, which raises blood pressure, heart and respiration rate, thereby causing the heart to work harder. This may implicate nicotine in acute episodes of some diseases, such as stroke, impotence, and heart disease.

Nicotine may have some health benefit. Studies have shown that nicotine derived from smoking and other tobacco use may lower the risk of developing Parkinson's disease. A recent study showed that eating foods that contain naturally-occurring nicotine may also reduce the risk of Parkinson's disease. However, the negative health effects of nicotine appear to outweigh the positive.

Combustion is the most efficient method of delivering nicotine to the brain, with cigarette smoking being the most prevalent delivery system. Ingesting a compound by smoking is one of the most rapid and efficient methods of introducing it into the bloodstream, second only to injection, which allows for the rapid feedback that supports the smokers' ability to titrate their dosage. After inhaling on a cigarette, nicotine is delivered rapidly to the pulmonary venous circulation, from which it moves quickly to the left ventricle of the heart and to the systemic arterial circulation, taking about 10–20 seconds for the substance to reach the brain. The amount of nicotine absorbed by the body from smoking depends on many factors, including the type of tobacco, whether the smoke is inhaled, and whether a filter is used.

With recognition of the dangers inherent in combustible tobacco products, new non-combustible alternatives are on the rise. These products claim to reduce the toxic exposures caused by combustion and include non-combustible cigarettes (i.e. «smokeless» electronic cigarettes) and oral tobacco (e.g., lozenges, strips, snus, orbs), some of which are dissolvable. Electronic cigarettes, or e-cigarettes, are by far the fastest growing product, with an estimated 1.3 million users in the UK and more than 20% of adult smokers in the U.S. having tried an e-cigarette. This product aims to imitate conventional cigarettes whilst delivering nicotine in a toxin-free vapour. An electronic cigarette, also known as a personal vaporiser, consists of a plastic cartridge (which serves as a mouthpiece and contains a nicotine liquid), a battery and a heating element. When a consumer inhales through the device the liquid is heated and the resulting vapour is inhaled and absorbed principally through the mouth. When the user exhales, a plume of what appears to be smoke is emitted but which is actually largely water vapour. The liquid commonly contains glycerol, propylene glycol, flavourings, and nicotine. Most laboratory analyses have shown this liquid to contain no carcinogens and to be less toxic than regular cigarettes. However, the benefits and risks of electronic cigarette use remain uncertain and health organizations, including the *World Health Organization*, have called for urgent clinical studies on their effects on human health.

Nicotine and heart rate

The effects of consuming nicotine on the cardiovascular system can be detected almost immediately after a person starts to smoke a cigarette. Within one minute after smoking begins, the smoker's heart rate starts to increase: it may increase by as much as 30% during the first 10 minutes of smoking [30]. Even in habitual smokers, there can be a rise in heart rate of up to 37+4 bpm [31]. Blood pressure also increases when a person smokes a cigarette.

These increases are temporary but, as most smokers smoke cigarettes several times a day, these effects occur often and may cause a chronic problem that ultimately undermines longer-term health. This proposition has been tested. In one study, 10 normotensive smokers were asked to smoke one cigarette every 15 minutes for 1 hour. Blood pressure and heart rate were monitored continuously during the smoking period and during the preceding non-smoking hour. Six other normotensive smokers were asked to smoke two cigarettes per hour throughout the whole day, with blood pressure and heart rate being monitored non-invasively in ambulatory conditions every 10 minutes for 8 hours. In the first condition (four cigarettes over 1 hour), the first cigarette caused an immediate and marked increase in blood pressure and heart rate, and the peak blood pressure and heart rate achieved were similar for the remaining three cigarettes. In each instance, the hemodynamic effects were prolonged, with blood pressure and heart rate remaining persistently higher than during the non-smoking hour. In the second condition (two cigarettes per hour for 8 hours), daytime blood pressure and heart rate were also persistently higher during smoking than during non-smoking. The authors concluded that heavy smoking is associated with a persistent rise in blood pressure and heart rate [32].

Reductions in heart rate and blood pressure have been detected 20 minutes after ceasing to smoke. However, most research indicates that clinically meaningful reductions are only achievable after a full cessation of smoking. For example, one study found once subjects with angina stop smoking there is a decrease in heart rate and an improvement in ST segment changes provoked by exercise [33].

Studies have demonstrated a rise in heart rate in consumers of tobacco, both smoked and smokeless (chewed and snuffed). One study (n = 135), after adjusting for potentially confounding variables, found daytime ambulatory heart rates were significantly (P<0.05) elevated in both smokeless tobacco users and smokers compared with nonusers (69 ± 14 and 74

± 13 bpm, respectively, versus 63 ± 12 bpm). The authors conclude that the higher heart rates (and blood pressures) noted during the daytime in smokers and smokeless tobacco users were most likely due to the effects of nicotine [34]. A similarly conducted study, using 24-hour ambulatory blood pressure measurement to examine the effects of smoking in normoalbuminuric insulin-dependent diabetes mellitus patients found that the 24 smokers had significantly higher 24-hour heart rate that the 24 nonsmokers were matched for sex, age, and diabetes duration (80 ± 7.2 compared to 72 ± 9.2 bpm, $P<0.001$) [35].

Heart rate has been shown to increase as a consequence of passive smoking in healthy young females (n = 30). Heart rate measurements at 15th and 30th minute of exposure were higher than at baseline and 5th minute of exposure (88 ± 3.2 and 90 ± 3.7 vs. 76 ± 3.9 and 78 ± 4.5 bpm, $P<0.05$). Heart rate decreased notably at 15th minute and returned to baseline values at 30th minute after exposure (80 ± 1.2 and 76 ± 3.2 vs. 88 ± 4.5 bpm, $P<0.05$) [36].

It should be noted that elevations in heart rate are detected, not only in high-nicotine containing products like tobacco cigarettes, but also in low-nicotine containing products such as nicotine replacement products. Regarding electronic cigarettes, there is currently little evidence looking at the impact of nicotine contained in these products and the data that does exist may be unreliable due to the variable nicotine content in products, as discussed above. The studies that have explored the effects of e-cigarette use on heart rate are conflicting. In one study, 32 participants inhaled one e-cigarette cartridge per day for 4 weeks, but no abnormal changes in blood pressure or heart rate were observed [37]. Another small study (n = 42) used echocardiography to compare the cardiac function of 20 young smokers (aged 25 to 45 years of age) before and after smoking one tobacco cigarette to the cardiac function of 22 young e-cigarette smokers before and after using an e-cigarette for seven minutes, who were of a similar age. Results showed that smoking a tobacco cigarette had important hemodynamic consequences, with significant increases in blood pressure and heart rate (+8% systolic BP, +6% diastolic BP, and a 10% rise in heart rate). In contrast, e-cigarettes produced only a slight elevation in diastolic blood pressure (+4%). The authors concluded that, although nicotine is present in e-cigarettes, it is absorbed at a lower rate compared to regular cigarette smoking [38].

However, in contrast to these results, a recent study has reported that, relative to baseline, plasma nicotine and heart rate increased significantly within 5 minutes of first inhalation from an e-cigarette, and remained elevated throughout the ad lib puffing period [39]. This finding is supported with a qualitative article in which some e-cigarette users reported changes in heart rate and palpitations [40].

Regarding other nicotine replacement products, these do not appear to deliver high levels of nicotine when used as instructed. For example, regarding nicotine patches, despite increased nicotine concentration with concomitant use, the evidence from two studies, (n = 10) [41] and (n = 12) [42], suggests there are no increases in the incidence of side effects or significant changes in physiological parameters such as blood pressure and heart rate.

Discussion

Cigarette smoking has a considerable influence on cardiovascular risk and is one of the most significant modifiable risk factors for acute myocardial infarction [43]. Evidence outlined in this review points towards elevated resting heart rate being an important variable in cardiovascular disease. For example, high heart rate, among other things, is a marker of increased sympathetic nervous system activity, which itself is linked to increased heart ischemia, and is associated with promoting atherosclerosis and susceptibility to arrhythmia. Evidence also indicates that nicotine is a significant cause of an acute and often sustained rise in heart rate that, for the nicotine addict, effectively becomes a chronic elevated heart rate. With heart rate holding such a prominent position in cardiovascular health, any factors, especially modifiable, which serve to raise heart rate above a normal, healthy and appropriate level should cause concern and prompt intervention.

Heart rate is a measure not just of poor outcomes, but of the management of patients. Ensuring heart rate is within a healthy range is likely to become an increasingly important message for primary and secondary care. It is important for clinicians to remember that one problem in assessing patients consuming nicotine is that the acute effects of nicotine may escape clinic blood pressure measurement. Ambulatory monitoring may therefore be a more accurate way of assessing 16- or 24-hour heart rate (and blood pressure) in this population.

The link between nicotine and elevated heart rate is especially important at the current time. Although developed counties have seen a slow reduction in smoking and tobacco use over recent years, the issue of smoking remains a problem in both developed and developing countries. The nicotine content of popular American-brand cigarettes has slowly increased over the years, and one study found that there was an average increase of 1.78% per year between the years of 1998 and 2005. This was found for all major market categories of cigarettes [44]. There are increasing calls to reduce the nicotine content in cigarettes to prevent children from becoming addicted smokers and giving people greater freedom to stop smoking if they decide to quit by reducing the addictiveness of cigarettes.

The debate over nicotine products as aids to smoking cession is complicated with the recent rise in electronic cigarettes and their potential to deliver high doses of nicotine, thereby perpetuating a nicotine addition, albeit using a less toxic delivery system. There is urgent need for research and possibly regulation of these products if they are found to deliver harmful levels of nicotine. Although the evidence currently suggests that up to half of the nicotine content may be exhaled in the vapour, there are also suggestions that nicotine replacement products such as e-cigarettes simply promote a slower absorption of nicotine.

In terms of the limitations of this review, the evidence contained herewith needs to be considered within the context of methodological shortcomings, such as the difficulties of comparing different nicotine delivery systems, and the paucity of data on newer nicotine products, such as electronic cigarettes.

Conclusion

Smoking cessation is fundamental to cardiovascular disease prevention, and it is associated with a significant reduction in risk of all-cause mortality in those with coronary heart disease. Inflammatory markers, which can indicate atherosclerotic disease, have been shown to return to baseline levels five years after quitting, suggesting that the inflammatory component of cardiovascular disease resulting from smoking is reversible with reduced tobacco exposure and smoking cessation [45]. With a greater understanding of the chronic impact of nicotine use on chronic resting heart rate, it is hoped that clinicians will take a long-term view and redouble their efforts to encourage and support abstinence from all forms of excess nicotine consumption.

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013

Journal of the Cardioprogress Foundation

REVIEW PAPERS

Phytosterols: another way to reduce LDL cholesterol levels

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Summary

Phytosterols are sterols found naturally in various oils from plants. Phytosterols compete with cholesterol for a place in the mixed micelles, needed for cholesterol absorption by the small intestine. As a result, cholesterol absorption, either from food or from bile salts is lowered by about 50%, leading to a lowering of about 10% of blood cholesterol level, despite an increase in hepatic cholesterol synthesis. This reduction is achieved when phytosterols are given both as monotherapy, and in addition to statin therapy. The average Western diet contains about 400–800 mg of phytosterols per day, while the dose needed for lowering the blood cholesterol level is about 2–3 grams per day. Therefore, for the purpose of reducing blood cholesterol, they should be given either as phytosterol-enriched food or as supplements. The reduction in the level of low-density lipoprotein (LDL) cholesterol achieved with phytosterols may reduce the risk of coronary disease by about 25%. For this reason the American Heart Association has recommended the consumption of phytosterols, as part of a balanced diet, for lowering blood cholesterol levels.

High levels of LDL cholesterol is a well known risk factor for atherosclerosis, which is the main cause of mortality in Western countries [1]. Statins are the drugs of choice for people who are at high risk of developing cardiovascular diseases, and who have LDL cholesterol levels higher than recommended [2]. Following recent studies, low LDL cholesterol target levels have been set for high-risk patients. Such target levels mandate the use of high doses of potent statins in many cases [2]. Some of these high-risk patients fail to reach LDL cholesterol target levels even with intensive statin therapy. Moreover, 10–20% of statin-treated patients develop side effects (mainly myopathy), which limit the ability to use intensive statin therapy [3]. Potential therapies in such cases include ezetimibe, bile acid sequestrants and niacin [2]. Another treatment option which gathered renewed interest in recent years is the use of phytosterols. Phytosterols are plant-derives sterols that inhibit the intestinal absorption of cholesterol. This review covers current knowledge on cholesterol absorption and the available data concerning phytosterols efficacy and safety.

Keywords

Phytosterols, sterols, stanols, cholesterol

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The mechanism of intestinal cholesterol absorption

The human body contains about 140 grams of cholesterol, and is able to produce its daily need of about 1200 mg [4]. A typical Western diet contains about 300–500 mg of cholesterol per day. Bile acids present another 800–1300 mg of cholesterol daily to the intestine. About half of the cholesterol reaching the intestine from these two sources is absorbed and transferred to the liver [5].

Cholesterol absorption starts with the formation in the intestinal lumen of mixed micelles, which contain cholesterol, bile salts, fatty acids, phospholipids and monoacylglycerols [4]. The micelles enable fatty molecules to cross the hydrophilic layer and reach the brush border, where they are absorbed by the enterocytes. Cholesterol molecules not entering these micelles will not be absorbed.

The second phase of cholesterol absorption involves the selective entrance of cholesterol molecules into the enterocytes, via a sterol transporter. This transporter was recently identified as the Nieman-Pick C1 Like 1 protein (NPC1L1) [6,7]. This protein, which contains a sterol-sensing domain, is expressed mainly in proximal jejunum cells, where most of the cholesterol absorption takes place. This protein is the target of ezetimibe, a drug that inhibits cholesterol absorption [7]. Other sterols, such as phytosterols, are also taken up by the enterocytes using NPC1L1.

Cholesterol absorbed by the enterocytes enters the endoplasmic reticulum, where it is esterified by the enzyme acyl-Coa: cholesterol acyltransferase (ACAT) [8]. The formed cholesterol-ester molecules are packed into chylomicrons and secreted to the lymphatics on their way to the liver. Unlike cholesterol, phytosterols are of no use to the body, and therefore are secreted back to the intestinal lumen. This process is carried out by a heterodimer of two adenosine triphosphate (ATP) binding cassette transporters, ABCG5 and ABCG8 [9]. For this reason, the plasma concentration of phytosterols is lower by several orders of magnitude than that of cholesterol [10].

Phytosterols and their use as cholesterol absorption inhibitors

Phytosterols are plant-specific phytochemicals that are essential components of cell membranes. Phytosterols and their saturated forms (saturation of the double bond at carbon-5), termed phytostanols, are structurally related to cholesterol, although they differ in the complexity of their side chain which is attached to the steroid ring. They are not synthesized by animals and humans and, therefore, always originate from the diet. There are two types of phytosterols: sterols, which have a double bond in the sterol ring; and stanols, which do not have that double bond.

Lipid-rich plant foods such as nuts, legumes and seeds contain a relatively high amount of phytosterols. Over 40 phytosterols have been identified. Of those identified, campesterol, stigmasterol and β-sitosterol account for more than 95% of total phytosterol dietary intake. The typical Western diet contains 400–800 mg of phytosterols per day, of which only a minute amount is absorbed [11]. Because of the low bioavailability of unesterified phytosterols they should be given as esters of fatty acids [12].

Phytosterols have been known to reduce plasma levels of cholesterol since 1953 [13]. The mechanism of cholesterol absorption inhibition by phytosterols involves competition for a place in the mixed micelles, required for intestinal cholesterol absorption, since phytosterols are more hydrophobic and have higher affinity for micelles than cholesterol. As a result, cholesterol absorption (both exogenous from food and endogenous from bile salts) is reduced by about 50%. Reduction of cholesterol absorption leads to reduction of plasma levels of cholesterol, despite a compensatory increase in cholesterol synthesis by the liver [14].

Supplementation with phytosterols in the form of functional foods (margarine, yogurt) or in tablet form reduces plasma LDL cholesterol levels by 10–15%. High-density lipoprotein (HDL) cholesterol and triglyceride levels are unaffected by phytosterols supplementation. The required phytosterols dose to produce a maximal effect on LDL cholesterol levels is 2–3 grams per day, and higher doses do not produce further reductions in LDL cholesterol levels [11,14]. Supplementation with phytosterols is effective when added both to a typical Western diet and to a low-fat diet [14]. For example, in a study of 194 subjects with moderate hypercholesterolemia (LDL cholesterol between 130 and 190 mg/dL), supplementation with 1.6 grams per day of phytosterols in the form of a phytosterols-enriched yogurt reduced LDL cholesterol levels by 9.5% compared to supplementation with a regular yogurt [19].

Addition of phytosterols to patients treated with statins enables a further reduction of LDL cholesterol levels by 7–11% [15–18], a reduction similar to that achieved by doubling the dose of the statin [20]. This further reduction enables more patients to reach their LDL cholesterol target levels. In a study of 84 subjects (both with and without coronary heart disease), supplementation with 1.6 grams per day of phytosterols in the form of a phytosterols-enriched yogurt reduced LDL cholesterol levels by 10% compared to supplementation with a regular yogurt, including in statin-treated patients. About 50% of the subjects treated with phytosterols achieved their LDL cholesterol target levels (less than 130 mg/dL for subjects without and less than 100 mg/dL for subjects with coronary heart disease) compared with only 20% of subjects treated with a regular yogurt [21].

The effect of phytosterols on reduction of cholesterol levels was found to be similar in many subgroups of patients at high risk of cardiovascular morbidity and mortality, such as diabetics [22] and postmenopausal women [27].

A dietary portfolio of cholesterol-lowering foods containing a margarine enriched in phytosterols (providing 1.0 g plant sterols per 1000 kcal) was found to significantly reduce the levels of apolipoprotein B (apo B) and the ratio of apo B to apo A-I, both considered risk factors for atherosclerosis [23].

Recent evidence suggests that inhibition of cholesterol absorption may not be the only mechanism through which phytosterols affect cholesterol levels and atherogenesis [24], since phytosterols do not need to be present in the intestinal lumen simultaneously with cholesterol to inhibit its absorption.

Liver X Receptors (LXRs) α and β are broadly expressed in the body and act as a global regulator of cholesterol homeostasis, mainly by preventing excess cholesterol accumulation in tissues. These LXRs are expressed in the intestine, which suggests that these transcription factors may play a role in intestinal cholesterol metabolism. The induction of LXR by ligand binding enhances the transcription of several members of the ABC gene family such as ABCA1 and ABCG5/ABCG8. Phytosterols have been shown to act as LXR ligands, suggesting that cholesterol metabolism within the enterocytes may change as a result of LXR agonist activity induced by these compounds. Transcriptional ABCA1 activation has been proposed as a mechanism to explain the reduction in intestinal cholesterol absorption induced by phytosterols. Mixed micelles enriched with sitostanol were found to be potent inducers of ABCA1 expression in a model of human intestinal cells. LXR activation may also reduce intestinal cholesterol absorption independently of ABCA1, probably by increasing the intestinal transcription of ABCG5 and ABCG8. Therefore, activation of these efflux transporters could also explain the phytosterol-mediated inhibition of intestinal cholesterol absorption. However, in other studies, transcriptional changes in intestinal ABCA1, ABCG5 and ABCG8 did not correlate with an intestinal cholesterol absorption decrease in phytosterol-treated mice and hamsters, so the question of the significance of this mechanism remains open.

Other studies have proposed that phytosterols may act through an effect on cholesterol esterification and lipoprotein assembly (ACAT), or cholesterol internalization (NPC1L1), but conclusive evidence for these proposed mechanisms is lacking.

Consumption of phytosterols may also reduce oxidative stress, which may exert another beneficial effect on the development of atherosclerosis. Subjects consuming a phytosterols-enriched yogurt had a grater reduction in the levels of the highly atherogenic oxidized LDL compared to control subjects [19]. Phytosterols have also been shown to reduce plasma levels of 8-isoprostane, a measure of oxidative stress [25].

Phytosterols may also have an anti-inflammatory effect. In one study, supplementation with a phytosterols-enriched margarine resulted in a 42% reduction in the level of C-reactive protein (CRP), a marker of inflammation considered by some to be a risk factor for atherosclerosis [26].

In animal models, phytosterols have an anti-atherogenic effect. In a model of transgenic LDL-receptor deficient mice, phytosterols reduced the formation and may even have regressed atherosclerotic plaques [27]. This effect was even noted in mice treated with atorvastatin.

The effect of phytosterols on the incidence of cardiovascular events in humans was not tested. However, other methods of cholesterol absorption inhibition were associated with a reduction in cardiovascular events. In the Program on the Surgical Control of the Hyperlipidemia (POSCH) trial, reduction of cholesterol absorption by a partial intestinal bypass was associated with a reduction in cardiovascular events in patients after a myocardial infarction [28]. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), reduction of cholesterol absorption with cholestyramine was associated with a reduction of cardiovascular events in patients without coronary heart disease [29].

Some safety concerns have been raised about supplementation with phytosterols, since sitosterolemia, a rare genetic disorder characterized by high plasma levels of phytosterols, is associated with a high risk of cardiovascular events. However, plasma phytosterols levels in sitosterolemia are several orders of magnitude higher than the levels seen with supplementation with phytosterols [30].

The absorption of beta-carotene is slightly reduced by phytosterols. The absorption of other lipid-soluble vitamins, such as alpha-carotene, lycopene, vitamin E, vitamin D and the level of vitamin K dependent clotting factors are unaffected by phytosterols supplementation [31].

Summary

A high level of plasma cholesterol is a significant risk factor for cardiovascular diseases. Reduction of LDL cholesterol with statins reduces morbidity and mortality. In patients who fail to achieve their LDL cholesterol target levels despite maximally tolerated statin therapy, and in patients at low risk for cardiovascular diseases, supplementation with phytosterols may help to reduce LDL cholesterol levels. The *AHA/ACC* secondary prevention guidelines for patients with coronary and other atherosclerotic vascular disease recommend the consumption of up to 2 grams per day of phytosterols, as part of a heart-healthy diet, to help reduce LDL cholesterol levels by 6–15% [32].

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

REVIEW PAPERS

The adverse cardiovascular effects of aromatase inhibitors and its management in patients with breast cancer

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Summary
The purpose of this systematic review is to summarize adverse cardiovascular effects of aromatase inhibitors (AIs) in postmenopausal patients diagnosed with breast cancer (BC) and outline a management plan for these patients. Aromatase inhibitors are indicated as a first-line adjuvant endocrine therapy in postmenopausal women with estrogen-positive BC. Although AIs have better efficacy and toxicity profiles compared to tamoxifen, adverse cardiac events are important considerations due to estrogen deprivation and the probability of worse lipid profile outcomes. A systematic PubMed literature search through April 2011 was conducted. Studies comparing adverse cardiovascular events from AIs with tamoxifen as primary or secondary outcomes and published as a full text manuscript in English were included. Many trials that prospectively analyzed the effects of AIs on the cardiovascular system were found. When compared with tamoxifen, AIs had worse outcomes in short-term follow-up, but had similar outcomes in long-term follow-up. Several trials suggested that regular assessment of serum lipids, cardiac parameters which might be effected by adjuvant therapy, and management of hypertension and weight control are important to minimize cardiovascular risks, especially in women aged >65 years, who constitute >50% of the BC population. In conclusion, we found no direct comparison between the AIs in adjuvant therapy, but the decision to use one specific AI should depend on its toxicity and efficacy profile. Reducing the severity and frequency of adverse cardiac events may improve quality of life for patients taking AIs and yield continuation of this well-documented and beneficial therapy.

Review criteria
Information on adverse cardiac events from AIs was collected via a search for primary trials comparing AIs with tamoxifen and review literature in PubMed *using the terms «AIs», «adverse cardiovascular events», «breast cancer» and «cardiac management of adverse cardiac events». This data was then gathered with other relevant articles such as those comparing AIs and placebos.*

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Message for Clinic

AIs are one of the best options for adjuvant treatment in patients with BC; however concerns about their cardiac effects should be taken into account in management strategies. Recently, published data on cardiac events implied that AIs can be selected as a first-line therapy or switched therapy based on the patient's tolerance. Cancer patients are vulnerable to many conditions; they can be protected from adverse events with better therapy regimens and regular assessment.

Keywords

Aromatase inhibitors, breast cancer, adverse cardiovascular effects

Introduction

BC is the most often diagnosed cancer, the second cause of cancer mortality following lung cancer, and a common health problem in the Western world comprising about one to third of all cancers in women [1]. BC incidence increased about 0.2% annually between 1997 and 2000; during the same time, incidence of mortality due to BC reduced 2.3% per year. Endocrine treatment remains the mainstay of adjuvant therapy for postmenopausal women with hormone-responsive BC. Women with early stage BC are now surviving longer by means of improved outcomes with chemo and hormone therapy; one disadvantage of this improvement is the risk of long-term adverse cardiovascular effects from BC therapy.

Cardiovascular disease is one of the most major health problems in many developed countries, with a prevalence of 42.7 million in 2005 and mortality of 459,000 in 2004 in the United States [2]. In addition, cardiovascular disease constitutes an important health concern in older, postmenopausal women independent of BC [2,3].

For a long time, tamoxifen was the standard adjuvant endocrine therapy for postmenopausal women with BC, resulting in a reduction of the odds of recurrence of BC by 40% and death by 26% after five years [4]. In women with estrogen-receptor (ER) — positive (or ER unknown) disease, five years of treatment with tamoxifen after definitive surgery reduces the annual recurrence rate by 41% and BC mortality by 34%, translating into an absolute reduction of 9.2% in patients dying from BC by 15 years [5]. Results from meta-analyses showed that tamoxifen had lipid lowering effects; a potential cardio-protective effect of the drug was observed in which the rate of death from serious cardiovascular events such as myocardial infarction (MI) was reduced during active treatment [5–8]. However, tamoxifen was associated with some potential and sometimes life-threatening side effects because of its partial estrogen agonist activity. These side effects include an increased incidence of endometrial cancer [5,9] and thromboembolic events [10] related to duration of drug exposure. *Cancer Research Network* results have demonstrated that the third generation AIs have been replacing tamoxifen as adjuvant endocrine therapy for postmenopausal women with early BC since 2000 [11].

Third generation AIs are highly selective for the aromatase enzyme and substantially well tolerated. Currently, three third-generation AIs are being used clinically in the U.S. All third-generation AIs reduce systemic estrogen levels by 98% [12]. A review of 25 studies reported that AIs showed a significant survival benefit in the treatment of metastatic BC compared to other endocrine therapies [13]. The AIs have proven between 15% and 25% more effective than tamoxifen in reducing the relative risk of recurrence [14–16]. Both anastrozole and letrozole improved disease-free survival (DFS), but not overall survival (OS), compared to tamoxifen for five years. A meta-analysis [17] of first line and sequential strategies endorsed the recommendation in guidelines that AIs should be included in adjuvant therapy for postmenopausal women with endocrine-responsive BC [18,19].

Women with BC live longer due to effective therapies; most may not suffer recurrence of BC despite the fact that they are all vulnerable to toxicities. Therefore, there are at higher risk of both cardiovascular disease [20] and the cardiovascular side effects of BC treatments [21]. Cardiovascular disease will remain as a cause of death in these patients. It has been reported that in the U.S. as high as 2.3 million women live with such risk [20].

The risk of cardiovascular disease increases after menopause and is the greatest cause of morbidity and mortality in postmenopausal women. Estrogen deprivation has been demonstrated to be an independent risk factor for coronary heart disease in symptomatic women [22]. The effects of estrogen in cardiovascular disease are still being investigated, but it has been concluded that estrogen contributes to the cardiovascular system in many ways, affecting endothelial integrity, inflammation, thrombosis [23], and lipids. It is still being investigated whether the increasing rate of cardiovascular events seen with AIs compared to tamoxifen results from direct AI cardiac toxicity, or is due to the cardio-protective effect of tamoxifen.

Considering the incidence of cardiovascular disease that is mostly unrecognized in women and the potential BC therapy-related adverse effects of cardiovascular disease, it is important to assess the cardiovascular risk factors in postmenopausal women who are receiving adjuvant treatment for BC. An updated analysis of the Breast International Group (BIG) 1–98 trial demonstrated higher rates of cardiac events in a letrozole treated arm than a tamoxifen treated arm, particularly for women between 65 and 74 years old [24]. Recent data suggest that women with early BC are more likely to die of heart disease than recurrent cancer [25].

The aim of this review is to summarize the adverse cardiovascular effects of AIs in postmenopausal patients diagnosed with BC and outline a management plan for these patients.

The effect of estrogen in cardiovascular disease

Estrogen protects against cardiovascular disease in premenopausal women compared to age-matched men, but these advantages in women disappear with increasing age and decreasing estrogen levels with menopause. The two classical estrogen receptors, ER-α, and ER-β, effect the cardiovascular system via intracellular interactions. Estrogen has been shown to promote endothelial progenitor cell mobilization [26], increase mesenchymal stem cell-mediated vascular endothelial growth factor (VEGF) release [27,28], and improve endothelial and myocardial function after ischemia. Lately, a new membrane-bound and G protein-coupled estrogen receptor 30 (GPR30) has been described. Ischemic reperfusion injury was reduced and cardiac function was preserved via activation of the GPR30 receptor in the heart. The decreasing effect of estrogen is related to the increase in methylation of the promoter region of the estrogen receptor with age in menopausal women. Estrogen receptors expression in the arterial wall diminishes sharply with menopause [29,30].

Clinical studies with tamoxifen and aromatase inhibitors

There are two approaches used for the treatment of hormone receptor positive BC through blocking of estrogen synthesis or its action. Several prospective studies compared the effects of various AIs (anastrozole, exemestane, and letrozole) with tamoxifen. These studies examined the effects of these approaches on behalf of their therapeutic effects in postmenopausal women with hormone receptor positive BC. The third generation AIs showed better efficacy than tamoxifen in regards to improvement in disease-free survival and possibly overall survival rate in women with BC [16,31–33].

Nonsteroidal aromatase inhibitors

Anastrozole

Anastrozole, a nonsteroidal AI, binds reversibly to the heme group of the aromatase enzyme. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared the efficacy and safety of one of the third generation AIs, anastrozole (1 mg), with tamoxifen (20 mg), both given orally every day for five years as first line adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive early BC. This trial compared anastrozole with tamoxifen in 9,366 women with newly diagnosed early stage BC, and 84% of whom hormone-receptor positive. This trial failed to point out statistically significant differences in cardiac events between anastrozole and tamoxifen therapies; also the trial's definition of cardiovascular events was limited to ischemic heart disease (IHD). The event rate was 4.1% and 3.4% in the anastrozole and tamoxifen groups, respectively (P = 0.1) [15]. ATAC was the first trial to reveal that an AI is more effective and has fewer serious adverse effects than tamoxifen in adjuvant treatment.

A 120 months follow up of the ATAC trial was recently published [34]. The highest relative reduction in time to recurrence, contralateral BC, and disease-free survival was observed in the anastrozole group compared to the tamoxifen group in the first two years of the active treatment and these differences were maintained all through the entire follow-up period, including after treatment completion of between treatment groups. An absolute reduction of recurrence for the anastrozole group was 2.7% at five years and 4.3% at 10 years follow-up compared to tamoxifen in the hormone receptor-positive BC patients [34]. Tamoxifen has shown a carryover benefit for recurrence in the first five years after treatment, but not after that [5]. The carryover effect for recurrence was more prolonged for anastrozole than for tamoxifen in the present study and remained statistically significant for the 10 year follow up period.

Generally, treatment-related serious adverse events were lower in the anastrozole group than in the tamoxifen group (OR 0.84, 95% CI 0.60-1.19; $P = 0.3$), but were similar after completion of treatment (OR 0.84, 95% CI 0.60-1.19; $P = 0.3$) [34]. Of note, the increased fracture rate with anastrozole during treatment did not continue after treatment, assuming that this short-term effect could be managed with dual energy x-ray absorptiometry scans and bisphosphonates when needed [15,35,36]. Since the study's definition of cardiovascular events was limited to IHD the 68 month follow-up did not provide safety data on all cardiovascular diseases. At the 68 month follow-up, the incidence of IHD was not significantly higher with anastrozole compared to tamoxifen (4.1% vs. 3.4%, $P = 0.10$) (Table 1). Angina pectoris was a little higher in the anastrozole treated group than in the tamoxifen treated group, but the difference was not statistically significant (2% vs. 1.5%, $P = 0.07$). The myocardial infarctions rate was similar (1%) in both treatment arms, both during treatment and after its completion; when they were only captured as serious events at 68 months, 34 (0.27) and 33 (0.27) on treatment, 26 (0.28) and 28 (0.30) off treatment until 100 months follow-up. The incidence of both vascular and thrombotic events reduced significantly with anastrozole versus tamoxifen overall (2.8% vs. 4.5%, $P = 0.0004$) [15] and the incidence of thromboembolic events at 100 months was similar to that at 68 months [20]. Cerebrovascular events were less common in patients receiving anastrozole during treatment (OR 0.59 [0.32–1.05], $P = 0.056$), but not afterwards (OR 1.10 [0.57–2.13], $P = 0.75$) for those events defined as serious [36]. Additionally, the number of cardiovascular deaths was similar between the anastrozole and tamoxifen (49 vs. 46 at 68 months follow-up, 2% vs. 2% at 100 months follow-up, 2.9% vs. 3.0% at 120 months follow-up). It can be assumed that the prevalence of cardiovascular death is less in the anastrozole treated group. This has been verified in several studies with AIs [17,37].

Also, trials in which tamoxifen was switched to anastrozole in women with BC have been conducted. In the Arimidex-Nolvadex (ARNO) —95 / Austrian Breast and Colorectal Cancer Study Group (ABCSG) — 8 trials (in which patients were switched to anastrozole after two-three years of tamoxifen), the incidence of MI was low in both the anastrozole and the tamoxifen groups (Table 1). The Italian Tamoxifen Arimidex (ITA) trial compared continued tamoxifen therapy to switching to anastrozole after two-three years. Overall, the serious adverse event rate was similar (40 vs. 37 $P = 0.7$); additionally there was no difference in cardiovascular event rates between the two arms (14 vs. 16 $P = 0.4$ at preliminary and 14 vs. 17 $P = 0.6$ at update).

Letrozole

Another nonsteroidal AI is letrozole, which binds reversibly to the heme group of the aromatase enzyme and has a longer half-life at 96 hours. The Breast International Group (BIG) 1–98 trial is the only study with a four-arm design comparing the five-year sequence of either tamoxifen followed by letrozole or the inverse (letrozole followed by tamoxifen) head to head over five years. The BIG 1–98 trial was designed to gather the potential effects of letrozole on cardiac risk. These included any cardiac adverse effects, IHD, cardiac failure, hypertension, peripheral atherosclerosis, thromboembolic events, and other cardiovascular adverse effects. Specific adverse events were graded according to the Common Toxicity Criteria of the *National Cancer Institute* (version 2) at each study visit during treatment [38]. All data were collected separately on adverse effects of any grade and especially for grade 3 to 5 only. The safety data at median 30.1 months follow-up showed that the incidence of cardiovascular events was similar and low in both the letrozole and tamoxifen treated arms [38], meanwhile, letrozole was related to significantly more peripheral atherosclerosis and other cardiovascular events of any grade. When all events were reassessed for grade 3 to 5 adverse effects, it was concluded that tamoxifen resulted in more grade 3 to 5 thromboembolic events and letrozole resulted in significantly more grade 3 to 5 cardiac events of any type, especially cardiac failure (2.4% vs. 1.4%, $P = 0.001$), whereas the events rate was relatively low in both arms [38].

The incidence of ischemic heart disease was higher with letrozole than tamoxifen but results did not reach statistical significance ([1.1%] vs. [0.7%], $P = 0.06$) [38]. The fifty-one months follow-up showed that despite letrozole being associated with higher cardiac events in each grade than tamoxifen, there was no statistically significant difference in cardiac events overall (5.5% vs. 5.0%), IHD (2.2% vs. 1.7%), and cardiac failure (1% vs. 0.6%) between the letrozole and tamoxifen monotherapy groups [39] (Table 2). Although the number of events was small in each arm, there was an increase in the incidence of grade 3 to 5 cardiac events with letrozole (Fisher exact test, $P < 0.001$) [39]. At a median follow-up of 71 months after randomization, the incidence of any type or grade cardiac events was similar between women who were treated with one of the regimens that included letrozole and women who were treated

TABLE 1 **Anastrozole: rever sibl, third-generati on nonsteroidal aromatase inhibitor**	**ATAC (Arimidex, Tamoxifen, alone or in Combination)**									**ITA (The Italian Tamoxifen Anastrozole Trial)**			**ABCSG8/ARNO 95 (The Austrian Breast and Colorectal Study Group / Arimidex - Nolvadex 95)**		
	Tamoxifen for 5 years vs Anastrozole for 5 years (Tamoxifen + Anastrozole arm was discontinued at 47 months)									**Tamoxifen for 5 years vs Tamoxifen for 2-3 years followed by Anastrozole**			**Tamoxifen for 5 years vs Tamoxifen for 2-3 years followed by Anastrozole**		
Design	First line adjuvant									Combined adjuvant			Combined adjuvant		
Median Follow-up	68 months			100 months			120 months(overall)			64 months			28 months		
	ANA	TAM	P value	ANA	TAM	P value	ANA	TAM	P value	ANA	TAM	P value	ANA	TAM	P value
Number of patients	3125	3116								223	225		1618	1606	
Median age	64.1 years(+5.7 years)			72 years			+13 months			63 years			62 years		
Disease free-survival	HR: 0.83(0.73-0.94)		P=0.005	HR: 0.85(0.76-0.94)		P=0.003	HR: 0.86(0.78-0.95)		P= 0.003	**HR: 0.42(A>T)		P=0.001	HR: 0.42(A>T)		P=.0001
Time to distant recurrence	HR: 0.84(0.70-1.00)		P=0.06	HR: 0.84(0.72-0.97)		P= 0.022	HR: 0.85(0.73-0.98)		P=0.02						
Time to recurrence	HR: 0.74(0.64-0.87)		P=0.0002	HR: 0.76(0.67-0.87)		P=0.0001	HR: 0.79(0.70-0.89)		P=0.0002	NA			NA		
Overall survival	HR: 0.97(0.85-1.12)		P= 0.7	HR: 0.97 (0.86-1.11)		P=0.7	HR: 0.95(0.84-1.06)		P=0.4	HR: 0.56(0.28-1.15)		P=0.1	HR: 0.7 (A>T)		P= 0.038
Ischemic cardiovascular events	127(4.1%)	104(3.4%)	P= 0.10	NA			NA			NA					
Myocardial infarction	37(1.0%)	34(1.0%)	P= 0.5	60(1.9%)	61(1.9%)		NA			NA			3(<1%)	2(<1%)	P= 1
Angina	71(2.0%)	51(1.5%)	P=0.07	NA			NA			NA					
Cerebrovascular events	62(2.0%)	88(3.0%)	P= 0.03	64	91	P= 0.03	NA			NA			2(<1%)	9(<1%)	P= 0.064
Thromboembolic Disease	87(2.8%)	140(4.5%)	P= .0004	NA			NA			NA			3(<1%)	12(<1%)	P= 0.034
All cardiac events	NA	NA		NA			NA			All cardiovascular diseaseA: 7.6%,T:6.2%		P= 0.6	NA		
Cardiovascular deaths	49(2%)	46(1%)		67(2%)	66(2%)		91(2.9%)	95(3.0%)							
Cerebrovascular deaths	14(<1%)	22(1%)	P= NS	25(0.8)	29(0.9)		33(1.1%)	36(1.2%)							

ATAC: Results from ATAC study were from HR+ group,
NA: Not available, HR: Hazard ratio,
** 36 Months follow-up

TABLE 2 **Letrozole: reversible, third-generation nonsteroidal aromatase inhibitor**	**BIG 1-98**												**MA.17**		
	Adjuvant Endocrine Therapy for Early Breast Cancer Using Letrozole of Tamoxifen (four-arm trial comparing 5 years of monotherapy with tamoxifen or with letrozole with sequences of 2 years of one of these agents followed by 3 years of the other)												**Letrozole vs placebo after 5 years tamoxifen treatment**		
Design	First line adjuvant												Extended adjuvant		
Median follow-up	25.8 months			30.1 months			51 months**			74 months**			30 months		
	LET	TAM	P value	LET	TAM	P value	LET	TAM	P value	LET	TAM	P value	LET	TAM	P value
Number of patients	4003	4007		3975	3988		2448	2447		2448	2447		2583	2587	
Median age	61 years			61 years			61 years			61 years			62 years		
Disease free survival	HR:0.81(0.70-0.93)		P=0.003	NA			HR: 0.88(0.71-0.95)		P=0.007	HR:0.83(0.74-0.94)		P=0.03	HR: 0.58(0.45-0.76)		P<0.01
TTR	HR:0.72(0.61-0.86)		P<0.001	NA			231(0.65)	291(0.92)	P=0.004	NA			NA		
TTDR	HR:0.73(0.60-0.88)		P=0.001	NA			HR: 0.81(0.67-0.98)		P=0.03	HR:0.80(0.67-0.94)		P=0.05	HR: 0.60(0.43-0.84)		P=0.002
Overall survival	HR:0.86(0.70-1.06)		P=0.16	NA			HR: 091(0.75-1.11)		P=0.35	HR: 0.82(0.70-0.95)		P=0.08	HR: 0.82(0.57-1.19)		P=0.3
Cardiac events	162(4.1)	153(3.8)	P=0.61	191(4.8)	188(4.7)	P=0.87	134(5.5)	122(5.0)	P=0.48	169(6.9)	152(6.2)	P=0.36	NA		
Grade 3-5	85(2.1)	44(1.1)	P<0.001	96(2.4)	57(1.4)	P=0.001	74(3.0)	45(1.8)	P<0.001	93(3.8)	51(2.1)		NA		
Ischemic heart disease	57(1.4)	46(1.2)	P=0.28	68(1.7)	60(1.5)	P=0.48	54(2.2)	41(1.7)	P=0.21	69(2.8)	49(2.0)	P=0.08	NA		
Myocardial infarction	NA			NA			NA			NA			9(0.3)	11(0.4)	NS
Angina	NA			NA			NA			NA			31(1.2)	23(0.9)	NS
Cardiac failure	31(0.8)	14(0.4)	P=0.01	40(1.0)	29(0.7)	P=0.19	24(1.0)	14(0.6)	P=0.14	30(1.2)	25(1.0)	P=0.59			
Other cardiovascular events	19(0.5)	8(0.2)	P=0.04	26(0.7)	11(0.3)	P=0.01	19(0.8)	6(0.2)	P=0.014	24(1.0)	13(0.5)	P=0.10	100(3.9)	95(3.7)	NS
CVA/TIA	39(1.0)	41(1.0)	P=0.91	47(1.2)	49(1.2)	P=0.92	34(1.4)	35(1.4)	P=0.90	45(1.8)	38(1.6)	P=0.51	17(0.7)	15(0.6)	NS
Thromboembolic	61(1.5)	140(3.5)	P<0.001	68(1.7)	154(3.9)	P<0.001	50(2.0)	94(3.8)	P<0.001	63(2.6)	104(4.3)	P<0.001	11(0.4)	6(0.2)	NS
Cardiac death	13(0.3)	6(0.2)		NA			12(0.5)	7(0.3)		NA			5*	5*	
Cerebrovascular death	7(0.2)	1(0.03)		NA			8(0.3)	3(0.1)		NA			2*	1*	

TTDR: Time to distant recurrence, TTR: Time to recurrence, NA: Not available, NS: Not significance, HR: Hazard ratio,
*Lymph node-negative patients,
** Results from monotherapy arms.

with tamoxifen monotherapy (6.1 to 7.0% and 5.7%, respectively; *P* = 0.45)[37]. The incidence of thromboembolic events was significantly lower with letrozole than tamoxifen before switching tamoxifen to letrozole or inverse (1.5% vs. 3.5%, *P*<0.001, 1.7% vs. 3.9%, *P*<0.001 at 25.8 months) [14] (Table 2). Furthermore, the reduction in thromboembolic event with letrozole remained significant after switching analysis of the monotherapy arms at 51 months and 74 months (2% vs. 3.8%, *P*<0.001 at 51 months, 2.6% vs. 4.3%, *P*<0.001 at 74 months follow-up) [39,40]. Hence, the reduction in letrozole monotherapy remained significant comparing one of the regimens that included tamoxifen at a median follow-up of 71 months (*P*<0.001) [37].

Letrozole has a similar incidence of cerebrovascular accidents / transient ischemic attacks (CVA / TIA) as tamoxifen before switching tamoxifen to letrozole or inverse (Table 2) [38]. Also, the incidence of CVA / TIA remained similar after 51 months and 74 months follow-up (1.8% 1.6%). Furthermore, there were similar rates of CVA / TIA patients who were assigned to one of the regimens that included tamoxifen and those who were assigned letrozole monotherapy [37].

The MA.17 trial was designed to evaluate the impact of letrozole on lipid parameters compared to placebo in postmenopausal women who had already taken five years adjuvant tamoxifen treatment for early stage BC [41]. The incidence of cardiovascular disease was similar between the letrozole group and the placebo group at 2.5 years follow-up [41]. MI was occurred in only in <1% of both groups.

Steroidal aromatase inhibitor

Exemestane

Exemestane is a third-generation steroidal AI which is orally active and binds irreversibly to the substrate-binding pocket of the aromatase enzyme. Exemestane is indicated as an adjuvant treatment for hormone-receptor positive early stage BC after two-three years of tamoxifen treatment in postmenopausal women. When exemestane is used as a first line adjuvant treatment in patients not previously exposed to AIs, there was an increased response rate (from 31% to 46%) and progression-free survival (from 5.8 to 9.9 months) compared to tamoxifen [42]. There are three trials evaluating the use of exemestane as an adjuvant treatment in postmenopausal women with early stage BC; IES (Intergroup Exemestane Study), TEAM (Tamoxifen Exemestane Adjuvant Multinational) and NSABP (National Surgical Adjuvant Breast and Bowel Project) B-33 [43].

The IES study randomized 4,724 postmenopausal patients with unilateral invasive, estrogen-receptor-positive (or unknown) BC who were disease free after two-three years of tamoxifen treatment to switch to exemestane (n = 2,352) or to continue tamoxifen (n = 2,372). At a median follow-up of 55.7 months, exemestane had a 3.3% absolute benefit by the end of the treatment. When the estrogen receptor negative patients were excluded, the hazard ratio (HR) emerged as 0.75 (0.65–0.87; *P* = 0.0001) and the absolute benefit as 3.5%; furthermore, there was a plausible difference in overall survival reaching statistical significance with an HR of 0.83 (0.69–1.00) [16]. An updated analysis was reported at the 2009 San Antonio Cancer Symposium [44] verifying the statistically significant improvement in overall survival with an HR of 0.86 (0.75 – 0.99, *P* = 0.04) translating into an absolute survival benefit of 2.4% after eight years of randomization.

The IES trial compared the toxicity profile of exemestane with tamoxifen in patients who had already received adjuvant tamoxifen for two-three years before randomization in women with early stage BC. Cardiac events were defined as ischemic and others. Results from the trial shows the overall rates of ischemic events were 9.9% in the exemestane group and 8.6% in the tamoxifen group, the rates of MI were 1.3% for exemestane and 0.8% for tamoxifen, and angina rates were 7.1% for exemestane and 6.5% for tamoxifen; even though overall rates were higher in exemestane group compared with tamoxifen group, none of these became statistically significant [45]. At 55.7 months follow-up, the incidence of cardiovascular events was not statistically significance different between the exemestane and tamoxifen groups either during treatment (16.5%, 15%, respectively) or post-treatment [16]. The incidence of ischemic cardiovascular disease was comparable between the two arms; 8% for the exemestane group and 6.9% for the tamoxifen group (*P* = 0.17) and there was no statistical significance in terms of MI (1.3% vs. 0.8%, respectively; *P* = 0.08). But, in the exemestane arm, patients who experienced an MI had higher histories of hypertension compared to tamoxifen (71.1% vs. 31.6%, respectively). These findings emphasize that blood pressure monitoring for patients who are receiving adjuvant exemestane is crucial [16]. The incidence of venous thromboembolic events was 1.2% in patients who switched to exemestane and 2.3% in patients who stayed on tamoxifen (*P* = 0.004) and similar results were observed in the overall study (*P* = 0.01) (Table 3). The incidence of cerebrovascular events occurred in similar proportion between exemestane and tamoxifen in the IES (2.5% vs. 2.4%, *P* = 0.89). Consequently, the number of cardiovascular deaths was very low in both treatment groups.

TABLE 3 Exemestane: irreversibl, third generation steroidal aromatase inhbitor	**IES (Intergroup Exemestane Study)**			**TEAM (The Tamoxifen Exemestane Adjuvant Multicenter)**		
	Tamoxifen vs Exemestane after 2-3 years Tamoxifen(total of 5 years)			**Exemestane vs Exemestane after 2-3 years Tamoxifen(total of 5 years)**		
Design	Combined adjuvant			First line adjuvant		
Median follow-up	55.7 months			5.1 years		
	TAM--EXE	TAM	P Value	TAM--EXE	EXE	P Value
Number of patients	2352	2372		4868	4898	
Median age	<60: 32.4%, 60–69: 42.7%	<60: 32.0%, 60–69: 42.8%		64 years		
Disease free survival	HR: 0.75(0.64-0.88)		P=0.0003	HR: 0.97(0.88-1.08)		P= 0.60
TTDR	HR:0.83(0.70-0.98)		P=0.03	HR: 0.93(0.81-1.07)		P=0.30
Overall survival	HR:0.83(0.69-0.99)		P=0.04	HR: 1.00(0.89-1.14)		P>0.99
All cardiac events	483(20.8)	441(18.9)	P=0.09	NA		
Cardiac events	NA	NA		NA		
Ischemic heart disease	229(9.9)	200(8.6)	P=0.12	NA		
MI or ischemia	31(1.3)	19(0.8)	P=0.08	64(1%)	82(2%)	P=0.171
Angina	7.1%	6.5%	P=0.44	NA		
Cardiac failure	1.8%	1.8%	P=0.94	26(<1%)	50(1%)	
Other cardiovascular events	261(11.3)	262(11.2)	P= 0.96	73(2%)	77(2%)	P=0.843
CVA/TIA	2.5%	2.4%	P=0.89	60(1%)	87(2%)	P=0.035
Thromboembolic	45(1.9)	572(3.1)	P=0.01			
Venous thrombosis				99(2%)	47(<1%)	P=0.0001
Cardiac death	14	13		28(<1%)	43(<1%)	P=0.11
Cerebral related				14(<1%)	19(<1%)	
Vascular related	17	11		3(<1%))	4(<1%)	

IES: HR+ group, TEAM: Phase 3, HR+ group. MI: myocardial infarction, NA: Not available, HR: Hazard ratio, TTDR: Time to distant recurrence.

The TEAM phase 3 trial was primarily designed to evaluate the efficacy and safety of five years of adjuvant exemestane against five years of tamoxifen in postmenopausal women with early stage BC. Albeit during that period results were in favor of the exemestane group, a recent update analyzing five years of disease free survival showed similar rates between the groups (85.7% vs. 85.4%) randomized to upfront exemestane or sequential treatment with tamoxifen followed by exemestane, with no differences in time to recurrence or overall survival [46]. The incidence of hypertension was higher in the exemestane arm than in the sequential arm, but not significantly important (4% vs. 3%, respectively; P = 0.38). The frequency of arrhythmia was 4% vs. 3% for the exemestane arm vs. the sequential arm, respectively (P=0.038); the frequency of myocardial ischemia or infarction was 2% vs. 1%, respectively (P = 0.171); and the frequency of cardiac failure was 1% vs. <1%, respectively (P = 0.009). Although the overall incidence of cardiovascular events was higher in the exemestane group than in the sequential arm, none of these reached statistical significance. The benefit of AI on tamoxifen in terms of reducing vascular thrombotic events was evident in women with previous exposure to tamoxifen. In the TEAM study, vascular thrombotic events occurred in 2% of patients who switched to exemestane, compared to <1% of patients exposed only to exemestane (P = 0.0001).

Cardiovascular deaths were numerically higher with exemestane than with sequential treatment; however, this difference was not statistically significant (<1%). Depending on the differences between exemestane monotherapy and sequential treatment in terms of adverse events, the safety of these treatment strategies might play an important role in treatment decisions.

It is important to consider the impact of patient age on cardiovascular health, as demonstrated by the prevalence of comorbid illness among patients increased with age in newly diagnosed BC, the most common comorbid illness being cardiovascular disease. History of hypertension was a significant predictor of IHD, CVA / TIA, and thromboembolism. Hypercholesterolemia was associated with any adverse cardiac events, especially IHD.

Discussion

Current treatments for BC, which is the most common malignancy among women, involve the adjuvant use of endocrine therapy for hormone receptor positive BC after surgery [47,48]. AIs have been shown to be more effective and safer than tamoxifen for adjuvant endocrine strategy for either early or advanced stage hormone receptor positive BC in postmenopausal women [13,49–54]. As an endocrine therapy, increasing use of AIs either sequentially or instead of tamoxifen seems to provide benefit in lowering the incidence of common serious events, such as thromboembolism and stroke, which are increased with tamoxifen treatment. The molecular differences between third-generation AIs might effects not only selectivity for aromatase binding but also adverse cardiovascular events via upon cardiovascular receptors or small alterations in serum lipid levels. However, the weight of evidence from large clinical trials shows no major differences with respect to overall cardiovascular safety between AIs [21,55]. Anastrozole is mostly specific to the aromatase enzyme and has fewer interactions with other enzymes. Hence, anastrozole is emerging as one plausible standard adjuvant treatment for hormone sensitive early BC [56]. A recently published 10 year analysis of the ATAC trial confirmed the previously reported efficacy and tolerability benefits of anastrozole as an initial adjuvant therapy for hormone sensitive BC. Treatment-related serious adverse events were fewer in the anastrozole arm than the tamoxifen arm (P<0.0001); however, rates were similar in the post treatment period (P = 0.3) [34]. Although deaths without recurrence were higher with anastrozole (10.8% vs. 9.8%; P = NS), cardiovascular deaths were less common with anastrozole than tamoxifen (2.9% vs. 3.0%). Also, it can be assumed that the incidence of cardiovascular deaths is decreasing with anastrozole in the off-treatment period comparing to tamoxifen (Table 1). Even though median age was 72 years and having cardioprotective effect of tamoxifen, decreasing with anastrozole can be thought remarkable. Regard to reduction in distant recurrence, it assumed that decreasing with anastrozole on behalf of cardiovascular mortality might become significantly lower than tamoxifen in the future. At the 100 month follow-up, fewer cerebrovascular accidents were reported in patients receiving anastrozole (P = 0.056), but not in the off-treatment period (P = 0.75) [36]. After publishing 74 months of BIG 1–98 follow-up data, the incidence of cardiac and thromboembolic events were proportionately consistent during follow-up. Incidence of IHD was higher in the letrozole arm than in the tamoxifen arm, despite overall similar cardiac events (Table 2). An increase in the incidence of grade 3 to 5 cardiac events with letrozole carried on with 74 months follow-up; even though the number of events was small in each arm (3.8% vs. 2.1%, respectively). In the BIG 1–98 trial, the incidence of heart failure was similar at 74 months median follow-up between monotherapy groups of letrozole and tamoxifen (1.2% vs. 1.0%), even though it was statistically different at 25.8 months follow-up (0.8% vs. 0.4%, P = 0.01). It can be assumed that incidence of heart failure was lower after cessation of treatment with letrozole than active treatment period.

In the IES, at 55.7 months follow-up, the frequency myocardial infarction was very low in both treatment groups, despite the fact that the patients consisted of a population at risk for adverse cardiac events because of their age [16]. Mostly, patients who experienced MI in the exemestane group had a history of hypertension (71.1%) compared to the tamoxifen group (31.6%). The importance of monitoring blood pressure should be stressed [16]. Disregarding the other cardiovascular risk factors, advanced age and uncontrolled blood pressure may be related to these cardiac events. In the TEAM trial, at a median 5.1 years follow-up, no significant differences were reported between the exemestane and sequential groups in terms of disease free survival (P = 0.60) and overall survival (P>0.99) [4]. Data on disease free survival was consistent with that from the BIG 1–98 trial, in which tamoxifen followed by letrozole or the reverse sequence versus letrozole alone were not associated with statistically significant differences in efficacy after a median 71 month follow-up [37]. Cardiac-related deaths were not significantly different, even though they were higher with exemestane than the sequential group (P = 0.11). The incidence of cardiac failure was significantly higher in the exemestane monotherapy group than in the sequential group (P = 0.009). This result did not emerge previously in AI monotherapy trials. However, it is plausible to see the result from next follow-up because about 20% of patients were still on trial treatment. Consequently, treatment compliance appears suboptimum, particularly in the sequence group (47% of patients in the sequence and 19% of patients in the exemestane group discontinued before five years for reasons other than disease free survival).

The lipid-lowering effect of tamoxifen may clarify the reason for increasing lipid levels with AIs versus tamoxifen [57]. Whether AIs had long-term detrimental effect on lipids is not known, despite the findings that significantly more patients had hypercholesterolemia in the aromatase group than in the tamoxifen group in the ATAC and BIG 1–98 trials [14,15]. Although it has been thought that a steroidal AI (exemestane) may have beneficial effects on lipid metabolism [58], all third-generation AIs have similar effects on lipids [59]. Also, cardiovascular events were similar between the letrozole and placebo groups after five years of tamoxifen treatment in the MA.17 trial. All studies comparing safety of AIs against tamoxifen have shown an overall decreased risk of thromboembolic events in patients taking AIs versus those taking tamoxifen [5]; however, postmenopausal women who are taking endocrine therapy for BC live longer with their disease, and remain at risk for such adverse events. Since receiving AIs carry risk for cardiovascular events; these patients should be evaluated more carefully than age-matched individuals to minimize cardiovascular events during therapy.

Management

Recent advancements in curative-intent therapies have led to significant improvements in BC survival, but at the direct expense of increased risk of cardiovascular event or injury. It is important to recognize cardiac toxicity and to attempt to mitigate its onset; not only by selecting appropriate patients for adjuvant therapy, but also selecting appropriate therapy based on patient risk factors and risk of recurrence. Increasing awareness and educating patients about cardiac toxicity is crucial. Overall, women with BC had a notably worse cardiovascular risk profile in comparison to age-matched controls [60,61]. Adjuvant therapies are selected on the basis of a complex schema, including patient factors (age, comorbid illness, and patient preference) and tumor factors (grade, size, lymph node involvement, estrogen receptor [ER] and human epidermal growth factor receptor 2 [HER2]) [62].

Women diagnosed with BC are already at risk for cardiovascular disease, and practically all adjuvant therapies are associated with unique and varying degrees of cardiovascular injury. When selected for a treatment regimen, they will be subjected to a series of sequential cardiovascular injury risks coupled with lifestyle perturbations that leave patients with obvious or sub-clinical cardiovascular disease. Unfortunately, each of the chemotherapeutic agents used in BC treatment has identically unique acute and long-term cardiac complications. IHD (MI, angina pectoris), cardiac failure, hypertension, peripheral atherosclerosis, and thromboembolic events are the major complaints of these agents. The mechanism of chemotherapy-associated cardiac dysfunction or injury remains to be elucidated.

Measurement of left ventricular ejection fraction (LVEF) by echocardiography is a frequently used effective approach to monitor cardiac function and its impairment by chemotherapy. LVEF is one of most important predictors of prognosis while patients with significantly reduced ejection fraction usually have poorer prognosis. However, current imaging techniques (echocardiography, coronary angiography etc.) have limited ability to detect early cardiac damage [63]. It has been proven that the use of sensitive monitoring modalities (magnetic resonance imaging, exercise or dobutamine stress testing, etc.) and biochemical markers (troponin I, brain natriuretic peptide) permit more accurate detection and quantification of subclinical cardiac damage. It has been reported that increase in troponin I level was a significant predictor of left ventricular dysfunction after chemotherapy among cancer patients [64].

Decreases in physical activity with diagnosis of BC may trigger increases in body weight and body fat which may lead to a worse cancer prognosis [65,66]. It was reported that a greater decrease in physical activity was observed among obese BC patients than normal weight and overweight patients ($P<0.05$) suggesting a potential weight gain among already obese women [65,66]. Furthermore, obesity is significantly associated with increased recurrence risk in BC patients without any connection to age or menopausal status [67,68]. Results from one weight gain study reported that 84% of 535 BC patients gained weight (mean 1.6 kg) in the first year after diagnosis [69], and the Women's Healthy Eating and Living (WHEL) study reported that 60% of 1,116 women gained weight (mean 2.7 kg) from one year before diagnosis to up to four years after diagnosis [70]. The effects of weight gain on BC are unclear. Although some studies have associated weight gain with an earlier disease recurrence [71–73], others have failed to show similar results [69,74–77]. One study in which 646 patients were followed for a median of 6.6 years found that premenopausal women who gained more than 5.9 kg were 1.5 times more likely to relapse and 1.6 times more likely to die from BC than those were gaining less weight [72]. While it remains to be elucidated whether post-diagnosis weight gain influences risk for progressive disease, it is known that weight gain unfavorably affects risk for cardiovascular disease, hypertension, and diabetes [78–80].

Several strategies have been advised to prevent or to reduce cardiac toxicity. One of them is angiotensin converting enzyme inhibition (ACEI), which has shown a significant reduction in left ventricular dysfunction in patients with increased troponin I soon after chemotherapy [81]. The management of risk factors in patients with BC is crucial. Recommendations for the treatment of these risk factors include either pharmacotherapy or lifestyle modification. Mostly, beta-blockers and/or ACEI are suggested as the initial therapies for hypertension, with the addition of other agents (thiazides, etc.). In case of hypercholesterolemia, statins are recommended to reduce low-density lipoprotein cholesterol under 100 mg/dL. Furthermore, statins have been associated with reduced incidence of thromboembolism in patients with cancer [82]. Also, management of diabetes mellitus is related to cardiovascular disease, considering utility of using biguanides or sulfonylurea for women with type II diabetes to achieve a 7% glycosylated hemoglobin (HbA1c) [83]. Exercise training may be favorable with regard to its demonstrated effects on cardiovascular reserve, individual risk factors, and overall reductions in cardiovascular mortality [84,85]. A meta-analysis reported that exercise training resulted in a significant increase in exercise capacity among women with early BC while epidemiologic data recommended that greater physical activity after therapy was related to a reduction in all causes of mortality, including BC-specific causes [86].

Of note, data on adverse cardiovascular effects of AIs must be interpreted with caution in conjunction with baseline cardiovascular disease, LVEF, and cardiac risk factors. All the safety analyses have been conducted by comparing tamoxifen, whereas the mechanisms of cardiovascular events have not been clearly elucidated. It is difficult to know how to apply the results of these safety analyses to patients with an elevated risk of cardiovascular disease without analyzing baseline cardiovascular risk factors. Because of this weak evidence regarding to cardiovascular toxicity and short-term follow-up, there is no consensus about management of cardiovascular toxicity and its consequences.

Further research is required to anticipate the relative portion of cardiovascular morbidity and mortality attributable to either lifestyle modification or an adjuvant therapy among women with BC.

Conclusion

Cardiotoxicity is one of the most serious complications of endocrine therapy and/or cancer chemoprevention. AIs produce some cardiovascular adverse events, including IHD, heart failure, etc.; however, their toxicity mechanisms on the heart are not well-known. While women with BC live longer due to these effective therapies, most of them may not suffer recurrence of BC despite the fact that they are all vulnerable to toxicities. Patients at higher risk are mre susceptible to these detrimental effects. Since, cardiac morbidity and mortality can be reduced by detecting patients who are at higher risk, several different strategies have been advised in an attempt to prevent or to reduce cardiac toxicity. Regular assessment of serum lipids and management of hypertension and weight control are important to minimize cardiovascular risks, especially in women over 65 years old, who constitute more than 50% of BC population [87]. Also, switching to other therapies and regular assessment of patients on AI therapy may reduce and prevent adverse cardiovascular event. Even considering adverse cardiac events of AIs compared to tamoxifen, further evaluation is needed for long term results and assessment of novel adverse events which may be attributable to AIs.

Reducing the severity and frequency of adverse cardiac events may improve quality of life for patients taking AIs and yield continuation of this well-documented and beneficial therapy.

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

ORIGINAL PAPERS

Prevalence of cardiovascular risk factors in a random sample of Russian men and women

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Summary

The aim of the study was to assess the prevalence of cardiovascular risk factors and total cardiovascular risk profiles in a random sample of the adult population of Cheboksary (Russia).
Random sample of 749 men and 1,051 women (n=1,800), aged 30 to 69 years from of the city of Cheboksary (Volga Federal District, Russia). The study was completed by 1,570 people (87.2%). All respondents completed a standardized questionnaire and had a number of examinations, including anthropometric measurement and measurement ofblood pressure (BP), blood lipids, fasting glucose and glucose after a two-hour glucose load.
A high prevalence of traditional risk factors was detected in this random sample of a working age population. Nutritional disturbances, with different degree of manifestation, were revealed in 76.1% of participants, hypercholesterolemia in 62%, sedentary lifestyle in 52.6%, hypertension in 39.2%, and low levels of high-density lipoprotein (HDL) cholesterol in 25%. Tobacco addiction and excess alcohol consumption, leading to physical disorders, was detected in 43% and 27.4% men, respectively. Most common metabolic factors were hypertriglyceridemia (27%) and 42 abdominal obesity (22.1%). One in four participants scored positively for a high level of psychological stress. Low or medium total cardiovascular risk was observed in one in 25% of participants, with high total risk detected in 19% of cases. Risk assessment was performed using the Systematic COronary Risk Evaluation (SCORE) scale. A significant correlation was identified between total cardiovascular risk and metabolic risk factors, and a lack of correlation was detected between tachycardia and chronic anxiety.

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An urban population in Russia is characterized by a high prevalence of traditional risk factors and metabolic risk factors,most of which have a linear association with age but with differences between sexes.

Keywords
Epidemiology, cardiovascular disease, risk factors

Introduction

Cardiovascular disease (CVD) and associated complications, such as myocardial infarction and cerebrovascular accidents (stroke), are the leading cause of high morbidity and mortality among adults in the Russian Federation [1,2]. According to *World Health Organization* (WHO) statistics, the Russian Federation has the highest cardiovascular mortality among European countries [3,6]. One of the main reasons for high CVD prevalence in Russia is poor detection and correction of risk factors [1,4].

Epidemiological studies investigating the prevalence of CVD risk factors were conducted at different times in the USSR and in the Russian Federation. They revealed that hypertension, smoking, alcohol consumption and anxiety are the main risk factors for CVD among adults [5,6,7]. However, over recent years, metabolic risk factors have also become a popular theme for discussion. It should be emphasized that the possibility of developing CVD and associated complications increases two- or threefold, when metabolic risk factors are combined with traditional risk factors [8]. Success in primary prevention of CVD depends on the successful management of risk factors and requires large-scale population-based studies [9].

In recent years, few epidemiological studies have been conducted which explore risk factor prevalence, the combination of risk factors, and the contribution of individual risk factors to total cardiovascular risk, so it is difficult to develop evidence-based prevention strategies and estimate their efficacy [11].

The objective of this study on cardiovascular risk factors in a random sample of adults from the Russian city of Cheboksary is to help optimize approaches to the implementation of prevention programs conducted in the region.

Materials and methods

This study was performed as a part of planned project approved by the National Research Center for Preventive Medicine and the Ministry of Health and Social Development of Chuvashia.

Sampling

Cheboksary is the capital city of the Chuvash region in Western Russia, with a population of 453,721 (2010 Census). Having used a table of random numbers, thirty districts from the city of Cheboksary, each covered by family doctors, were selected from 224 districts, attached to 7 healthcare facilities (k = 224:30 = 7; every seventh district). Then one in every thirty respondents (aged 30–69 years) was selected from each included district with the help of a list of citizens registered in the healthcare facility (1,800:30 = 60; 60 respondents from one district). As a result, 1,800 citizens (men = 749, women = 1,051) were enrolled in the study. The study was completed by 88.7% of those enrolled.

At the first stage of the study, 1,718 participants completed the standardized questionnaire, which included information about family history, heredity, smoking habits, alcohol consumption, physical activity, nutrition habits, information to the Rose questionnaire, psychological and diabetic status, information on the course of hypertension and comorbidities, and drug usage. Later, 148 respondents (8.7%) for various reasons did not take part in the instrumental (BP, heart rate, waist circumference, ECG at rest) and biochemical examinations (total cholesterol, triglycerides, HDL cholesterol, oral glucose tolerance test).

A smoker was defined as a person, who smokes one or more cigarettes a day. Investigators distinguished several smoking statuses: never smoked, smoker in the past, smoker at the present time.

Assessment of alcohol consumption was made in accordance with the following criteria. For men: no alcohol consumption during the previous year; low or intermediate amount of alcohol (<168 g of ethanol per week); high alcohol consumption (≥168 g of ethanol per week). For women: no alcohol consumption during the previous year; low or intermediate amount of alcohol consumption (<84 g of ethanol per week); high alcohol consumption (≥ 84 g of ethanol per week).

Physical activity was considered as normal if it met following criteria: sitting less than 5 hours a day, walking at least 30 minutes a day, and/or doing physical exercises at least 2 hours per week. Physical activity was considered sedentary if it met following criteria: sitting 5 or more hours a day, walking less than 30 minutes a day, and/or doing physical exercises less than 2 hours per week or walking less than 30 minutes a day and doing physical exercises less than 2 hours per week.

Nutritional assessment was performed using the *WHO* questionnaire, which included questions on the frequency of meals, dietary salt, carbohydrates, animal fats and protein consumption. Excess salt consumption was defined as additional salting of a cooked meal and/or everyday consumption of salty foods. Excess animal fat intake was assessed when sausage products were consumed every day, and/or 4 teaspoon of dairy butter was consumed during a day, and/or at least 3 eggs were consumed per week. Excess consumption of carbohydrates was defined as everyday intake of starchy foods and confectioneries. Nutrition disorders were classified as mild (one type of disorder in carbohydrate, fat and mineral metabolism), moderate (two types of nutritional disorders) and severe (three specified types of nutritional disorders). Healthy nutrition was defined as the absence of all aforementioned nutrition disorders.

Stress level was investigated with a questionnaire based on the Reeder scale, that included 7 questions for evaluating psycho-emotional states in work and private lives. The level of chronic anxiety was classified as severe (1–2 points), moderate (2.01–3 points), and mild (3.01–4 points).

Physical and instrumental examination

Anthropometric examination: body weight was measured to the nearest 0.1 kg. Body mass index (BMI) was defined as the individual's body mass divided by the square of their height (BMI = weight/height^2; weight is measured in kg, and height in meters). According to the *WHO* guidelines waist circumference is measured at a level midway between the lowest rib and the iliac crest to the nearest 0.1 cm. Abdominal obesity was evaluated by using Adult Treatment Panel (ATP) III criteria (men's waist circumference ≥102 cm; women's waist circumference ≥88 cm) and the *International Diabetes Federation* (IDF) criteria (men's waist circumference ≥94 cm; women's waist circumference ≥80 cm).

BP was measured in a sitting position at rest two times with a 5-minute interval to the nearest 2 mmHg. The average value of these two measurements was used for the analysis. Hypertension was defined as BP ≥ 140/90 mm Hg and/or antihypertensive drug usage. Awareness — the patient is informed about the presence of hypertension. Treatment — the therapy is administered, but inefficient, i.e. BP is higher than targeted. Efficacy of the treatment — antihypertensive therapy is administered and BP reaches target levels.

All participants were measured using a 12-ead ECG at rest. ECG was interpreted according to a special scheme, which was developed for the study (adapted from Minnesota code, *National Research Center for Preventive Medicine*).

Laboratory assessment

Blood sampling was made from the cubital vein in the morning on an empty stomach after 12 hours of fasting.

The content of total cholesterol (mmol/L) and triglyceride levels in serum were determined using enzyme kits 'Human' and biochemical automatic analyzers, 'ALCYON 160' (serial number 14161416), using a method of endpoint photocalorimetry CHOD — PAP (Reagents Company HUMAN). The same method was used for the evaluation of HDL cholesterol levels after deposition from the serum of low-density lipoproteins (LDL) and very-low-density lipoproteins by sodium phosphotungstate and $MgCl_2$. LDL levels were calculated by the formula, suggested by Friedwald and co-authors: LDL cholesterol (mmol/L) = total cholesterol — (triglycerides (TG)/ 2.2 + HDL cholesterol). Hypercholesterolemia was defined at total cholesterol levels >5 mmol/L. Hypertriglyceridemia was defined, when TG levels were higher than 1.7 mmol/L, low levels of LDL cholesterol for men were defined below 1.1 mmol/L and for women below 1.3 mmol/L.

Oral glucose tolerance test was performed after night fasting of 8–12 hours. After providing blood samples, participants consumed 75 g of glucose, diluted in 250–300 ml of water, in less than 5 minutes. Two hours later a second blood sample was taken. Glucose concentration in venous blood was measured by photoelectric colorimeter KFK-3 using glucose oxidase test. According to the WHO criteria, fasting hyperglycemia was defined when glucose level ≥6.1 mmol/L; post-load hyperglycemia was defined when glucose level >7.8 mmol/L two hours after glucose load.

Statistical analysis

Data input was performed in regional research center with ACCESS MS OFFICE. Editing and statistical analysis were performed by the National Research Center for Preventive Medicine staff with the help of the Statistical Analysis System (SAS). Descriptive numerical characteristics of tested variables (mean, frequency ratio, standard deviation, standard error) were analyzed with the help of the following procedures: PROC SUMMARY, PROC UNIVARIATE, PROC FREQ. Authors used standard significance criteria: c-squared, Student-t (two-sample) and Fisher's ratio test.

Results and discussion

Sociodemographic characteristics of the sample are comparable with similar data in other population studies [6,7,14]. In a random sample, the number of women was 50% more than men (Table 1). The age of 65% of participants varied from 40–49 years to 50–59 years. Analysis of the ethnic composition showed that two-third of participants were Chuvash and 30% were Russian. Most respondents were married (76.4%). Divorced participants accounted for 9% of the total, unmarried participants 7.3% and widowers 7.3%. One in four respondents graduated from universities, whereas the majority of participants finished colleges (38.2%) or had secondary education (35%). 64.6% of respondents were employed.

Traditional risk factors include smoking, hypertension, tachycardia, alcohol abuse, a sedentary lifestyle, unhealthy diet, hypercholesterolemia, low levels of HDL cholesterol, family history of CVD and metabolic disorders. New risk factors include hypertriglyceridemia, fasting hyperglycemia, impaired glucose tolerance after two-hour glucose load, abdominal obesity and chronic stress [11].

According to the results, about 43% of men were smokers, about one third had never smoked, and 23% had given up smoking. During assessment of the smoking prevalence among men of various age groups it was found that every second man at the age of 30–59 years was a smoker, whereas there was a 2-fold decrease in smoking prevalence in the elder age group (60–69). Only 12% of young adults had given up smoking, whereas there was a 3-fold increase of ex-smokers in the elder age group. No more than 3% of women were regular smokers. These results differ from previous Russian studies. According to Rimma Potemkina's data, obtained during a phone survey and conducted in 3 Russian cities, it was found that 56% to 61.1% of men and 19.6% to 31.7% of women smoked. It is possible that these differences are due to social and ethnic characteristics of the sample [5,12].

There is no doubt that alcohol abuse dramatically increases all-cause mortality and mortality from ischemic heart disease (IHD), in particular [7,9]. This problem is challenging in Russia. In our sample almost every third man drinks alcohol above the recommended levels, causing somatic disorders, and this tendency is more pronounced at the age of 30–59 years. In the older age group alcohol abuse was slightly lower, at 18%. The prevalence of alcohol abuse among women is significantly lower and no more than 1.5%.

According to Iestra *et al.* the relative risk associated with a sedentary lifestyle is comparable with a significant risk factor such as smoking, hypertension or hypercholesterolemia [13]. Currently, questionnaires are a common method for detecting individuals with low physical activity [7]. In our study, physical activity was assessed by using a standard questionnaire

Table 1. **Socio-demographic characteristics of a random sample of adults**

Age			
30–39 years	40–49 years	50–59 years	60–69 years
15.4%	29.7%	35.7%	19.2%
Ethnicity			
Chuvash	Russian	Ukrainian	Others
67.7%	29.5%	0.8%	1.7%
Marital status			
unmarried	married	divorced	widower
7.3%	76.4%	9%	7.3%
Education			
higher	college	secondary	incomplete secondary
24.5%	38.2%	35%	2.4%
Employment			
unemployed		employed	
35.4%		64.6%	

which included information about sitting duration during working hours, duration of everyday walking and engaging in physical exercises. It was found that every second respondent had a sedentary lifestyle, and no statistically significant difference was found between men and women. Interestingly, the prevalence of a sedentary lifestyle among different age groups of men and women was the same.

We also assessed the degree of nutritional disorders in a random sample. According to the data collected, only one in four working age individuals had a balanced diet. About 40% of responders had mild nutritional imbalance, 27% had a moderate imbalance, while less than 8% had severe nutritional imbalance. The number of cases among women without nutritional disorders was statistically higher than among men, whereas moderate and severe nutritional disorders were more common among men. No difference in the prevalence of moderate and severe nutritional disorders among different age groups was found.

This was greatly facilitated by the implementation of the Federal Target Program of 2002–2008 years. Hypertension is one of the important and well studied risk factors in the Russian Federation [11,14]. Our study revealed that different degrees of hypertension were experienced by, on average, 39.2% of respondents. It was less common among men than among women. These results are comparable with national average values [14]. There is a linear relationship between age and BP levels. For example, hypertension at a young age was found in 11% of the respondents, with an increase in prevalence corresponding to the age of participants: 40–49 years — 26.1%, 50–59 years — 48.8%, and, 60–69 years — 64%.

One of this study's objectives was to analyze the validity of drug treatment used in people suffering from hypertension. Most patients (77.6%) were receiving antihypertensive therapy, and only 22.4% of hypertension patients were not receiving treatment. Seventy two percent of men with hypertension received antihypertensive therapy, while more than 80% of women received antihypertensive therapy (P<0.04). Single agent therapy was delivered to 48% of participants with hypertension, and among them target BP levels were obtained in every second case (55% of men and 49% of women). Combined antihypertensive therapy delivered to 29% of patients with hypertension, and among them target BP levels were obtained in every third patient (41% of men and 22.8% of women). In general, the awareness and effectiveness of hypertension treatment in the city of Cheboksary are higher than average in Russia [14].

Our study has revealed that hypercholesterolemia is a common CVD risk factor. Hypercholesterolemia in a random sample of working age participants was diagnosed in 62%. Elevated levels of total cholesterol were revealed in 58.9% of men and 64% of women. The majority of respondents (43.7%) had mild hypercholesterolemia, whereas moderate and severe hypercholesterolemia was detected in 14.8% and 2.7% of cases, respectively. These results are comparable with the data obtained in other regions. In an epidemiological study conducted in different regions of Russia by the *National Research Center for Preventive Medicine,* it was shown that total blood cholesterol levels of >5.2 mmol/L were detected in about 60% of adults and levels of >6.5 mmol/L detected in about 20% of adults [15,16].

At the same time we estimated the prevalence of the low levels of antiatherogenic particles — HDL cholesterol, which is an independent risk factor for IHD [17]. In this study, low levels of HDL cholesterol were detected in every fourth participant (n=399). Low HDL cholesterol levels among men were diagnosed in 18% of cases, with significantly higher levels among women, 30% of cases (P<0.001). In general, the prevalence of low HDL cholesterol levels among men and women increased with age. Comparing two age groups of men and women, it was detected that the prevalence of low HDL cholesterol levels in women was much higher than in men (25.5% vs. 13.2%, P<0.05; 29.9 vs. 16.2%, P<0.005). The prevalence of traditional risk factors among men and women is shown on figure 1.

According to the international INTERHEART study (30,000 participants from 52 countries) the development of myocardial infarction results from traditional as well as other risk factors, including stress, depression, obesity, diabetes and low consumption of fruits and vegetables [1].

In a random sample of individuals of working age, hypertriglyceridemia was diagnosed in 27% of cases (28.5% among men and 26% among women). The majority of patients (25.5%) had mild (1.7–2.3 mmol/L) and moderate (2.3-4.5 mmol/L) hypertriglyceridemia. There was an increase in hypertriglyceridemia prevalence due to aging (from 20.8% of people aged 30–39 years to 28.7% of 60–69 years). Hypertriglyceridemia is a major metabolic disorder, which has close association with unhealthy lifestyle and other risk factors. According to the *National Research Center for Preventive Medicine*, among people with hypertension and high cardiovascular risk, hypertriglyceridemia was detected in 40.2% of cases, 35% of which were in combination with hypercholesterolemia [10].

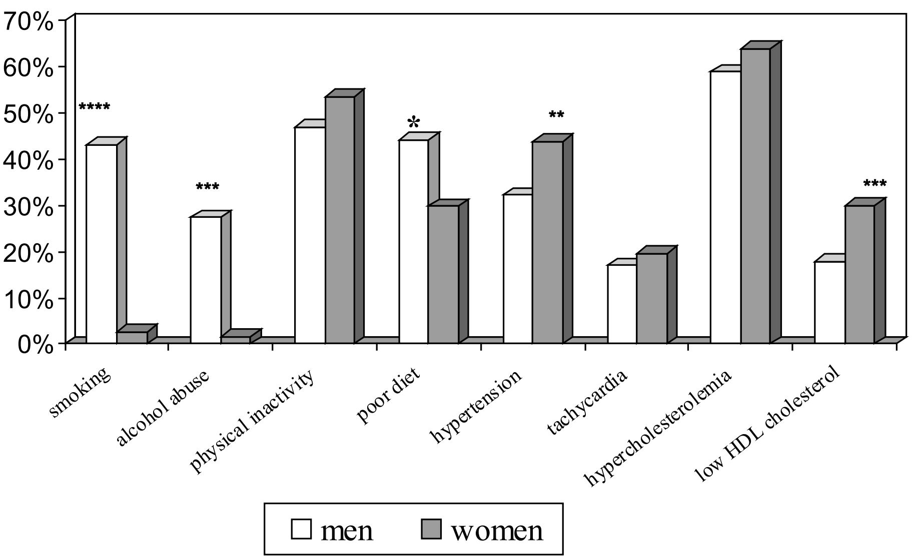

Figure 1. Prevalence of traditional risk factors in the adult population of the city of Cheboksary.
Note: *P<0.05, **P<0.002, ***P<0.001, ****P<0.0001 significant differences between men and women.

Over recent years obesity has been considered as a dominant metabolic risk factor for CVD. According to the epidemiological studies, conducted in the U.S., 61% of adults suffer from overweight and obesity [18]. Interestingly, over recent years there has been a 50% increase in the prevalence of obesity. Prevalence of obesity in Russia was found in 51% of cases, which is comparable to its prevalence in other European countries [19,20]. In our sample, 50% of men and 44.2% of women had normal body weight; 38.4% of men and 34.4% of women were overweight. The prevalence in obesity among women was three times higher than in men (21.4% and 7.4%, respectively). There was a significant increase in overweight / obesity prevalence due to aging (from 22.7% and 5.4% of respondents aged 30–39 years to 43.9% and 20.3% aged 60–69 years). We have also estimated the prevalence of abdominal obesity. Using ATP III criteria, we diagnosed abdominal obesity in 16.4% of men and 27.9% of women. According to Shalnova *et al*. in a Russian representative sample (5,760 men and 7,768 women), age-standardized values of abdominal obesity were 10.1% ± 0.5% in men and 38.9% ± 0.5% in women [21]. In this study, we also used *IDF* criteria for defining abdominal obesity, which was detected in about 48% of cases: 15% of men and more than 60% of women. The prevalence of abdominal obesity significantly increased with age (from 5% of participants aged 30–39 years to 29.6% aged 60–69 years). In general, abdominal obesity was observed more often than general obesity, because individuals with borderline values of BMI had already developed pronounced abdominal obesity.

Diabetes has been defined by *WHO* as a pandemic disease of the 21st Century. The medical and social importance of diabetes is determined by the development of early disability and high mortality due to both macro- and microvascular complications. Results of several reliable 12–20 year studies have showed that diabetes is a strong predictor and an independent risk factor for CVD [24,25]. Pre-diabetes, including fasting hyperglycemia and impaired glucose tolerance, is considered a metabolic stage, being a transitional stage between normal glucose homeostasis and diabetes [8]. On the other hand, pre-diabetes is considered an independent risk factor for CVD [25]. In November 2005, the joint committee of *WHO* and *IDF* adopted a resolution which stated that for a full assessment of glycemic status it is necessary to conduct an oral glucose tolerance test. In the present study, all respondents except for those with an established diagnosis of diabetes, completed a glucose tolerance test. According to the results, fasting hyperglycemia was detected in 3.9% of participants; whereas post-load hyperglycemia in 2.5% (P<0.04). Respondents aged 30–39 years had no impairments of carbohydrate metabolism. The prevalence of both fasting and post-load hyperglycemia was similar in patients aged 40–49 years (2.4–2.6%). In older age groups there was an increase in the prevalence of hyperglycemia, especially fasting hyperglycemia (two times more often than post-load hyperglycemia).

The first scientifically demonstrable data on the role of psychosocial factors in the development of CVD were presented in the mid-Twentieth Century. Experimental studies have shown that chronic stress causes, on the one hand, damage to the vascular endothelium, triggering processes of atherogenesis; and, on the other hand, activation of the sympathoadrenal system, which leads to the increased vasoconstriction and platelet activation [26]. According to

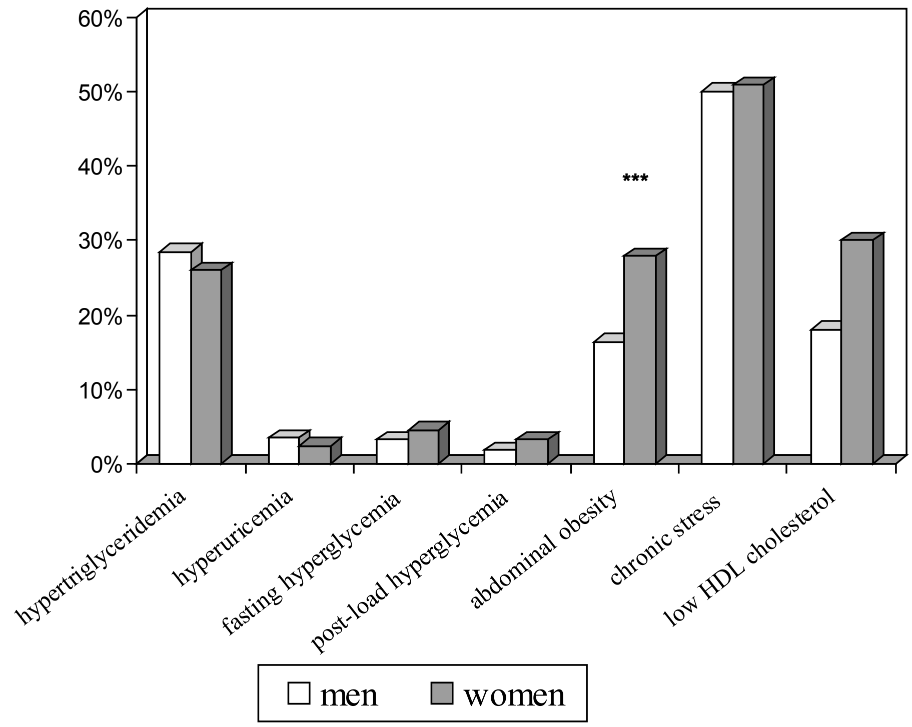

Figure 2. Prevalence of new risk factors in the adult population of the city of Cheboksary.
Note: ****P*<0.001 significant difference between men and women.

the current study data from Cheboksary, a minority of respondents were experiencing low stress (11.2%). The remaining respondents in this random sample had medium stress, whereas high stress was detected in 38.3% of respondents. The prevalence of different degrees of stress was similar among men and women. We also investigated the association between stress and age. At the age of 30–39 years, every forth respondent reported high or medium stress. In the middle age groups there was a two-fold increase in the number of people reporting medium stress, while the number reporting high stress was lower compared with the younger respondents. In the older age group, the number of respondents reporting high stress increased. There was no clear relationship between the frequency of high stress, different marital status, and level of education. A summary of prevalence of metabolic risk factors and chronic stress is shown in Figure 2.

Conclusion

This epidemiological study has demonstrated that the prevalence of traditional and metabolic risk factors is high in a single city of the Volga Federal District. The majority of risk factors have a linear relationship with age. The prevalence of some risk factors depends on gender. In the development of primary prevention strategies, not only traditional, but also new risk factors should be taken into account, due to the latter's high prevalence.

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

ORIGINAL PAPERS

Gene polymorphisms association with conventional risk factors and cardiovascular complications

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Summary
*The aim of this study was to evaluate the gene polymorphisms association with **conventional** risk factors and cardiovascular complications. The case control study was conducted in 2007-2011 and included 405 patients with coronary artery disease (CAD) and acute ischemic episodes admitted to the* Municipal Clinical Hospital "Sfânta Treime"*, Chisinău. Insertion/deletion (I/D) genotypes of angiotensin-converting enzyme (ACE) and A1166C polymorphism of angiotensin II type 1 receptor gene, Asp298Glu (A/G) genotypes of the endothelial nitric oxide synthase (eNOS) and PlA1/2 (A_1/A_2) genotypes of A_2/A_2 genotype **of glycoprotein (GP) IIb/IIIa** receptor gene (GPIIb/IIIa) receptor polymorphisms were identified by amplified polymerase chain reaction and restricted fragment length polymorphism. The authors concluded that the carrier of D/D genotype and D allele in ACE gene, being positively correlated with the risk C/C polymorphic variant of angiotensin II type 1 receptor gene, was associated with hypertension and cardiovascular death. A_2/A_2 genotype **of GP IIb/IIIa** receptor gene was associated with susceptibility to CAD and high frequency of myocardial infarction and dyslipidemia, particularly in smokers. The impact of eNOS polymorphic markers for CAD proved to be hypertension-mediated.*

Keywords
Gene polymorphisms, conventional risk factors, cardiovascular complications

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Background

Detection of the genetic factors that cause or predispose to CAD remains the topic of many scientific papers in this field. They have been investigated separately or in association within the European population, but the genetic complexity of this CAD was not foreseen and new approaches are needed [2,6].

Studies aimed at identifying the genes responsible for the heritability of CAD have uncovered several candidate genes with different roles in vascular biology that are believed to be involved in the pathogenesis of CAD. Of these, the more important are the renin-angiotensin system, endothelial dysfunction and homeostasis genes: ACE gene and angiotensin II type 1 receptor gene (AGT_1R), Asp298Glu (A/G) of eNOS and of platelets (PlA1/2) GPIIb/IIIa receptor polymorphisms. Polymorphisms within these system genes have been extensively studied in relation to CAD, however findings are conflicting [1,3,5,6,7]. To clarify these data, we studied the association of genes polymorphism with conventional risk factors and cardiovascular complications.

The aim of the current study was to assess the association of gene polymorphisms with conventional risk factors and cardiovascular complications in patients with CAD.

Material and methods

The case control study was conducted in 2007-2011 and included 405 patients with acute coronary episodes admitted to the *Municipal Clinical Hospital "Sfânta Treime"*, Chisinău. The control group consisted of 290 matched persons without CAD (data used for matching were age, sex, residence and professional activity). Sex-distribution in the study group was uniform, male/female ratio being 2:1, which was two times more males (P<0.001). Mean age was 57.93 ± 0.34 years, with insignificant variation in the control group (P>0.05).

The study was bicentric, case-control, approved by the *National Ethics Committee for Clinical Trials* and *Drug Development of Ministry of Health of the Republic of Moldova* (Nr.331, 03.06.2010). All subjects were native-born citizens and residents of the Republic of Moldova, had comparable socio-economic status, and were ethnically matched.

Patients were included in the study in the order of their hospital admission, after clinical and enzyme stabilization and informed consent obtained. This method of patient selection ensured randomness of the study group.

Criteria for inclusion in the study were the clinical diagnosis of acute Q wave and non-Q-wave myocardial infarction, unstable or exercise angina pectoris, consistent with recommendations of the *European Society of Cardiology* [4].

Exclusion criteria: hypercholesterolemia (total cholesterol ≥8mmol/L) and secondary hypertriglyceridemia; pacemaker implant with evidence of ventricular preexcitation; atrioventricular conduction blocks (2nd or 3rd degree sinoatrial or atrioventricular block); active liver disease; acute gastrointestinal diseases; severe kidney disease; and, associated diseases that influence life expectancy.

Standard questionnaires were used to collect data on past and current medical history, examination results, and also personal and demographic data, cardiovascular risk factors, family history of CAD, hemodinamic data; lipidogram, blood glucose level, cardiac enzymes, instrumental investigations- ECG and echocardiography.

Polymorphism of renin-angiotensin system: I/D of ACE gene and A1166C genotype (cytosine or adenine variants, A/C) of AGT_1R gene, Asp298Glu (A/G) of eNOS gene and PlA1/2 (A_1/A_2) genotypes of GPIIb/IIIa receptor gene were identified by amplified polymerase chain reaction and restricted fragment length polymorphism in *the Institute of Genetics and Plant Physiology, a branch of the Academy of Sciences of Moldova* [3,5].

Data were computer processed by variation, association and descriptive analysis methods. The relationships between the studied phenomena were determined by using simple linear regression, quantitatively expressed by the correlation coefficient "r". For estimating genetic frequencies we used POPULATION GENETIC ANALYSIS by Nei Masatoshi, Director of the *Institute of Molecular Evolutionary Genetics*; and, the Diploid Data Set at *the Genetics Center*, New York University, Langone. Frequency of studied genes loci was calculated with the help of the Hardy-Weinberg equilibrium.

Results

Stratification of coronary patients according to ACE I/D polymorphism confirmed the prevalence of homozygous individuals with risk deletion/deletion (D/D) genotype as compared with the controls (19.64% vs. 11.03%, respectively, x2=8.77, P<0.05), while genotype I/I was present in the control group (33.11% vs. 19. 64%, x2 13.31, P<0.01). There were no significant differences in the number of heterozygous I/D in both groups (60.72% vs. 55.86%, respectively, P>0.05). ACE I/D polymorphism genotyping and the estimation of the allele frequency revealed significant differences in the presence of risk D allele in patients with CAD compared with controls (78.65% vs. 61.24%, OR=1.29, x2=8.77, $P<0.05$). Compared with those in which this was not present (I/I), the analysis of the risk factors and clinical manifestations showed that ACE D/D homozygous or ACE I/D heterozygous genotypes in patients with CAD was associated with increased prevalence of hypertension (90.91% and 88.24% vs. 78.18 %), systolic blood pressure (155.32 ± 1.46 mm Hg and 140.5 ± 1.31 mm Hg vs. 125.42 ± 1.36 mm Hg), diastolic blood pressure (95.42 ± 1.35 mm Hg and 90.6 ± 1.28 mm Hg vs. 80.5 ± 1.84 mm Hg) and recurrent angina pectoris (40.00% vs. 34.11% vs. 23.64%, respectively, $P<0.01$).

No statistically significant differences were found between carriers of genotypes I/I, D/D or I/D in terms of degrees of hypertention. Considering the spectrum of risk factors and the clinical presentation according to ACE gene polymorphism recorded in this study, it appears that the presence of D allele and, in particular, homozygous D/D state are associated with blood pressure values exceeding the optimal level [r_{xy}=0.81, $P_{(D/D-I/I)}<0.01$]. The carrier of D allele and heterozygous I/D state was associated with recurrence of angina symptoms [r_{xy} =0.42, $P_{(I/D-I/I)}<0.05$] and a significantly higher risk of cardiovascular death [r_{xy}= 0.27, $P_{(I/D-I/I)}<0.05$].

Genotype frequencies of AGT_1R cytosine or adenine variants (A/C) in the group of patients with CAD were: A/A genotype was detected in 72 (25.74%) of the patients, C/C – in 47 (16.78%) and A/C – in 161 (59.28%). In the control group genotype frequencies were: 31(10.69%) C/C carriers, 162 (55.86%) A/C and 97 (33. 40%) A/A carriers. No significant differences in the presence of the studied genotypes were found ($P>0.05$).

Genotyping AGT_1R A/C polymorphism showed no conclusive differences between the presence of the risk allele C in CAD patients (72.83% vs. 70.71%, $P>0.05$), or non-risk allele A frequency (27.17% vs. 29.29%, $P>0.05$), compared with controls.

Comparative analysis of the characteristics of CAD patients grouped according to A/C polymorphism of AGT_1R gene, revealed the association of homozygous C/C state or heterozygous A/C state with increased prevalence of hypertension (95.49% and 89.44% vs. 68.33%, $P<0.05$).

Estimation of the association between clinical determinants and A/C polymorphism of AGTR gene showed that the presence of the risk C/C genotype in the coronary patients is associated with increased prevalence of hypertension [r_{xy}= 0.88, $P_{(C/C-A/A)}<0.01$] compared with homozygous A/A genotype. Analysis of association indices in patients with CAD certify that between the carrier of the D risk allele of ACE gene and the C risk allele of the gene AGT_1R was a moderate positive correlation (r_{xy} = 0.58, x^2= 35.30, $P<0.001$).

The distribution of Asp298Glu eNOS gene polymorphism frequencies in CAD patients showed no differences between them and control in terms of frequency of A/G genotype (53.21% vs. 57.93%, $P>0.05$) and risk allele A/A frequency (63% vs. 79%, $P>0.05$). No significant age-related differences were found, but there was a tendency towards accumulation in women (37.84% vs. 24.27%, $P=0.06$).

Comparative analysis of the characteristics of CAD patients grouped according to Asp298Glu eNOS gene polymorphism, revealed that homozygous state with risk genotype A/A or heterozygous A/G state are associated with increased prevalence of hypertension (96.00% and 87.91% vs. 69.64%, $P<0.05$), with no clear difference in terms of obesity (57.33% and 44.96% vs. 37.50%, $P>0.05$).

Analysis of clinical manifestations shows that almost 89.33% of the A/A genotype carriers had arterial hypertension grade II-III, while such levels of hypertension were found in only 69.64% of the G/G carriers and in 85.23% of A/G carriers. Analysis of echocardiographic findings showed reduced ejection fraction <50% in more than half of A/G genotype (57.05%), the same being also found in patients with genotypes G/G and A/A (42.86% vs. 46.67%, respectively).

Estimation of the association between clinical determinants and Asp298Glu eNOS gene polymorphism has shown that, compared with non-carrier individuals (G/G), homozygous A/A state and heterozygous carriers (A/G) in coronary patients are associated with increased prevalence of arterial hypertension [r_{xy} = 0.84, $P_{(AA-GG)}<0.01$].

Analyzing the frequencies of PlA GPIIb/IIIa receptor genotypes according to the polymorphism detected by MspI enzyme digestion we found that risk haplotype A_2/A_2 was detected in 63 (22.50%) of the patients and 28 (9.66%) controls, the difference being statisticaly significant (x2=16.28, $P<0.001$). Significant age-group differences were not found, but a trend of male prevalence (53.39% vs. 43.24%, $P=0.06$).

Analysis of A_1/A_2 GPIIb/IIIa polymorphism genotyping revealed that mutant A2 allele tents to be more common in the CAD patients compared with controls (72.85% vs. 70.71%, $P=0.06$). At the same time, the frequency of recessive A1 alleles in the coronary patients was lower than in the controls.

Platelet membrane glycoproteins play an important role in platelet adhesion and aggregation. The allelic variants for GPIIb/IIIa bind to fibrinogen being the key reaction in the process of platelet aggregation. The presence of PlA_2 allele leads to increased functional activity of receptors and is associated with intense adenosine diphosphate induced platelet aggregation *in vitro*.

The analysis of the relationship between the carrier-state of different genotypes and risk factors revealed a significant difference between genotypes A_1/A_1, A_1/A_2 and A_2/A_2 carriers and the prevalence of smoking (48.68% and 53.90% vs. 69.84 %, respectively, $P<0.01$), and mixed dyslipidemia (59.21% and 75.17% vs. 63.49%, $P<0.05$). Of note was the statistically significant difference between groups in terms of the share of old myocardial infarction in the history of the study patients: A_2/A_2 genotype was detected more frequency than A_1/A_1 (20.63% vs. 9.21%, respectively, $P<0.05$).

Analysis of biochemical characteristics in relation with A_1/A_2 GP IIb/IIIa gene polymorphism showed that A_2/A_2 genotype was associated with higher prothrombin levels as compared to A_1/A_1 and A_1/A_2 variants (106.96 ± 0.52% vs. 90.83 ± 0.59% vs. 80.00 ± 1.05%, $P<0.05$). Signs of grade II and III heart failure were present in 25.53% of A_1/A_2 genotype carriers , 15.87% of A_2/A_2 and 14.47% of A_1/A_1 ($P>0.05$) genotype.

It is noteworthy that one fourth of the risk A_2/A_2 and A_1/A_2 genotype carriers presented Q wave acute myocardial infarction, compared with A_1/A_1 carriers (28.36%, 22.22% vs. 19.73%, respectively, $P<0.05$).

It can be said that the presence of the A_2 allele and homozygous state A_2/A_2 were associated with the presence of dyslipidemia [r_{xy}= 0.53, $P_{(A2/A2-A1/A1)}<0.05$], smoking [r_{xy} = 0.64, $P_{(A2/A2-A1/A1)}<0.01$], as risk factors and a high frequency of previous myocardial infarction.

Conclusion

Carrier state of D/D genotype and D allele in ACE gene is a marker of increased risk for CAD and is associated with a high frequency of hypertension and cardiovascular death, being positively correlated with the risk C/C polymorphic variant of AGTR1 gene. The A_2/A_2 genotype of GP IIb/IIIa receptor gene is associated with susceptibility to CAD and high frequency of myocardial infarction and dyslipidemia, particularly in smokers. The impact of eNOS polymorphic markers for CAD was proved to be hypertension-mediated.

Conflict of interest: None declared

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International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

Guidelines for authors

International Heart and Vascular Disease Journal
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