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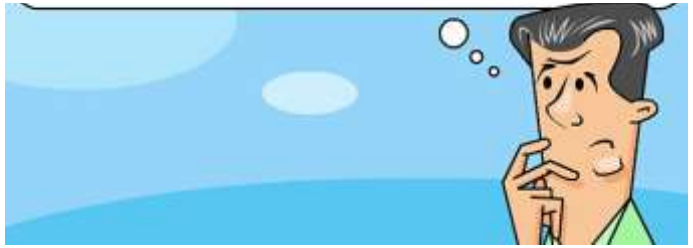
Hypertension in malignancy

Hypertension? Cancer ?



Outline

- Hypertension as a comorbidity
- Hypertension as a complication of the therapy
- Monitoring and management
- Special issues

Estimated New Cases

Males			Females		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All Sites	**856,370**	**100%**	**All Sites**	**878,980**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**	**All Sites**	**286,010**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2018.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

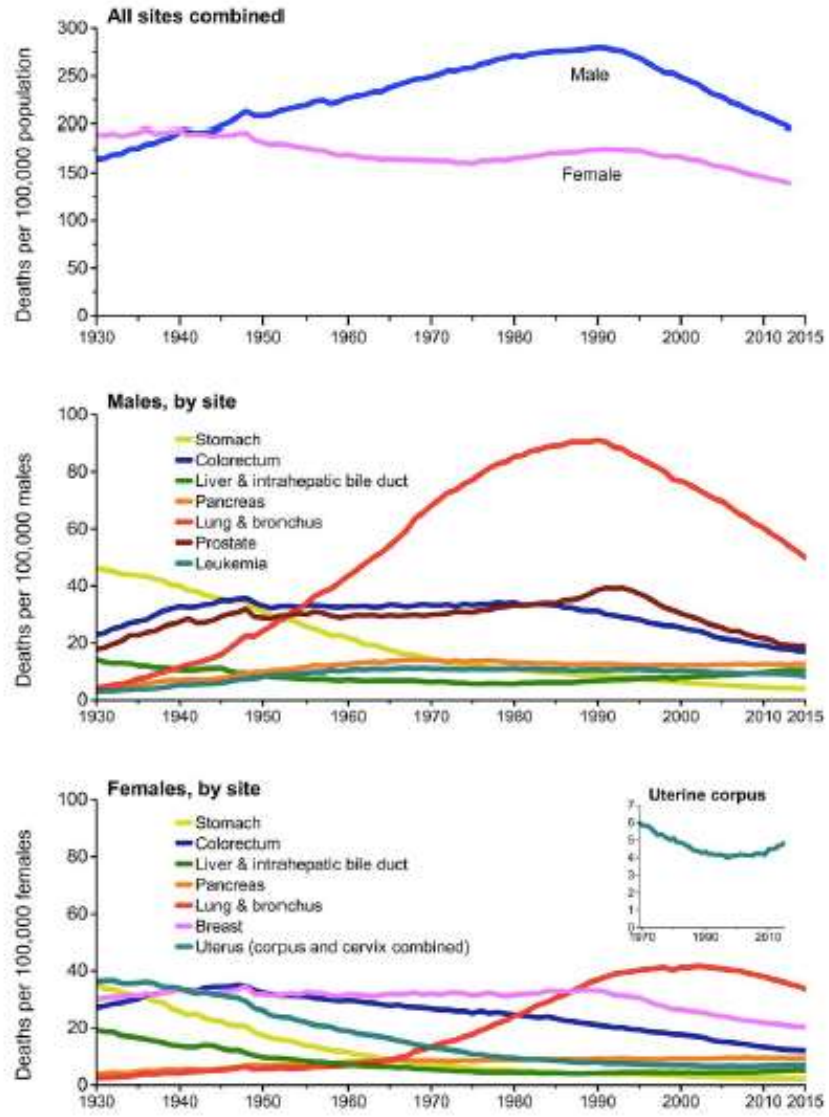


FIGURE 7. Trends in Cancer Death Rates by Sex Overall and for Selected Cancers, United States, 1930 to 2015.
Rates are age adjusted to the 2000 US standard population. Due to improvements in International Classification of Diseases (ICD) coding over time, numerator data for cancers of the lung and bronchus, colon and rectum, liver, and uterus differ from the contemporary time period. For example, rates for lung and bronchus include pleura, trachea, mediastinum, and other respiratory organs.

TABLE 7. Ten Leading Causes of Death in the United States, 2014 and 2015

RANK		2014			2015			RELATIVE CHANGE IN RATE
		NO.	PERCENT	RATE	NO.	PERCENT	RATE	
	All Causes	**2,626,418**		**724.4**	**2,712,630**		**732.5**	**1.1%**
1	Heart disease	614,348	23%	166.8	633,842	23%	168.3	0.9%
2	Cancer	591,699	23%	161.3	595,930	22%	158.6	−1.7%
3	Chronic lower respiratory diseases	147,101	6%	40.6	155,041	6%	41.8	3.0%
4	Accidents (unintentional injuries)	136,053	5%	40.4	146,571	5%	43.1	6.7%
5	Cerebrovascular disease	133,103	5%	36.5	140,323	5%	37.6	3.0%
6	Alzheimer disease	93,541	4%	25.4	110,561	4%	29.4	15.7%
7	Diabetes mellitus	76,488	3%	21.0	79,535	3%	21.3	1.4%
8	Influenza and pneumonia	55,227	2%	15.1	57,062	2%	15.2	0.7%
9	Nephritis, nephrotic syndrome, & nephrosis	48,146	2%	13.2	49,959	2%	13.4	1.5%
10	Intentional self-harm (suicide)	42,773	2%	12.9	44,193	2%	13.3	3.1%

Death counts include unknown age.

Rates are per 100,000 population and age adjusted to the 2000 US standard population.

Source: National Center for Health Statistics, Centers for Disease Control and Prevention.

TABLE 8. Ten Leading Causes of Death in the United States by Age and Sex, 2015

	ALL AGES		AGES 1 TO 19		AGES 20 TO 39		AGES 40 TO 59		AGES 60 TO 79		AGES ≥80	
	MALE All Causes 1,373,404	FEMALE All Causes 1,339,226	MALE All Causes 12,621	FEMALE All Causes 6,941	MALE All Causes 71,130	FEMALE All Causes 32,112	MALE All Causes 228,199	FEMALE All Causes 147,555	MALE All Causes 556,520	FEMALE All Causes 427,097	MALE All Causes 491,831	FEMALE All Causes 715,031
1	Heart diseases 335,002	Heart diseases 298,840	Accidents (unintentional injuries) 4,442	Accidents (unintentional injuries) 2,230	Accidents (unintentional injuries) 27,692	Accidents (unintentional injuries) 9,877	Heart diseases 51,810	Cancer 48,995	Cancer 170,331	Cancer 138,798	Heart diseases 141,863	Heart diseases 193,226

TABLE 14. Five-Year Relative Survival Rate (%) for the Most Common Childhood and Adolescent Cancers, United States, 2007 to 2013

	BIRTH TO 14	15 TO 19
All ICCC groups combined	83.0	84.2
Lymphoid leukemia	90.5	74.2
Acute myeloid leukemia	65.1	61.5
Hodgkin lymphoma	97.6	96.1
Non-Hodgkin lymphoma	90.6	87.1
Central nervous system neoplasms	72.5	78.9
Neuroblastoma & other peripheral nervous cell tumors	79.0	62.8*
Retinoblasoma	95.2	†
Renal tumors	91.8	72.7*
Hepatic tumors	79.0	50.9*
Osteosarcoma	69.8	65.5
Ewing tumor & related bone sarcomas	77.7	61.5
Soft tissue and other extraosseous sarcomas	74.6	68.2
Rhabdomyosarcoma	69.8	45.9
Germ cell and gonadal tumors	92.4	92.0
Thyroid carcinoma	99.4	99.5
Malignant melanoma	93.3	94.0

ICCC indicates International Classification of Childhood Cancer.

Survival rates are adjusted for normal life expectancy and are based on follow-up of patients through 2014.

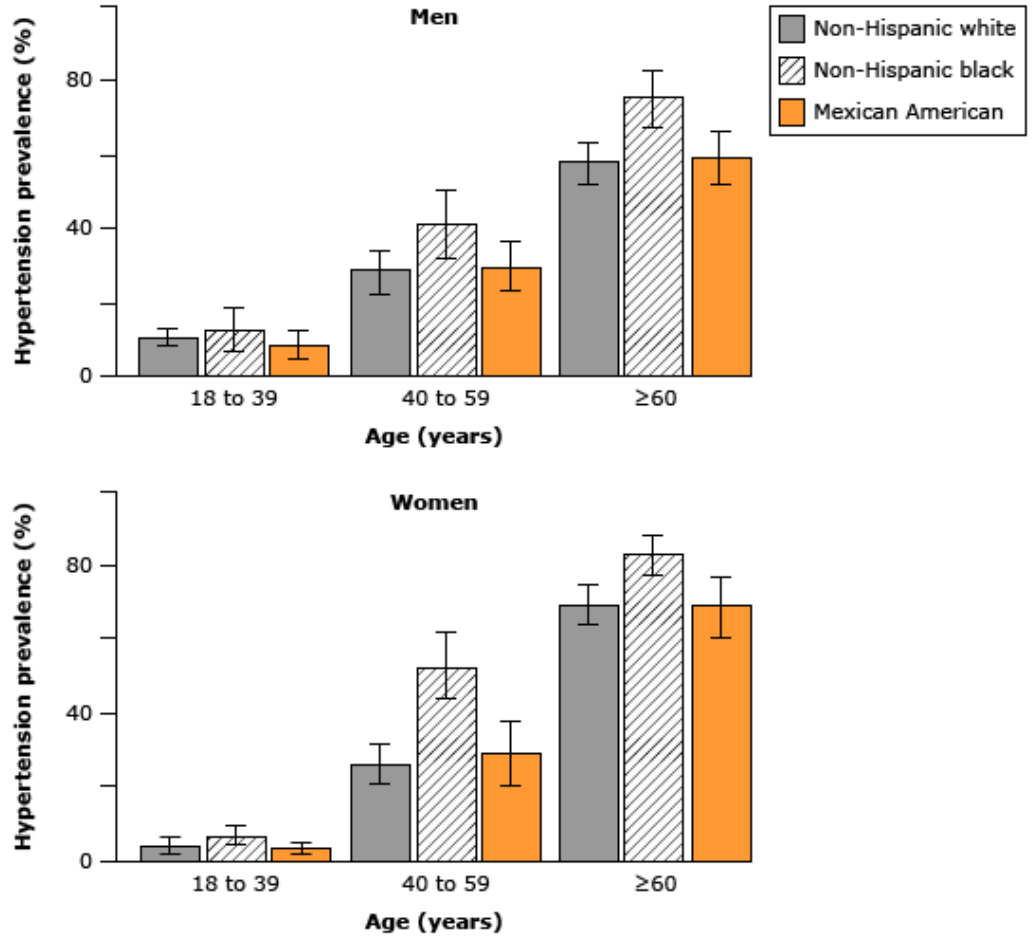
*The standard error of the survival rate is between 5 and 10 percentage points.

†Statistic could not be calculated due to fewer than 25 cases during 2007 to 2013.

Hypertension prevalence

- Prevalence of hypertension (defined as 140/90 mmHg or higher) ranged from 20 to 55%,
- Prevalence estimates among adults from 90 countries worldwide (approximately 31 percent in 2010) were similar to those in the United States [NHANES data].
- In China in adults aged 35 to 75 years prevalence of hypertension of 45 percent.
- The estimated global prevalence of hypertension is increasing (31% of the global population, or 1.39 billion people.
- With new definition (report of taking antihypertensive medication or a systolic pressure ≥130 mmHg and/or a diastolic pressure ≥80 mmHg) from 2017 by ACC/AHA prevalence of hypertension in US increased from 32 to 46%.

Prevalence of hypertension in the United States



Prevalence of hypertension in men (upper graph) and women (lower graph) according to age and race/ethnicity in the United States from the National Health and Nutrition Examination Survey (NHANES). Hypertension occurs earlier and more frequently in non-Hispanic blacks.

Data from: Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA 2010; 303:2043.

May Measurement Month 2017: an analysis of blood pressure screening results worldwide

Thomas Beaney, Aletta E Schutte, Maciej Tomaszewski, Cono Ariti, Louise M Burrell, Rafael R Castillo, Fadi J Charchar, Albertino Damasceno, Ruan Kruger, Daniel T Lackland, Peter M Nilsson, Dorairaj Prabhakaran, Agustin J Ramirez, Markus P Schlaich, Jiguang Wang, Michael A Weber, Neil R Poulter, on behalf of the MMM Investigators

Lancet Glob Health 2018

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	Mean age (SD), years	Women	Men	Participants receiving antihypertensive treatment
Southeast Asia and Australasia	42·8 (15·9)	218 155 (61·1%)	138 832 (38·9%)	78 973 (22·5%)
South Asia	39·9 (14·7)	118 707 (45·5%)	142 030 (54·5%)	27 691 (15·5%)
East Asia	55·0 (16·6)	95 836 (53·6%)	82 813 (46·4%)	44 843 (56·8%)
Sub-Saharan Africa	39·0 (14·7)	68 046 (54·2%)	57 591 (45·8%)	12 109 (9·6%)
Europe	52·2 (16·9)	64 566 (59·5%)	43 858 (40·5%)	42 354 (43·5%)
Americas	48·7 (17·8)	64 268 (60·3%)	42 351 (39·7%)	32 307 (30·6%)
Northern Africa and Middle East	37·4 (15·1)	19 747 (37·5%)	32 976 (62·5%)	1742 (3·3%)
Worldwide	44·9 (16·9)	649 325 (54·6%)	540 451 (45·4%)	240 019 (24·2%)

Data are n (%), unless stated otherwise. Percentages given exclude those where sex or treatment are unrecorded (appendix p11).

Table 1: **Worldwide and regional distributions of age, sex, and antihypertensive medication**

	Participants with hypertension*	Participants with hypertension and not receiving treatment	Participants receiving treatment but with uncontrolled blood pressure
Southeast Asia and Australasia	121 502 (34·1%)	42 529 (15·3%)	34 183 (45·0%)
South Asia	62 560 (31·1%)	34 869 (20·1%)	9177 (44·1%)
East Asia	61 897 (34·5%)	17 054 (12·7%)	16 125 (36·2%)
Sub-Saharan Africa	35 585 (28·3%)	23 476 (20·6%)	6601 (55·9%)
Europe	59 767 (55·0%)	17 413 (26·3%)	26 756 (63·6%)
Americas	42 693 (41·0%)	10 386 (14·4%)	11 859 (38·6%)
Northern Africa and Middle East	9921 (18·8%)	8179 (16·0%)	754 (43·7%)
Worldwide	393 924/1 128 635 (34·9%)	153 905/888 616 (17·3%)	105 456/227 721 (46·3%)

Data are n (%) or n/N (%). The denominators include those individuals with a mean of the second and third blood pressure readings after imputation. *The total number with hypertension includes an additional 12 298 individuals taking antihypertensive medication for whom an imputed mean reading was not available. An expanded table with all denominators is provided in the appendix (p 14).

***Table 3*: Total number of participants with hypertension, with and without treatment, for each region after imputation**

Hypertension as a comorbidity

- More than 13 million cancer survivors in the US alone and close to 30 million worldwide
- Prevalence of hypertension in patients with malignancy was around 30% [*Mouhayar E, Salahudeen A. Tex Heart Inst J. 2*011].
- It has been also the most common comorbidity reported in cancer registries [*Albini A, et al. J Natl Cancer Inst. 2010*].

Hypertension as a complication of the therapy

- Some renal cell carcinoma may cause secondary hypertension.
- Active treatments i.e. inhibitors of vascular endothelial growth factor-VEGF receptor may lead to or worse previously well controlled hypertension.
  - incidence of overall hypertension was 20–44%
  - and the high-grade hypertension was 6–17%, in particular during active therapy.
- Prevalence of hypertension depends upon age, prior hypertension or cardiovascular disease in anamnesis, type of malignancy (renal or non-renal), type of therapy and dose, chemotherapy regimen and concomitant medications.

Prevalence of hypertension depends upon:

- age,
- prior hypertension or cardiovascular disease in anamnesis,
- type of malignancy (renal or non-renal),
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Review

Hypertension in malignancy–an underappreciated problem

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Table 1: Anticancer drugs, type of nephrotoxicity, mechanism and prevention of renal adverse events

Medication	Cardiotoxicity	Mechanism of action	Likelihood of HT	Proposed hypotensive therapy
Alkylating agents cyclophosphamide	HT	endothelial dysfunction, arterial vasoconstriction, renal and vascular damage	+	RAAS blockade (ACEi, ARB)
Antimetabolites methotrexate gemcitabine	HF, HT,	Drug-induced- thrombotic microangiopathy-DITMA	+	
mTOR	HT	Podocyte damage,	+	RAAS (ACEi, ARB)
Platinum derivatives	HT	Oxidative stress, renal damage	+	
Proteasome inhibitors	Drug-indiced thrombotic microangiopathy		+	

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Anti-angiogenesis drugs VEGF pathway inhibitors- Bevacizumab, Aflibercept Sorafenib Sunitinib Pazopanib Vandetanib Axitinib Regorafenib cabozantinib	hypertension thrombotic microangiopathy	Peripheral vascular resistance, reduced formation of nitric oxide in endothelium, increased synthesis of vasoconstrictive factors, kidney damage	+++	RAAS (ACEi, ARB) CCB
glucocorticosteroids	HT	Salt and volume overload	+	diuretics
anthracyclines	LVD, HF/HT	Oxidative stress, apoptotic/ fibrotic changes in vascular wall, endothelial dysfunction	+	RAAS (ACEi, ARB), beta-blockers
HER2 inhibitors	LVD, HF/HT	Oxidative stress, apoptotic/ fibrotic changes in vascular wall, endothelial dysfunction	+	RAAS (ACEi, ARB), beta-blockers

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Platinum derivatives	HT	Oxidative stress, renal damage	+	
Proteasome inhibitors	Drug-indiced thrombotic microangiopathy		+	
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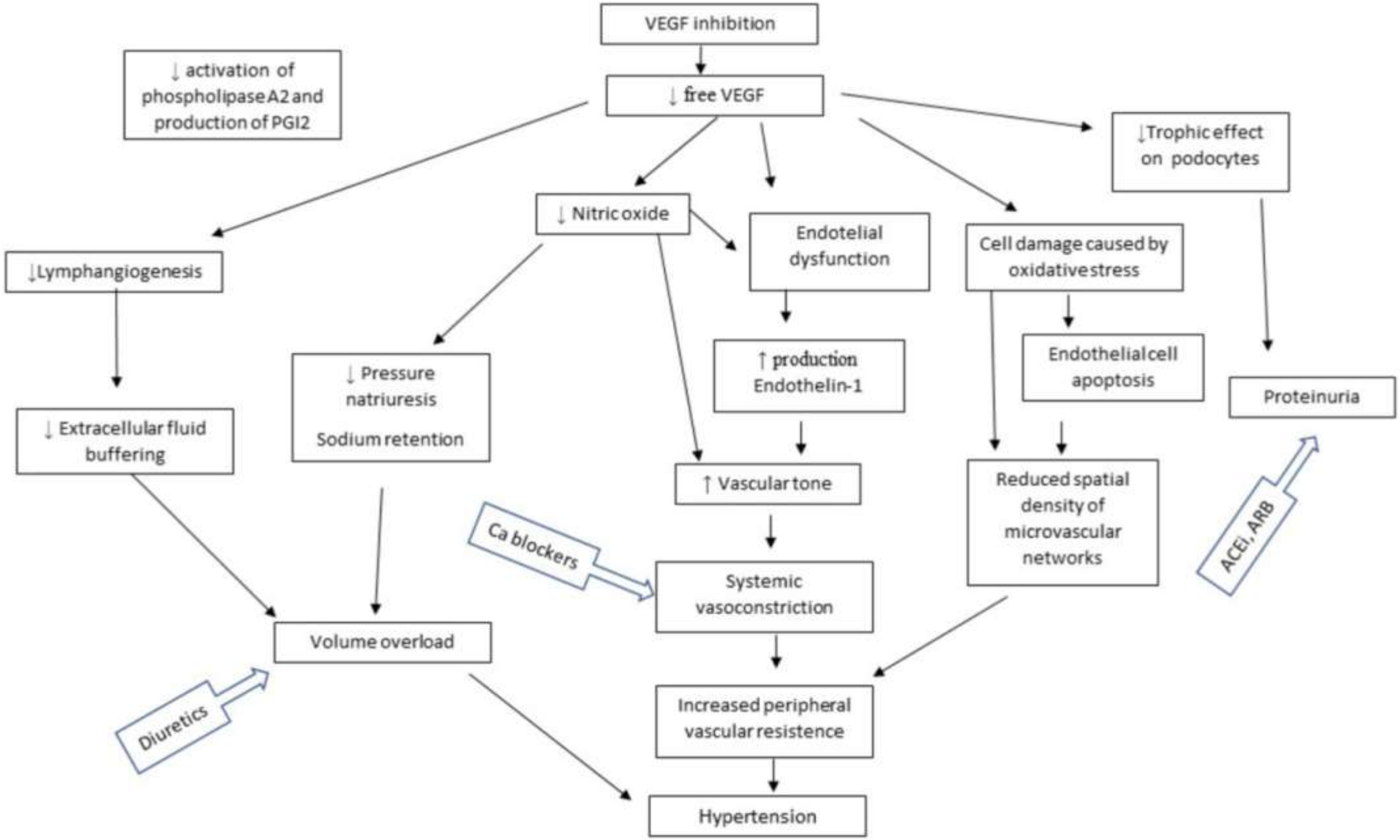

Figure 1: Proposed mechanisms of hypertension induced by anti-VEGF therapy (modified from 128).

Inhibition of VEGF by pharmacotherapy results in

- glomerular, endothelial and podocyte injury.
- It may lead to proteinuria as well.
- In kidney biopsy, the most common were TMA, reflecting vascular damage, followed by glomerulonephritis with crescents, focal segmental glomerulosclerosis (FSGS), glomerulonephritis with immune complexes, minimal change disease (MCN), and acute interstitial nephritis.

- worsening of kidney function may result from the nephrectomy in RCC subjects as the nephrons loss during nephrectomy either partial or radical is a predisposing factor for chronic kidney disease or development of contrast-induced nephropathy following computed tomography (CT) with contrast media in any malignancy.

- Hypertension (any grade) is reported in 17% - 49.6% of patients treated with VEGF/TKI,
- proteinuria is found in 8% to 73%
- elevated serum creatinine is found 5% to 65.6% of subjects.

Risk factors for rise in blood pressure under VEGFR therapy are prior hypertension,

- age ≥ 60 years,
- BMI ≥ 25 kg/m^2 .

The significant rise in BP as early as in the first week of treatment

Association with antitumor efficacy

- 4 prospective studies in patients with advanced RCC treated with sunitinib, rise in blood pressure over 140 mm Hg was associated with better antitumor efficacy (median OS, median PFS, and objective response rates were 30.9 versus 7.2 months, 12.5 versus 2.5 months, and 55 versus 9 percent, respectively)
- in 7 randomized trials with bevacizumab used for RCC, colorectal, breast, NSCLC, and pancreatic cancer, no association between early hypertension and clinical benefit from bevacizumab was found

- hypertension development predicted a better response of the tumor to the therapy with anti-VEGF drugs,
- in a case of hypertension de novo or worsening of the preexisting hypertension, maintaince of targeted therapy and hypotensive drugs are recommended rather than withdraw antineoplastic drugs.
- withdrawal of anti-VEGF treatment when severe adverse events appeared.
- treatment with bevacizumab combined with TKIs may result in development of severe hypertension and other life-threatening toxicities i.e. vascular and hematological

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity (EHJ 2016)

Data only for patients treated with VEGF/TKI

- For patients who develop hypertension while receiving treatment with an antiangiogenic agent, blood pressure should be monitored actively during the therapy
- Treatment with angiotensin system inhibitors (ASIs; eg, angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs]) may be preferred over other drugs.
- In subjects treated with VEGF inhibitors, when diarrhea is observed as a side effect, diuretics should not be given as first line hypotensive therapy.

Other considerations

- As ***sorafenib*** and ***sunitinib*** undergo partial metabolism via cytochrome P450,
  - a system inhibited by some antihypertensive agents (eg, verapamil, diltiazem), therefore,
  - these agents should probably be avoided in patients who develop hypertension while receiving sorafenib or sunitinib

- **In patients treated with cardiotoxic chemotherapy, who are considered Stage A Heart Failure (HF),**
  - preferred drugs are those preventing adverse cardiac remodeling, i.e. ACEis, beta-blockers, or ARBs.
- ACEi and beta-blockers are preferred as hypotensives in subjects with HF, left ventricular dysfunction or at risk of HF.

- **Valuable option could be nebivolol (beta1-blocker)** due to its properties affecting cell NO signaling **or carvedilol** with its vasodilation properties.
- **Phosphodiesterase 5 inhibitors such as sildenafil or tadalafil** may be taken into account, however, data on the efficacy are limited in this setting.
- **Diuretics** may lead to electrolyte disturbances and consequent QT prolongation, thus should be used cautiously.
- **Beta-blockers and ACE inhibitors** may be administered together with trastuzumab as prophylactic agents in patients with breast cancer as tolerated.

- Ambulatory blood pressure monitoring is to be considered in certain cases, especially treated with VEGFR inhibitors, particularly in the first weeks of the therapy.

Cardiovascular Toxicities Panel formed byThe Investigational Drug Steering Committee of the National Cancer Institute -recommendations

- perform a pretreatment evaluation and screening,
- formal risk assessment for potential cardiovascular complications
- identify and treat preexisting hypertension before using angiogenesis inhibitors

- it is crucial to adequately control pain and stress.

ESC/ESH Guidelines

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension

Authors/Task Force Members: Bryan Williams (ESC Chairperson) (UK)*, Giuseppe Mancia (ESH Chairperson) (Italy)*, Wilko Spiering (The Netherlands), Enrico Agabiti Rosei (Italy), Michel Azizi (France), Michel Burnier (Switzerland), Denis L. Clement (Belgium), Antonio Coca (Spain), Giovanni de Simone (Italy), Anna Dominiczak (UK), Thomas Kahan (Sweden), Felix Mahfoud (Germany), Josep Redon (Spain), Luis Ruilope (Spain), Alberto Zanchetti (Italy)†, Mary Kerins (Ireland), Sverre E. Kjeldsen (Norway), Reinhold Kreutz (Germany), Stephane Laurent (France), Gregory Y.H. Lip (UK), Richard McManus (UK), Krzysztof Narkiewicz (Poland), Frank Ruschitzka (Switzerland), Roland E. Schmieder (Germany), Evgeny Shlyakhto (Russia), Costas Tsioufis (Greece), Victor Aboyans (France), and Ileana Desormais (France)

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- Hypertension is the most common cardiovascular comorbidity reported in cancer registries, in which an elevated BP is usually found in more than one-third of the patients
- high prevalence of hypertension at an age in which cancer is also common.
- the pressor effect of two groups of widely used anticancer drugs, the inhibitors of the vascular endothelial growth factor signalling pathway (bevacizumab, sorafenib, sunitinib, and pazopanib) and the proteasome inhibitors (carfilzomib).

- office BP should be measured weekly during the initial part of the first cycle of therapy and at least every 2–3 weeks thereafter.
- After the first cycle is completed and BP values appear to be stable, BP can be measured at the time of the routine clinical evaluations or assessed by HBPM.

Patients developing hypertension (140/90mmHg), or showing an increase in DBP 20mmHg compared with pretreatment values, should initiate or optimize antihypertensive therapy, for which RAS blockers and CCBs may be considered the preferred drugs, and a RAS blocker-CCB combination is a frequently needed strategy.

CCBs should only be of the dihydropiridine type, because diltiazem and verapamil block the CYP3A4 isoenzyme, which is involved in the metabolic pathway of sorafenib, increasing the drug’s levels and leading to potential toxicity

temporary discontinuation may be considered when BP values are exceedingly high despite multidrug treatment, in th presence of severe hypertension-generated symptoms or when there is a cardiovascular event requiring a immediate effective BP control

Conclusions (1)

- There are no substantial long-term data is available and guidelines for a special therapeutic strategy in cancer patients.
- In regard, to the management of hypertension in malignancy, meticulous attention should be paid to pretreatment screening for risk factors.

Conclusions (2)

- **The initial treatment** usually include drug affecting renin-angiotensin aldosterone system i.e. ACE inhibitor or ARB, or a long-acting calcium channel blocker-CCB most often amlodipine.
- **The most common dual combination regimen** to reach the target blood pressure consist of ACE inhibitor or ARB and either a long-acting-CCB or thiazide diuretic.
- **In three drug therapy** the preferred regimen consists of ACE inhibitor or ARB with a long-acting CCB and a diuretic

Conclusions (3)

- Almost all medical oncologists administered cardiotoxic treatments, including anthracyclines (83%), trastuzumab (51%) and other antiangiogenic drugs (64%) *[Jovenaux L Int J Cardiol 2017].*

- Only 35% of oncologists managed cardiotoxicity on the basis of the guidelines from expert oncology societies, whereas recommendations from expert cardiology societies was virtually not known.

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Thank you