AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

UPDATE

# Farmaci antipertensivi e rischio di neoplasie

Franco Rabbia

# Le pillole per la pressione «aumentano il rischio di cancro ai polmoni»

SALUTE > RICERCA

*Giovedì 25 Ottobre 2018*

Le pillole per la pressione del sangue prese da milioni di persone in tutto il mondo potrebbero aumentare il rischio di cancro ai polmoni. A stabilirlo è uno studio condotto dai ricercatori della McGill University di Montreal, in Quebec, in Canada, che hanno chiesto la possibilità di «ulteriori studi, con follow-up a lungo termine, per studiare gli effetti di questi farmaci sull'incidenza del cancro del polmone».

BUSINESS | HEALTH CARE | HEALTH

# FDA Says Up to Two Million People Exposed to Likely Carcinogens in Blood-Pressure Drugs

Half or more of patients taking common hypertension medicines are in U.S., agency says

Attualità > Salute >

# Farmaci per la pressione cancerogeni: 700 lotti ritirati. Ecco la lista completa

Chiara Ridolfi | 6 Luglio 2018 - 13:23 | Commenti: 0

MeteoWeb

HOME » ALTRE SCIENZE » MEDICINA & SALUTE

## Un altro farmaco per l'ipertensione ritirato

HOME NEWS METEO NOWCASTING GEO-VULCANOLOGIA ASTRONOMIA ALTRE SCIENZE FOTO VIDE

[MARCHIO E LOTTO]

Un altro farmaco per la pressione alta è stato preso in esame da Aifa che ne ha disposto il ritiro dopo il riscontro di impurità nelle materie prime

# Salute, Ema: “Bisogna esaminare tutti i medicinali per impurità cancerogene”

Per precauzione, L’Agenzia europea per i medicinali vuole che sia verificato il rischio nitrosammine per ogni prodotto. La sostanza ha già portato il ritiro della ranitidina oggi e, nel 2018, del valsartan

# Considerazioni sul rapporto tra antiipertensivi e neoplasie

- **L'ipertensione arteriosa è il più frequente fattore di rischio cardiovascolare anche nei pazienti con neoplasia**
- **Si stima che il 37% dei pazienti con neoplasia siano ipertesi**
- **Le terapie anticancro sono spesso fattore di rischio di ipertensione arteriosa**
- **Un trattamento adeguato dell'ipertensione arteriosa ha un ruolo importante nella cura dei pazienti neoplastici.**
- **Vi sono evidenze di associazione tra alcune classi di farmaci antiipertensivi e determinati tipi di neoplasie nella popolazione generale**
- **Altri studi non hanno confermato tale associazione ma, al contrario hanno evidenziato un effetto positivo degli antipertensivi sulla sopravvivenza in pazienti neoplastici**
- **I diuretici, in particolare, sembrano possedere un ruolo nello sviluppo di determinate neoplasie**
- **Alcune sostanze derivate dai processi di lavorazione di farmaci inibitori del SRAA possono essere associate ad un aumentato rischio di neoplasia**

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

APRIL 25, 2019

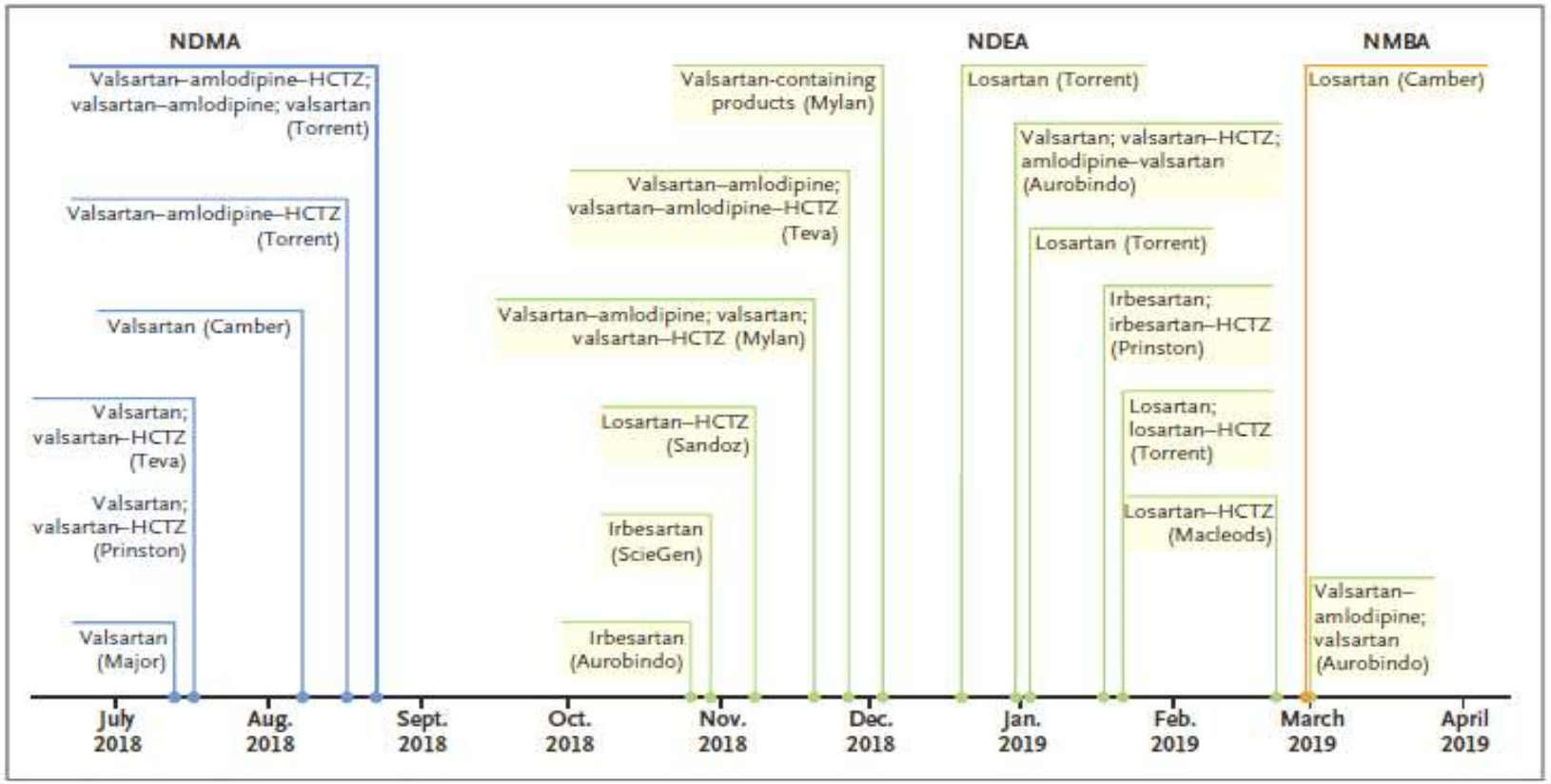
# Hypertension Hot Potato — Anatomy of the Angiotensin-Receptor Blocker Recalls

J. Brian Byrd, M.D., M.S.C.I., Glenn M. Chertow, M.D., M.P.H., and Vivek Bhalla, M.D.

NDMA: N.nitroso-N-dimetilammina

NDEA: N-nitroso-N-dietilammina

NMBA: N-nitroso-n-metil-4-acido aminobutirrico




**Recalls of Angiotensin-Receptor Blockers.**

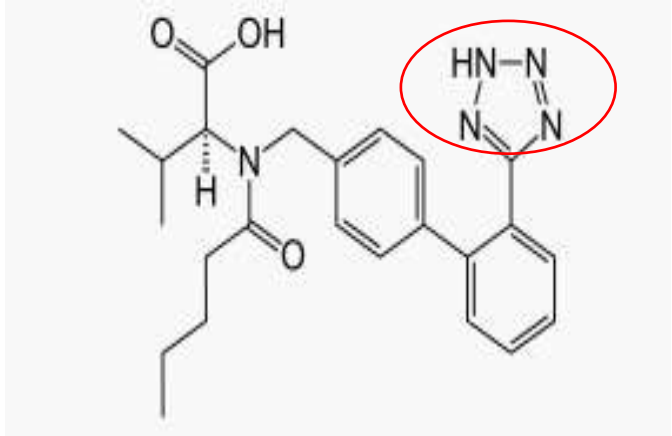
**NDMA** presente in minime quantità nel cibo stagionato o affumicato, ma è più spesso un sottoprodotto di lavorazioni industriali e trattamento delle acque.
E' usato in laboratorio come carcinogenetico sui ratti.
L'OMS lo ritiene cancerogeno nell'uomo (epatocarcinoma soprattutto), se vi è una esposizione cronica anche a basse dosi, per cui le dosi tollerate nell'H2O non devono superare i 7 ng/L.
L'FDA non ritiene accettabile alcun residuo di NDMA nei farmaci
**Nei lotti di compresse sequestrate sono stati trovati livello di NDMA variabili da 300 a 20 ng (limite tollerabile 96 ng/die)**

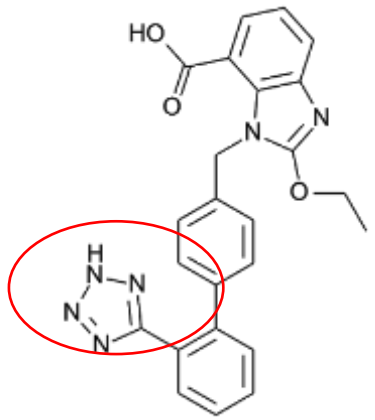
**NDEA**. Composto sintetico oleoso, solubile in H2O, lipidi ed altri solventi organici. E' usato come additivo di benzina e lubrificanti,antiossidante,e stabilizzatore nell'industria chimica. NDEA agisce sull'integrità del DNA tramite alchilazione, viene utilizzato in laboratorio come carcinogenetico

**NMBA** Composto carcinogeno presente in vari tipi di tabacco. Nel ratto induce carcinoma della vescica. FDA non ha ancora individuato le cause della presenza di tale composto in alcuni lotti di sartani.

# Perché questi composti erano presenti nelle compresse di alcuni lotti di sartani?

**La maggior parte dei sartani in commercio  contiene un anello tetrazolico ( irbesartan, valsartan, candesartan, olmesartan, losartan).**

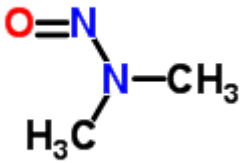


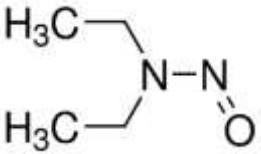

***La sintesi dell'anello tetrazolico è stata la chiave per la formazione delle nitrosoammine.***

Nei brevetti dei farmaci originali questo processo avveniva facendo reagire l'arilnitrile con tetrabutilstagno azide in xilene a riflusso (quindi 144°C). E probabilmente quando il brevetto del valsartan è scaduto (2011) i produttori di farmaco generico hanno registrato con FDA e EMA  il Drug Master File con questo processo.

# Perché questi composti erano presenti nelle compresse di alcuni lotti di sartani?



NDMA



NDEA

**Nel 2012 l'Industria cinese ZHP ha introdotto una modifica che abbassava i costi e aumentava le rese: arilnitrile più sodio azide e zinco cloruro (il catalizzatore) in dimetilformammide (solvente) senza variare il DMF (verosimilmente variato ma scritto in cinese).**

**Nel nuovo processo l'eccesso di sodio azide che non aveva reagito veniva distrutto con nitrito di sodio a caldo. Le formammidi sono soggette a decomporsi ad acido formico e corrispondente ammina, a caldo (è una decomposizione estremamente lenta). E una dialchilammina in presenza di nitrito e in condizioni acide reagisce a dare la corrispondente N-nitrosoammina. Il metodo è stato brevettato e successivamente utilizzato da MY e AB (costava meno..)**

# Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

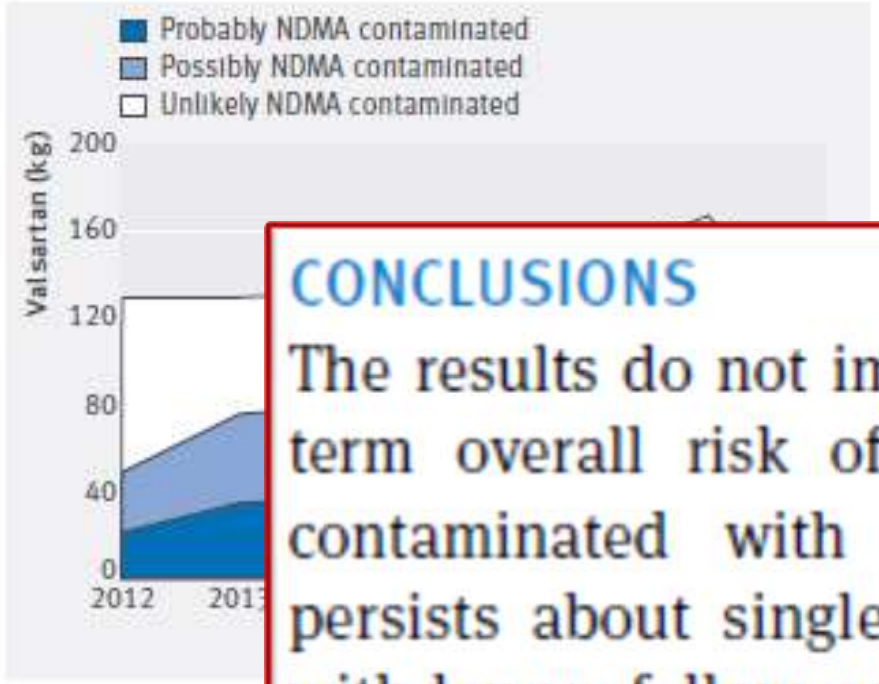



Fig 1 | Use of vals
substance, specif
probably, possibl
N-nitrosodimethy
results from data only being available to June 2018

Table 2 | Estimates for association between use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA) and cancer risk compared with non-contaminated valsartan products

| | Follow-up | Cancer | Incidence rate | Adjusted hazard ratio* | Fully adjusted hazard ratio† (95% CI) |
|---|---|---|---|---|---|
| | | | | CI) | |
| | | | | (ref) | 1.00 (ref) |
| | | | | (0.91 to 1.49) | 1.09 (0.85 to 1.41) |
| | | | | | |
| | | | | (0.92 to 1.72) | 1.15 (0.83 to 1.59) |
| | | | | (0.75 to 1.53) | 0.99 (0.69 to 1.43) |
| | | | | (0.84 to 1.54) | 1.11 (0.82 to 1.50) |
| | | | | 5 | P=0.70 |

uctase inhibitors, statins, spironolactone, oral
onic obstructive pulmonary disease, heart

†Defined by total amount of NDMA contaminated valsartan filled.
§Estimated using Cox regression across 10 000 mg stratums of NDMA contaminated valsartan filled.

## CONCLUSIONS

The results do not imply a markedly increased short term overall risk of cancer in users of valsartan contaminated with NDMA. However, uncertainty persists about single cancer outcomes, and studies with longer follow-up are needed to assess long term cancer risk.

Pottegard BMJ 2018

**Comunicazione EMA su medicinali sartani**

EMA Ha concluso che se 100.000 pazienti hanno assunto valsartan prodotto da ZHP (dove sono stati trovati i più alti livelli di impurità) ogni giorno per 6 anni alla massima dose, potrebbero esserci 22 casi extra di cancro a causa dell'NDMA durante la vita di quei 100.000 pazienti.
L'NDEA in questi medicinali potrebbe portare a 8 casi extra in 100.000 pazienti che assumono il medicinale alla dose più alta ogni giorno per 4 anni.
Le stime sono state estrapolate da studi su animali e sono molto basse rispetto al rischio di sviluppare cancro nell’arco della vita nell'UE.

EMA 2018

# Hydrochlorothiazide use and risk of non melanoma skin cancer: A nationwide case-control study from Denmark

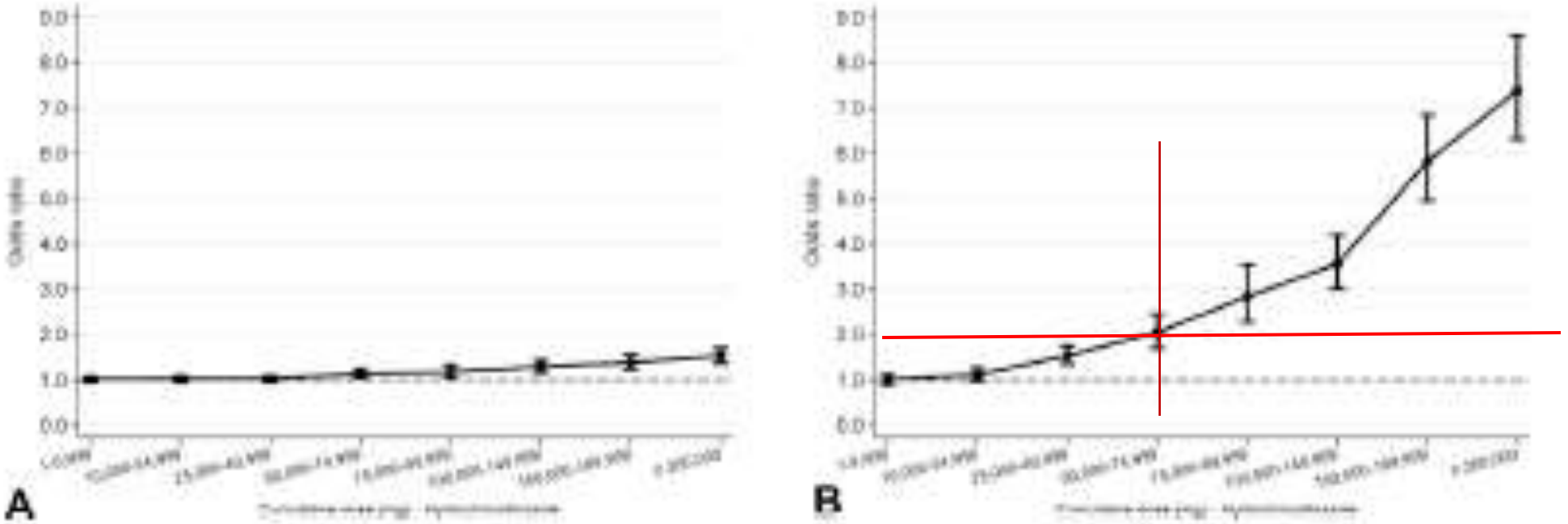



**Fig 2.** Dose-response pattern between cumulative hydrochlorothiazide dose and risk of basal cell carcinoma (**A**) and squamous cell carcinoma (**B**). Error bars represent 95% confidence intervals.

**50-70 g cumulativi**

**Assumendo 12,5 mg/die di idroclorotiazide (1DDD), in 1 anno ne assumo 4,66 g**

Pedersen J Am Acad Dermatol 2018

# Hydrochlorothiazide use is strongly associated with risk of lip cancer

**Table 3** *Association between exposure to hydrochlorothiazide and risk of squamous cell carcinoma of the lip, according to cumulative duration and intensity of hydrochlorothiazide use*

| Subgroup | Cases | Controls | Crude OR[a] | Adjusted OR[b] |
|---|---|---|---|---|
| Nonuse | 494 | 55 666 | 1.0 (ref.) | 1.0 (ref.) |
| Cumulative duration of use[c] | | | | |
| 0–1 year | 22 | 2365 | 1.1 (0.7–1.6) | 1.0 (0.7–1.6) |
| 1–2 years | 13 | 1091 | 1.3 (0.7–2.3) | 1.3 (0.7–2.2) |
| 2–3 years | 5 | 821 | 0.7 (0.3–1.7) | 0.7 (0.3–1.7) |
| 3–5 years | 25 | 1256 | 2.3 (1.5–3.5) | 2.3 (1.5–3.4) |
| 5+ years | 74 | 1868 | 4.7 (3.6–6.0) | 4.5 (3.5–5.9) |
| Intensity of use amongst high-users[d] | | | | |
| 6.25 mg day$^{-1}$ | ($n < 5$) | ($n < 5$) | (-) | (-) |
| 12.5 mg day$^{-1}$ | 13 | 672 | 2.3 (1.3–4.0) | 2.3 (1.3–4.0) |
| 18.75 mg day$^{-1}$ | 5 | 153 | 4.0 (1.6–9.9) | 3.8 (1.5–9.5) |
| 25 mg day$^{-1}$ | 44 | 745 | 7.0 (5.1–9.8) | 6.7 (4.8–9.3) |
| ≥32.25 mg da$^{-1}$y | 20 | 448 | 5.4 (3.4–8.5) | 4.9 (3.0–7.8) |

Pottegard JIM 2017

# Hydrochlorothiazide use is strongly associated with risk of lip cancer

**Table 4** *Associations between high use of hydrochlorothiazide (≥25 000 mg) and risk of squamous cell carcinoma of the lip, according to patient subgroups*

| Subgroup | Cases exposed / unexposed | Controls exposed / unexposed | Crude OR[a] | Adjusted OR[b] |
|---|---|---|---|---|
| Age group | | | | |
| <60 years | 8/81 | 131/8943 | 7.4 (3.4–16.0) | 6.7 (2.9–15.1) |
| 60–75 years | 34/239 | 1141/25 561 | 3.2 (2.2–4.7) | 3.2 (2.2–4.7) |
| 75+ years | 52/174 | 1499/21 162 | 4.3 (3.1–5.9) | 4.2 (3.0–5.9) |
| Gender | | | | |
| Male | 39/356 | 1507/38 008 | 2.8 (2.0–4.0) | 2.9 (2.0–4.0) |
| Female | 55/138 | 1264/17 658 | 5.8 (4.2–8.1) | 5.4 (3.9–7.6) |
| Other | | | | |
| No use of photosensitizing drugs[c] | 40/260 | 1298/31 598 | 4.1 (2.9–5.8) | 4.2 (2.9–6.1) |
| No previous NMSC | 91/478 | 2701/54 806 | 4.0 (3.2–5.1) | 3.9 (3.1–5.0) |
| CCI score = 0 | 53/297 | 1461/37 843 | 4.8 (3.6–6.6) | 4.5 (3.3–6.3) |
| No diabetics | 81/448 | 2232/51 810 | 4.3 (3.4–5.6) | 4.2 (3.3–5.5) |

Pottegard JIM 2017

Non associazione con altri diuretici o calcioantagonisti

# Reviewing the effects of thiazide and thiazide-like diuretics as photosensitizing drugs on the risk of skin cancer

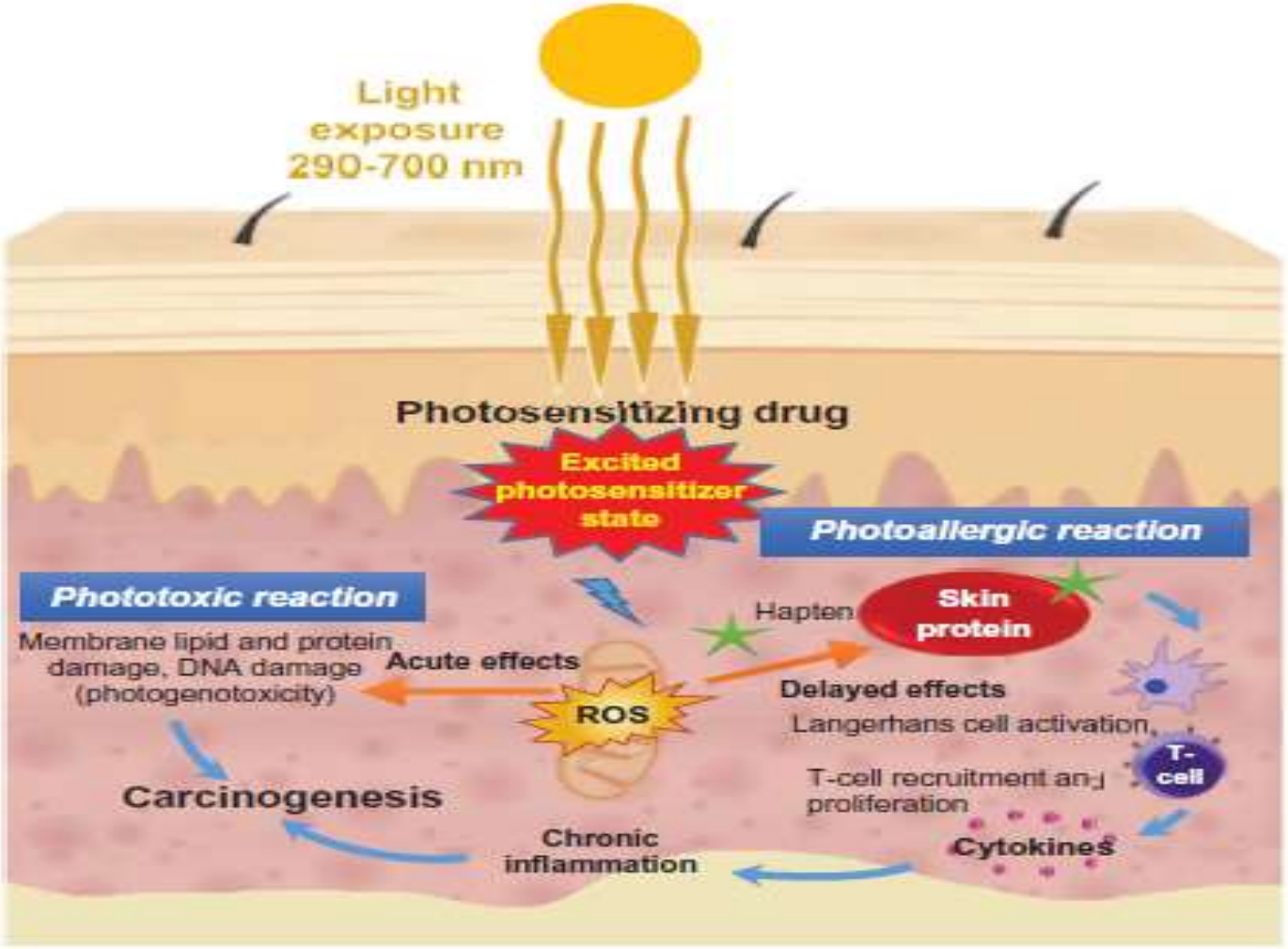



FIGURE 1 Mechanism of drug-induced photosensitizing reactions. A photosensitizing drug in the skin dermal/epidermal layer is photo-excited after absorption of photons of the appropriate wavelength, leading to generation of reactive oxygen species. ROS mediates damage of cellular components, causing acute cytotoxicity effects (–acute phototoxic reaction, left). Alternatively, a photosensitizing drug may act as a hapten that binds to skin proteins in presence of ROS, causing a delayed cell-mediated immunological response (–photoallergic reaction, right). Photosensitizing drugs may thus promote carcinogenesis through DNA damage or by chronic inflammation. ROS, reactive oxygen species.

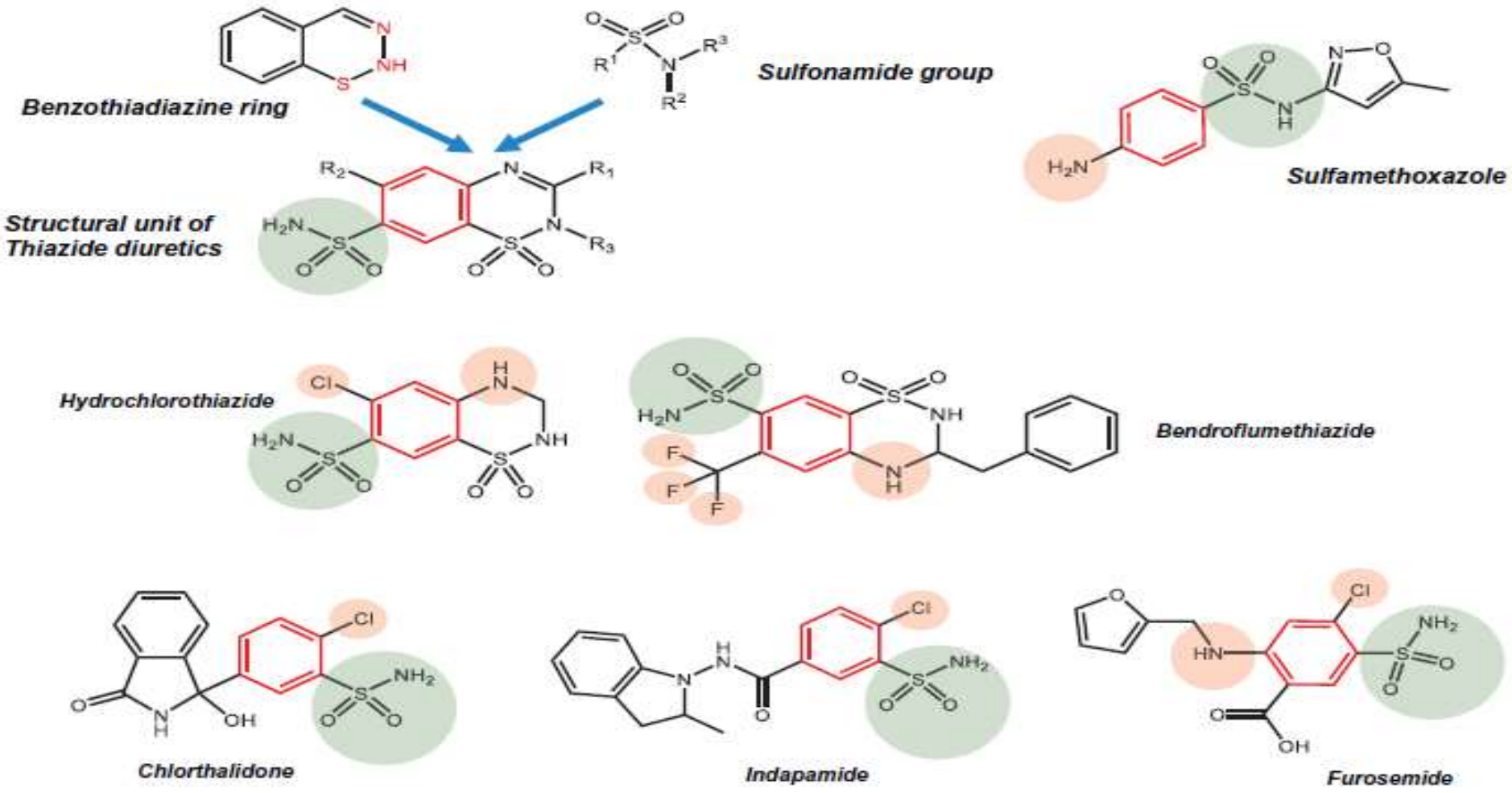
Kreutz J Hypertens 2019

# Antiipertensivi fotosensibilizzanti

| Classe | farmaco |
|---|---|
| Diuretici | |
| Tiazidici e tiazidici like | Bendroflumetiazide, benztiazide, clortalidone, clorotiazide, **idroclorotiazide**, indapamide, metolazone |
| Ansa | Furosemide |
| Risparmiatori di potassio | Spironolattone, triamterene |
| ACE inibitori | Captopril, enalapril, lisinopril |
| Calcio antagonisti | |
| Diidropriridinici | Nifedipina |
| Non diidropiridinici | Diltiazem |
| Beta bloccanti | Labetalolo, metoprololo, nadololo, timololo |
| Alfa bloccanti | Prazosina |
| Agonisti centrali | Clonidina, metildopa |

Kreutz J Hypertens 2019

# Strutture chimiche con potenziale effetto fotosensibilizzante



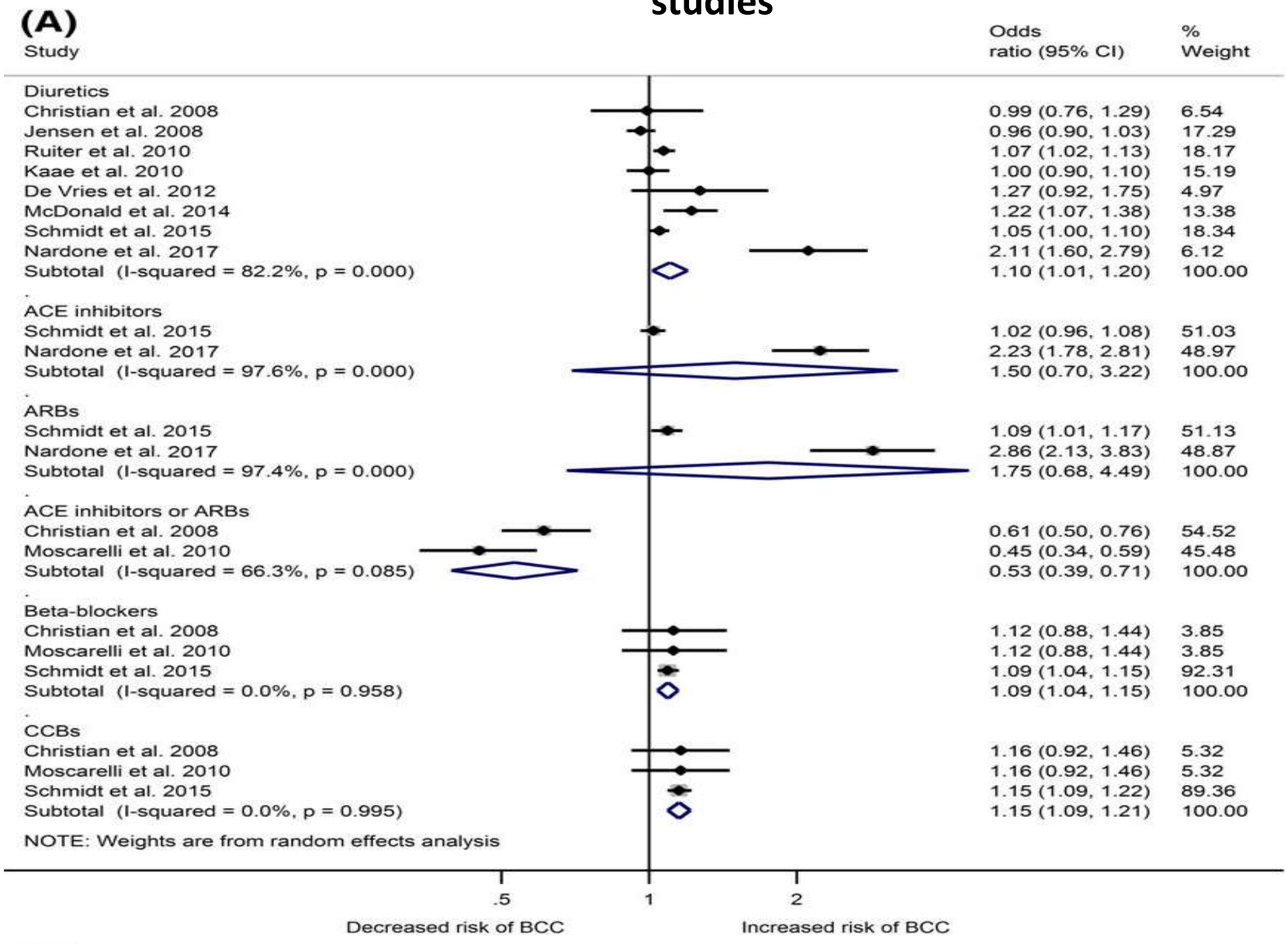

Kreutz J Hypertens 2019

**TABLE 4. Selected factors increasing the risk of skin cancer**

| Patient-related factors | Drug-related factors | Environmental factors |
|---|---|---|
| Genetic factors (e.g. family history, specific mutations, such as rs7023329 at 9p21) | Inherent photochemical activity of a photosensitizing drug | Ultraviolet light exposure [i.e. sun-exposure patterns, artificial ultraviolet light exposure (tanning bed)] |
| White skin | Drug exposure factors: drug pharmacokinetics, individual variations in drug handling, cumulative dose, duration of treatment | History of sun burns |
| Skin phenotypes (e.g. thickness of stratum corneum) | | Use of cosmetics, dyes, personal care products with photoreactive carcinogenic ingredients |
| Smoking status | | Use of protective sun-screens |
| Immune status | | |
| Co-infection with human papillomavirus | | |

Kreutz J Hypertens 2019

# Use of antihypertensive drugs and risk of keratinocyte carcinoma: A meta-analysis of observational studies




Tang Pharmacoepidemiol drug saf 2018

## *Riassunto*

• Studi farmacoepidemiologici hanno evidenziato un aumento del rischio di tumore cutaneo non melanoma (TCNM) (carcinoma a cellule basali, carcinoma a cellule squamose) con esposizione a dosi cumulative crescenti di idroclorotiazide (HCTZ).

• I pazienti che assumono HCTZ da sola o in associazione con altri farmaci devono essere informati del rischio di TCNM e devono essere avvisati di controllare regolarmente la loro cute per identificare eventuali nuove lesioni o modifiche di quelle esistenti e a segnalare al medico ogni lesione cutanea sospetta.

• Le lesioni cutanee sospette devono essere esaminate includendo possibilmente esami istologici di biopsie.

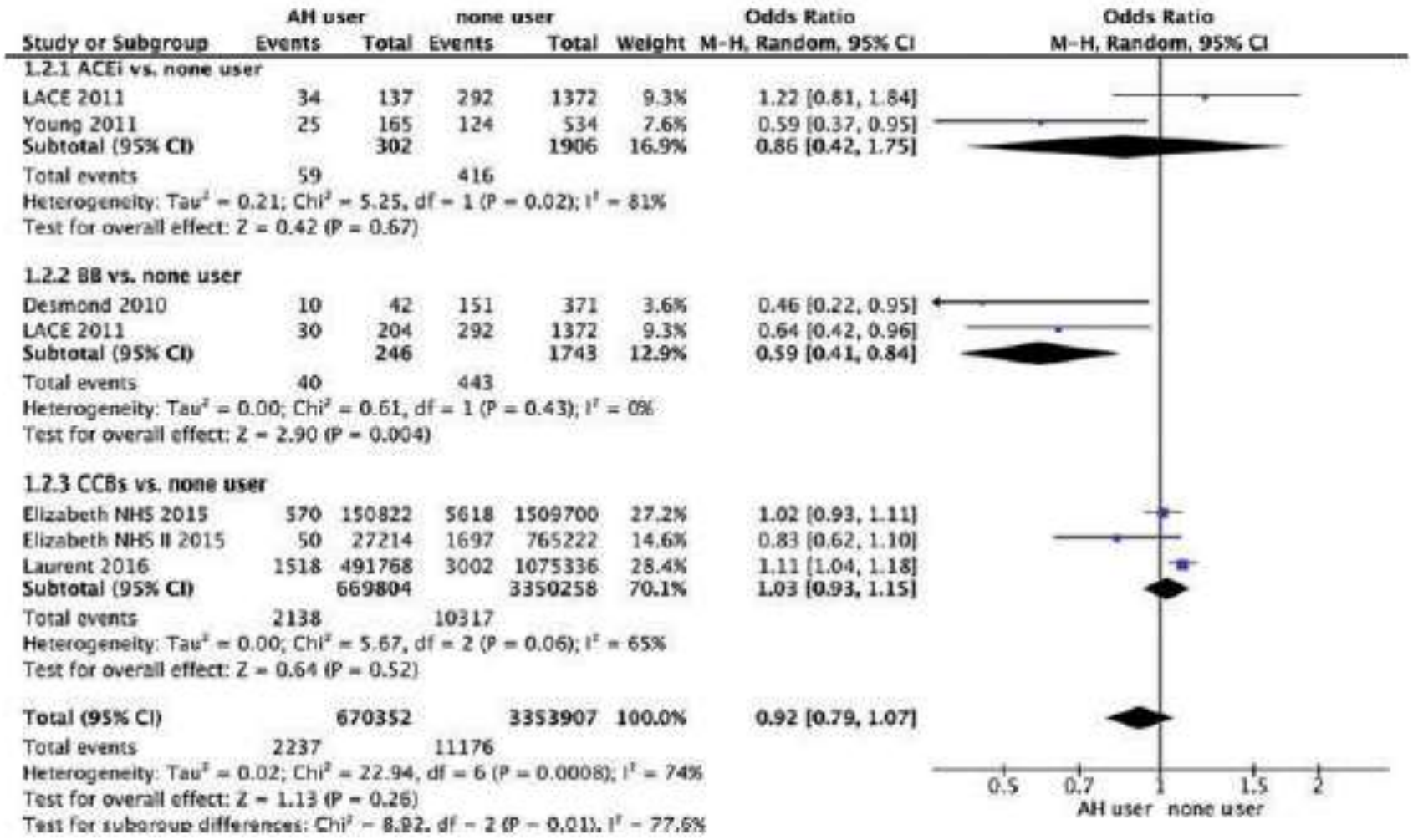
• I pazienti devono essere avvertiti di limitare l'esposizione alla luce solare e ai raggi UV e utilizzare una protezione adeguata quando esposti alla luce solare e ai raggi UV, per ridurre al minimo il rischio di cancro della pelle.

• L'uso di HCTZ deve essere attentamente valutato in pazienti che hanno avuto un precedente tumore della cute.

**I tassi di incidenza stimati variano tra le diverse regioni in Europa e sono previsti tassi da 1 a 34 casi ogni 100.000 abitanti/anno per SCC e da 30 a 150 ogni 100.000 abitanti/anno per BCC. Sulla base dei risultati dei due studi epidemiologici danesi, questo rischio potrebbe aumentare da circa 4 a 7,7 volte per SCC e 1,3 volte per BCC, a seconda della dose cumulativa di HCTZ.**

**Nota AIFA 2018**

# Effect of antihypertensive drugs on breast cancer recurrence in female hypertensive patients: Evidence from observational studies




Zhao Clin Exp Hypertens 2018

# Breast cancer and spironolactone: an observational postmarketing study

Table 1 Main characteristics of the studied population (women ≥ 50 years exposed or not to spironolactone) in the World Health Organization (WHO) pharmacovigilance database VigiBase® since 1981

| Spironolactone versus non-users | No bias controlled (N = 3,665,573) | | | | | Without competition* (N = 3,551,633) | | | | | Without competition* and without reports from non-health professionals (N = 1,748,950) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Non-exposed (N = 3,631,413) | | Exposed (N = 34,160) | | p | Non-exposed (N = 3,518,888) | | Exposed (N = 32,745) | | p | Non-exposed (N = 1,725,848) | | Exposed (N = 23,102) | | p |
| Age (mean ± SD) (min–max) | 66.1 (50.0–133.0) | ± 10.7 | 71.8 (50.0–104.0) | ± 11.3 | < 0.001 | 66.3 (50.0–133.0) | ± 10.8 | 72.1 (50.0–104.0) | ± 11.2 | < 0.001 | 66.9 (50.0–133.0) | ± 11.0 | 73.2 (50.0–104.0) | ± 11.2 | < 0.001 |
| Number of drugs (mean ± SD) (min–max) | 2.8 (1.0–108.0) | ± 3.1 | 8.4 (1.0–95.0) | ± 6.0 | < 0.001 | 2.7 (1.0–103.0) | ± 3.0 | 8.2 (1.0–76.0) | ± 5.7 | < 0.001 | 3.0 (1.0–90.0) | ± 3.3 | 8.0 (1.0–76.0) | ± 5.5 | < 0.001 |
| Completeness score (mean ± SD) (min–max) | 0.5 (0.0–1.0) | ± 0.2 | 0.6 (0.0–1.0) | ± 0.2 | < 0.001 | 0.5 (0.0–1.0) | ± 0.2 | 0.6 (0.0–1.0) | ± 0.2 | < 0.001 | 0.6 (0.0–1.0) | ± 0.3 | 0.6 (0.0–1.0) | ± 0.2 | < 0.001 |
| Continent of report (N (%)) | | | | | | | | | | | | | | | |
| Africa | 18,527 | 0.5 | 179 | 0.5 | < 0.001 | 18,113 | 0.5 | 176 | 0.5 | < 0.001 | 15,513 | 0.9 | 133 | 0.6 | < 0.001 |
| Americas | 1,709,312 | 47.1 | 12,823 | 37.5 | | 1,631,851 | 46.3 | 11,754 | 35.9 | | 619,078 | 35.9 | 5681 | 24.6 | |
| Asia | 794,337 | 21.9 | 3997 | 11.7 | | 790,746 | 22.5 | 3919 | 12.0 | | 273,723 | 15.9 | 2715 | 11.7 | |
| Europe | 1,000,286 | 27.5 | 16,292 | 47.7 | | 973,155 | 27.7 | 16,046 | 49.1 | | 757,447 | 43.9 | 13,967 | 60.5 | |
| Oceania | 108,951 | 3.0 | 869 | 2.5 | | 105,023 | 3.0 | 830 | 2.5 | | 60,087 | 3.4 | 606 | 2.6 | |
| Spironolactone versus pseudo-aldosterone antagonists | No bias controlled (N = 73,683) | | | | | Without competition* (N = 69,257) | | | | | Without competition* and without reports from non-health professionals (N = 42,592) | | | | |
| | Non-exposed (N = 33,835) | | Exposed (N = 39,853) | | p | Non-exposed (N = 32,449) | | Exposed (N = 36,808) | | p | Non-exposed (N = 22,921) | | Exposed (N = 19,671) | | p |
| Age (mean ± SD) (min–max) | 71.8 (50.0–104.0) | ± 11.3 | 69.87 (50.0–102.0) | ± 10.5 | < 0.001 | 72.1 (50.0–104.0) | ± 11.2 | 70.4 (50.0–102.0) | ± 10.5 | < 0.001 | 73.2 (50.0–104.0) | ± 11.2 | 70.7 (50.0–102.0) | ± 10.6 | < 0.001 |
| Number of drugs (mean ± SD) (min–max) | 8.4 (1.0–91.0) | ± 5.9 | 5.53 (1.0–99.0) | ± 4.2 | < 0.001 | 8.1 (1.0–76.0) | ± 5.6 | 5.3 (1.0–99.0) | ± 3.9 | < 0.001 | 8.0 (1.0–76.0) | ± 5.4 | 5.4 (1.0–69.0) | ± 3.9 | < 0.001 |
| Completeness score (mean ± SD) (min–max) | 0.6 (0.0–1.0) | ± 0.2 | 0.53 (0.0–1.0) | ± 0.2 | < 0.001 | 0.6 (0.0–1.0) | ± 0.2 | 0.5 (0.0–1.0) | ± 0.2 | < 0.001 | 0.6 (0.0–1.0) | ± 0.2 | 0.6 (0.0–1.0) | ± 0.2 | < 0.001 |
| Continent of report (N (%)) | | | | | < 0.001 | | | | | < 0.001 | | | | | < 0.001 |
| Africa | 174 | 0.5 | 202 | 0.5 | | 171 | 0.5 | 191 | 0.5 | | 128 | 0.6 | 179 | 0.9 | |
| Americas | 12,692 | 37.5 | 16,984 | 42.6 | | 11,646 | 35.9 | 14,718 | 40.0 | | 5641 | 24.6 | 5071 | 25.8 | |
| Asia | 3993 | 11.8 | 874 | 2.2 | | 3985 | 12.1 | 873 | 2.4 | | 2713 | 11.8 | 755 | 3.8 | |
| Europe | 16,115 | 47.6 | 19,701 | 49.4 | | 15,895 | 49.0 | 19,039 | 51.7 | | 13,839 | 60.4 | 11,949 | 60.7 | |
| Oceania | 861 | 2.6 | 2092 | 5.3 | | 822 | 2.5 | 1987 | 5.4 | | 600 | 2.6 | 1717 | 8.7 | |

Sabatier Eur J Clin Pharmacol 2019

## A cohort study of antihypertensive treatments and risk of renal cell cancer

**Table 3** Relative rates (RR) and 95% confidence intervals (CI) for the relation between antihypertensive medication use and renal cell cancer (RCC) by years of follow-up in North Jutland County, 1989–2002

| | <1 year | | | | 1–4 years | | | | 5+ years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Years of follow-up | Number RCC | Person-years | RR[a] | 95% CI | Number RCC | Person-years | RR[a] | 95% CI | Number RCC | Person-years | RR[a] | 95% CI |
| Any hypertensive | 33 | 95 484 | 2.0 | (1.4–2.9) | 89 | 323 680 | 1.6 | (1.2–2.0) | 69 | 287 264 | 1.4 | (1.0–1.8) |
| ACE inhibitor | 12 | 26 154 | 2.3 | (1.3–4.2) | 30 | 71 859 | 2.2 | (1.5–3.2) | 10 | 49 084 | 1.1 | (0.6–2.1) |
| Angiotensin II antagonis | | | | | | | | | | | 0.0 | — |
| Beta blocker | | | | | | | | | | | 1.4 | (0.9–2.1) |
| Calcium antagonist | | | | | | | | | | | 1.2 | (0.7–2.0) |
| Diuretic | | | | | | | | | | | 1.4 | (1.0–1.9) |
| Thiazides | | | | | | | | | | | 1.1 | (0.7–1.8) |
| Sulphonamides and other low-ceiling diur | | | | | | | | | | | 1.7 | (0.7–4.1) |
| Loop (high-ceiling) diuretics | 17 | 30 512 | 2.5 | (1.5–4.1) | 37 | 84 227 | 2.1 | (1.5–3.0) | 16 | 53 572 | 1.6 | (0.9–2.7) |
| Potassium-sparing agents | 9 | 6338 | 6.0 | (3.1–11.8) | 5 | 14 607 | 1.5 | (0.6–3.7) | 1 | 9606 | 0.5 | (0.1–3.6) |
| Diuretics and potassium-sparing agents in combination | 5 | 13 457 | 2.1 | (0.9–5.1) | 12 | 48 587 | 1.4 | (0.8–2.5) | 8 | 49 393 | 0.9 | (0.4–1.8) |

[a]All analyses adjusted for age, gender and calendar period.

**none of the AHTs studied was consistently associated with risk of RCC, and analyses by duration of follow up and number of prescriptions indicated that it is unlikely that any of these medications plays an important role in the aetiology of RCC.**

Fryzech BJC 2005

# Antihypertensive drugs and pancreatic cancer risk in patients with chronic pancreatitis: a Danish nationwide population based cohort study

**Table 1.** Risk of pancreatic cancer in 8,311 patients diagnosed with chronic pancreatitis in Denmark during 1996–2012 according to exposure to antihypertensive drugs

| | Events | Person-years | Incidence rate[a] | Crude HR | Adjusted HR[b] |
|---|---|---|---|---|---|
| *ACE inhibitor* | | | | | |
| Non-users | 134 | 52,828 | 2.56 (2.14–3.00) | 1.00 (reference) | 1.00 (reference) |
| Users | 19 | 7,536 | 2.52 (1.61–3.95) | 1.10 (0.68–1.77) | 0.81 (0.49–1.33) |
| *Aldosterone receptor antagonist*[c] | | | | | |
| Non-users | | | | | rence) |
| Users | | | | | –1.75) |
| *Angiotensin-II rec* | | | | | |
| Non-users | | | | | rence) |
| Users | | | | | –1.66) |
| *Beta-blocker* | | | | | |
| Non-users | 139 | 54,865 | 2.53 (2.15–2.99) | 1.00 (reference) | 1.00 (reference) |
| Users | 14 | 5,450 | 2.55 (1.51–4.30) | 1.07 (0.62–1.86) | 0.83 (0.47–1.47) |
| *Calcium channel blocker*[c] | | | | | |
| Non-users | >140 | 58,678 | 2.47 (2.10–2.91) | 1.00 (reference) | 1.00 (reference) |
| Users | <10 | 1,686 | 4.7[*c] (2.37–9.49) | 1.96 (0.96–4.00) | 1.56 (0.76–3.22) |
| *Diuretics* | | | | | |
| Non-users | 122 | 54,411 | 2.37 (1.99–2.83) | 1.00 (reference) | 1.00 (reference) |
| Users | 31 | 8,954 | 3.46 (2.43–4.92) | 1.50 (1.09–2.22) | 1.09 (0.71–1.69) |

[a]Per 1,000 person-years
[b]Adjusted for age (restricted cubic spline with three knots), sex, socioeconomic status, year of chronic pancreatitis diagnosis, Gagne Comorbidity score and use of other antihypertensive drugs
[c]Numbers collapsed for confidentiality
*Final number collapsed for confidentiality

**We did not observe any clinically relevant association between use of antihypertensive drugs and pancreatic cancer risk in patients with chronic pancreatitis.**

Kjrkegard BJC 2019

# Intriguing relationship between antihypertensive therapy and cancer

**Table 2**

Mechanisms of adverse and protective effect of different antihypertensive medications and pitfalls of investigated studies.

| Mechanisms of adverse effects | Mechanisms of protective effects | Pitfalls of included studies for all antihypertensive groups |
|---|---|---|
| **Angiotensin-converting enzyme inhibitor/ angiotensin II-receptor blocker** | | |
| • Different angiotensin I-converting enzyme genotypes<br>• AT1 receptors blockade with an ARB stimulate tumor angiogenesis | • Different angiotensin I-converting enzyme genotypes<br>• Blockade of angiogenesis<br>• Blockade of proliferation and inflammation | • Heterogeneity of studies<br>• Comorbidities<br>• Confounding factors (obesity, diabetes, smoking, concomitant therapy including chemotherapy and hormonal therapy, family history, sun exposure, professional exposure to carcinogens, lifestyle, diet, physical activity, diet, socio-economic status)<br>• Medications could be used for other indication (e.g. fluid retention) and not only as antihypertensive therapy<br>• Antihypertensive monotherapy is rare and it is difficult to distinguish effect of 2 or more concomitant antihypertensive drugs<br>• Interaction with other medications commonly prescribed in the cancer patients including corticosteroids, non-steroid anti-inflammatory drugs, as well as chemotherapeutic agents<br>• Compliance to antihypertensive medications was not determined and therefore one could not know if patients took therapy regularly or not<br>• Immortal-time bias<br>• Recall bias (questioner used for information about antihypertensive therapy and presence of hypertension)<br>• Misclassification bias (particularly in skin cancer patients)<br>• No clinical trials, only case-report studies and meta-analyses of these studies<br>• Studies investigated the whole group of antihypertensive medications and not each drug separately |
| **Calcium-channel blockers** | | |
| • CCB could inhibit cell apoptosis, which potentially could induce cancer development<br>• Some CCBs are associated with photosensitivity | • Inhibit proliferation of calcium-dependent neoplastic cells<br>• Decrease inflammation | |
| **Beta-blockers** | | |
| • Some BBs are photosensitizers<br>• Combination with other antihypertensive medications (diuretics or ACEI/ARB) | • By inhibition of sympathetic nervous system BBs decrease production of growth factors responsible for cancer occurrence, recurrence and dissemination<br>• Inhibition of tumor cell invasion, tumor-related inflammation, and vascular remodeling<br>• Inhibition of beta-2 receptors essential for modulation of cancer outcome | |
| **Diuretics** | | |
| • Photosensitivity<br>• Association with insulin resistance<br>• Combination with other antihypertensive medications | • Not known | |

ACEI – angiotensin-convertin enzyme inhibitor, ARB - angiotensin II-receptor blocker, BB – beta-blocker, CCB –calcium-channel blockers.

Grassi Pharmacol Res 2019


WORLD HYPERTENSION DAY
17 OTTOBRE
XVI Giornata Mondiale contro l'Ipertensione
17 Ottobre 2020
Campagna Mondiale di Sensibilizzazione
per la Lotta all'Ipertensione Arteriosa
MISURA E CONTROLLA LA TUA PRESSIONE PER VIVERE PIÙ A LUNGO
federfarma
SCITEC
UNIFAR
www.siia.it