



Review

Cardiovascular drugs-induced oral toxicities: A murky area to be revisited and illuminated

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ABSTRACT

Oral health is an imperative part of overall human health. Oral disorders are often unreported, but are highly troublesome to human health in a long-standing situation. A strong association exists between cardiovascular drugs and oral adverse effects. Indeed, several cardiovascular drugs employed clinically have been reported to cause oral adverse effects such as xerostomia, oral lichen planus, angioedema, aphthae, dysgeusia, gingival enlargement, scalded mouth syndrome, cheilitis, glossitis and so forth. Oral complications might in turn worsen the cardiovascular disease condition as some reports suggest an adverse correlation between periodontal oral disease pathogenesis and cardiovascular disease. These are certainly important to be understood for a better use of cardiovascular medicines and control of associated oral adverse effects. This review sheds lights on the oral adverse effects pertaining to the clinical use of cardiovascular drugs. Above and beyond, an adverse correlation between oral disease and cardiovascular disease has been discussed.

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1. Introduction

Cardiovascular disorders are major causes of morbidity and mortality worldwide. While we are acquainted with plenty of information about cardiovascular pathophysiology and pharmacotherapy [1], we are still in need of exploring more about

the adverse actions of cardiovascular drugs. Varieties of drugs employed clinically are known to induce oral illness [2]. In this review, we have selectively focused on cardiovascular drugs-associated oral adverse effects. The frequency of oral manifestations in patients receiving cardiovascular agents was reported to be 14.1% with xerostomia being the most common one among others [3]. Cardiovascular medications can cause oral adverse effects such as xerostomia, lichen planus, aphthous ulcers

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angioedema, dysgeusia, gingival enlargement, scalded mouth syndrome, cheilitis, glossitis and pemphigus. Important class of cardiovascular drugs known to cause oral adverse effects includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-AT₁ receptor blockers (ARBs), diuretics, calcium channel blockers (CCBs), beta-adrenergic blockers and alpha-adrenergic blockers [4,5]. In addition, anti-arrhythmics like phenytoin and amiodarone, and also potassium channel opener like nicorandil can cause oral adverse effects [4–7]. Other drugs such as aliskiren (direct renin inhibitor) and clopidogrel (antiplatelet agent) have also been shown to cause oral adverse effects [8,9]. The induction of oral complications might undesirably affect the beneficial clinical outcomes of cardiovascular drugs. We reviewed in detail the oral adverse effects caused by cardiovascular drugs. In addition, we discussed the adverse correlation between oral diseases and cardiovascular diseases.

2. Xerostomia: dry mouth

Xerostomia is not a disease, but is the subjective sensation of dry mouth, which occurs as a result of reduced secretion and flow of saliva. Dry mouth is likely to induce harmful effects to teeth, oral mucosa and in fact the general health. The estimated incidence of dry mouth is in between 10% and 26% in men, and 10% and 33% in women, which might or might not be because of reduced saliva secretion [10,11]. Women reported higher prevalence of dry mouth than men [12]. Moreover, incidence of xerostomia is age-related [12]. Saliva plays an integral role in maintaining the oral health as it lubricates the mouth to facilitate speech, maintains tooth enamel, neutralizes damaging food and bacterial acids, and helps in softening the food for easier chewing and swallowing, while the antibacterial, antifungal and antiviral agents in saliva help prevent oral infections [11]. Therefore, dry mouth could markedly affect the oral health. Various etiologies have been attributed to xerostomia of which the most common one being the side effect of using certain medications. The symptoms of xerostomia, commonly called as dry mouth, might be encountered in patients taking medications [13].

Salivary gland secretion is regulated by autonomic nervous system where the fluid component is generally produced by parasympathetic stimulation while the protein component is released in response to sympathetic stimulation [14]. Despite the fact that dry mouth has a variety of possible causes, use of medications possibly those with anticholinergic activity against M3 muscarinic receptors is one of the common causes of reduced salivation [14]. A number of cardiovascular drugs can cause dry mouth as an adverse effect (Fig. 1). However, it is unclear whether all those cardiovascular drugs causing dry mouth can affect the cholinergic system. Below we provide important examples of cardiovascular drugs that can cause dry mouth.

An antihypertensive drug, clonidine, a centrally acting alpha-2 adrenergic agonist and imidazoline receptor agonist, is well-known to cause dry mouth as a common adverse effect [15]. Other centrally acting antihypertensives such as guanfacine and alpha methyl dopa induce peripheral sympathetic inhibition as a result of alpha-2 adrenoceptor stimulation in the brain stem, and both drugs have a tendency of causing dry mouth as an adverse effect [15]. Since this adverse effect is mainly mediated through alpha 2 adrenergic receptor stimulation, it has been suggested that it would fundamentally be impossible to detach the adverse effect from the desired centrally-mediated blood pressure-lowering effects of centrally acting antihypertensives [16].

Alpha and beta-adrenergic blockers are employed for the management of hypertension. Of note, treatment with alpha-blocker like terazosin significantly reduced systolic and diastolic blood

pressure in benign prostatic hyperplasia patients, but caused dry mouth as an adverse effect [17]. In healthy volunteers and hypertensive patients, the effects of beta-blockers on saliva flow rate and composition were evaluated [12]. One week treatment with beta-blockers (propranolol or atenolol) in healthy volunteers affected the salivary composition but not saliva flow rates, while the total protein composition and amylase activity were noted to be significantly decreased during treatment with any of antagonists whereas atenolol treatment showed more accentuated action [12]. The observed effects on salivary composition in hypertensive patients treated with a beta 1-selective blocker (metoprolol) were essentially the same to that of healthy volunteers [12]. On the other hand, the whole saliva flow rate was noted to be significantly increased on drug withdrawal but decreased again on reintroduction to metoprolol in hypertensive patients [12,18]. These results implicate the possible correlation of alpha and beta-adrenergic blockers in inducing dry mouth.

ACE inhibitors are potent agents for the management of hypertension and congestive heart failure. ACE inhibitors (captopril, enalapril, lisinopril) have been reported to cause xerostomia [19]. Likewise, evidence supports that ARBs like losartan and eprosartan can, but less commonly, cause dry mouth [20,21].

Diuretics are the commonly used class of drugs for the management of hypertension and congestive heart failure. The use of diuretics is associated with an induction of dry mouth. An increase in urinary output during diuretics treatment might be a reason behind diuretics-associated dry mouth. The loop diuretic, furosemide has been reported to cause xerostomia. Furosemide oral treatment in normal individuals resulted in a five-fold increase in urinary output [22]. However, no significant difference in salivary flow rates and total protein concentrations was noted following the drug or placebo administration while xerostomia was experienced 10 times more frequently after having administered furosemide [22], suggesting that renal effect might directly play a role in diuretic-associated oral dryness. Nevertheless, treatment with thiazide diuretic, bendroflumethiazide in a low-dose was noted to significantly reduce the stimulated whole salivary flow rate and total sodium output in healthy volunteers [23], indicating the involvement of an additional mechanism accompanying to diuretics-associated dry mouth. Adding to this, Nederfors et al. [24] reported that in resting whole saliva, the output of sodium and chloride tended to decrease especially during bendroflumethiazide treatment, while in submandibular-sublingual secretion the output of all electrolytes was decreased, mainly for potassium and chloride and during the furosemide treatment. Of note, xerostomia tended to increase during furosemide treatment that was statistically significant at lunch time during chronic treatment [24]. The study demonstrated a modest effect on salivary flow rate, but a more pronounced effect on saliva composition in healthy volunteers treated with diuretics [24]. It is worth mentioning that diuretics significantly reduce salivary flow rates and alter salivary composition, which might have an impact on the incidence of dental caries, periodontal diseases and mucosal lesion formation [25].

CCBs are employed for the management of hypertension, cardiac arrhythmia and stable angina. Nifedipine, verapamil and diltiazem are a few commonly used CCBs for the management of cardiovascular disorders. They can cause dry mouth by inhibiting salivary secretion [26,27]. Hattori and Wang, [27] explicated a mechanism by which CCBs could cause dry mouth. The authors suggested that non-selective cation and voltage-dependent Ca²⁺ channels are involved in the resting salivation while CCBs can depress H₂O secretion by blocking Ca²⁺ channels and by this means can cause dry mouth [27]. Taken together, aforementioned cardiovascular drugs have an oral adverse effect of causing dry mouth (Table 1).

Table 1

List of cardiovascular drugs causing oral adverse effects such as dry mouth, lichen planus and aphthous ulcers.

Cardiovascular drugs	Class	Oral adverse effects	First author (Refs. #)
Clonidine (antihypertensive)	Centrally acting alpha-2 adrenergic agonist	Dry mouth	van Zwieten [15]
Guanfacine, and alpha methyl dopa (antihypertensives)	Alpha-2 adrenoceptor stimulants	Dry mouth	van Zwieten [15]
Terazosin (antihypertensive)	Alpha adrenergic blocker	Dry mouth	Lee and Lee [17]
Captopril, enalapril, and lisinopril (antihypertensives)	ACE inhibitors	Dry mouth	Mangrella et al. [19]
Furosemide (antihypertensive)	Loop diuretic	Dry mouth	Atkinson et al. [22]
Nifedipine, verapamil, and diltiazem (antihypertensives)	Calcium channel blockers	Dry mouth	Krevsky et al. [26]; Hattori and Wang [27]
Labetalol (antihypertensive)	Mixed alpha/beta adrenergic antagonist	Lichen planus-like drug eruptions	Fessa et al. [32]
Alpha methyl dopa (antihypertensive)	Alpha-2 adrenoceptor stimulant	lichen planus-like symptoms	Nair et al. [34]
Nicorandil (antianginal)	Potassium channel activator	Aphthous ulcers	Gupta and Morris [7]
Labetalol (antihypertensive)	Mixed alpha/beta adrenergic antagonist	Aphthoid stomatitis	Pradalier et al. [43]
Captopril (antihypertensive)	ACE inhibitor	Tongue ulceration	Nicholls et al. [44]
Losartan, candesartan and irbesartan (antihypertensives)	Angiotensin II-AT ₁ receptor blockers	Aphthous ulcers	Goffin et al. [45]; Chen et al. [46]; Manunza et al. [47]

3. Oral lichen planus

Oral lichen planus (OLP) is a chronic inflammatory disease in which the oral mucosa is affected. The etiology of the disease is not clear. OLP is the prototype of oral lichenoid lesions. Although there is a lack of valid epidemiological data, OLP is believed to be common, affecting about 1–2 % population [28]. OLP has been suggested to commonly affect middle-aged females [29]. The clinical manifestations of OLP are represented by rarely symptomatic bilaterally located white papules that form either a reticular, annular or plaque-like pattern. In addition, OLP can manifest with erythematous, erosive and ulcerative lesions [28]. The chronic course of OLP might be because of activation of the inflammatory mediator like nuclear factor- κ B [28].

Although the cause is not clearly known, the use of few cardiovascular medicines might produce oral and cutaneous lesions that resemble OLP (Fig. 1). It was suggested that impaired function of polymorphic cytochrome 450-enzymes (CYPs) might cause increased plasma concentration of some drugs resulting in lichenoid drug eruptions; however, a study by Kragelund et al. [30] did not find more patients with OLP with impaired CYP-genotype [30]. The OLP and oral lichenoid drug reactions have similar clinical and histologic findings [31]. Oral lichenoid drug reaction has been associated with the use of antihypertensive drugs [31]. A recent study reported beta-adrenoceptor antagonist-associated lichen planus-like drug eruptions (LDE) with a widespread, violaceous, papular and generalized exanthema with histologic features of a lichenoid reaction, which subsequently resolved with cessation of labetalol [32]. There were number of cases of previously reported beta-adrenoceptor antagonist-associated LDE, which was suggested to be present as classic lichenoid papules and had a preference for the limbs, chest, back and the oral mucosa [32]. Alpha methyl dopa (antihypertensive agent) and quinidine (antiarrhythmic agent) are among others that can cause lichen planus-like symptoms [33,34]. Likewise, CCB like amlodipine might cause OLP [35]; however, evidence is not available to support its class effect. Although there are few reports available in the literature (Table 1), more scientific evidences are needed to support the induction of OLP by cardiovascular drugs.

4. Aphthous ulcers

The term “aphthous” has been derived from a Greek word “*aphthae*” meaning ulceration. Aphthous ulcers are characterized by multiple, recurrent, small and round ulcers with circumscribed margins and erythematous haloes present in different size [36,37].

The projected point prevalence of oral ulcers worldwide is 4% with aphthous ulcers being the common one affecting around 25% of the population worldwide [37]. Aphthous mouth ulcers recur from time to time while the ulcers might usually heal without treatments in 10–14 days [38]. The etiology of aphthous ulcers is not precisely known. Aphthous ulcers have a substantial negative impact on the oral health affecting the quality of life. Few cardiovascular medicines might cause aphthous as an adverse effect (Table 1).

Nicorandil, a potassium channel activator, is employed for the management of angina pectoris. It has been reported to cause major aphthous ulcers [7]. Nicorandil is a potential inducer of severe mouth ulceration. It precipitates persistent ulcerative stomatitis in some patients [39,40]. The oral lesions, however, were noted to heal spontaneously after withdrawal of nicorandil [7]. Of note, a recent case study reported nicorandil-induced tongue ulceration with *Candida* infection [41]. Importantly, discontinuation of nicorandil failed to ameliorate the lesion whereas the second discontinuation of the drug after the control of *Candida* infection overlying the surface of the ulcer was noted to produce a favorable effect [41].

An association between beta-blockers and aphthous ulcers has also been reported [42]. Evidence supports that labetalol use has been associated with aphthoid stomatitis [43]. In addition, tongue ulceration has been reported to be associated with captopril, an ACE inhibitor [44]. Moreover, aphthous ulcers of the mouth may be associated with the use of ARBs like losartan and candesartan [45,46]; however, no strong evidence is available to further support it. Recently, a case of recurrent aphthous stomatitis due to irbesartan has also been reported [47], implicating the role of ARBs in aphthous induction. Furthermore, although CCBs have not been well reported to cause oral ulcerations, there is an evidence of recalcitrant oral ulcers caused by CCBs [48]. Importantly, these recalcitrant oral ulcers failed to heal in spite of interventions such as surgery, laser ablation and topical and systemic steroid therapy [48]. This might not be a class effect, and more studies are needed to confirm the incidence of recalcitrant oral ulcers by CCBs.

5. Angioedema

Angioedema is an extreme temporary swelling of a localized body area involving skin, mucosa and subcutaneous tissues. Areas that are commonly affected by angioedema include face, lips, tongue and pharynx [49]. ACE inhibitors are known to cause angioedema. In case of ACE inhibitors-induced angioedema, the tongue and the mucous membranes of oropharynx and perio-

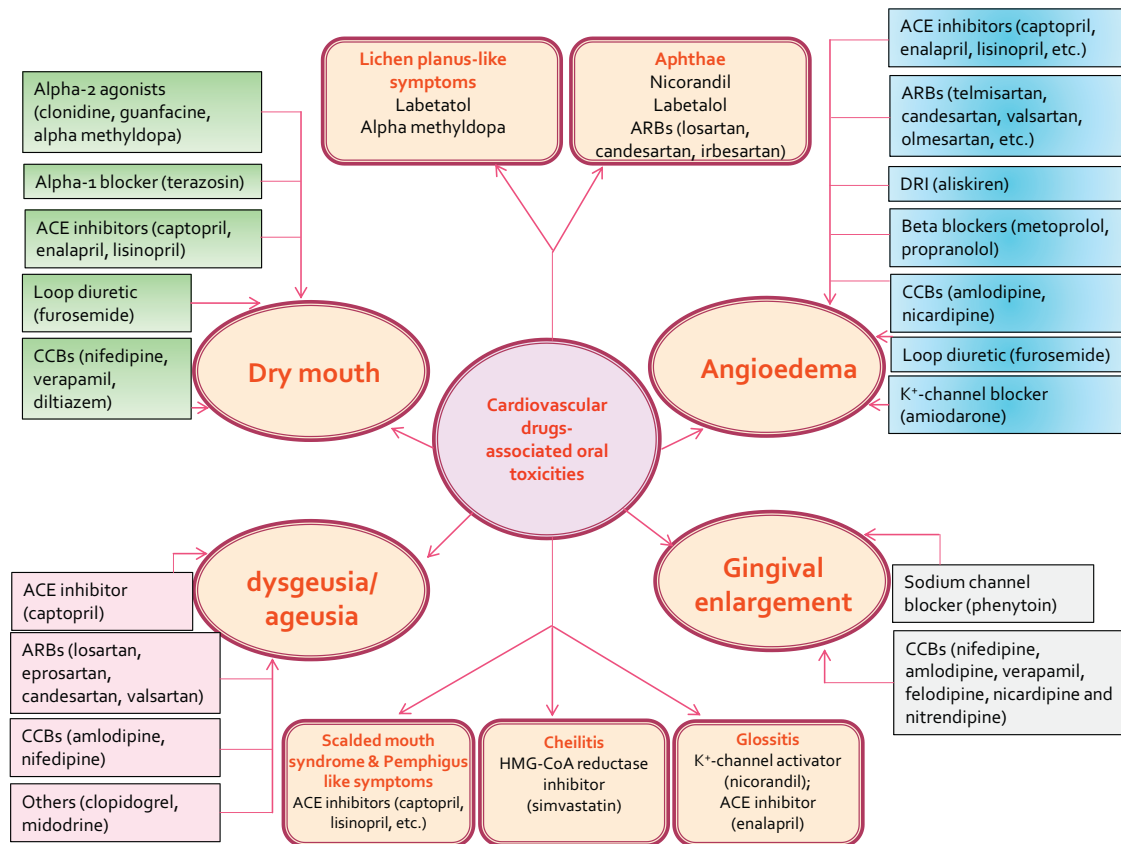


Fig. 1. Cardiovascular drugs-associated oral adverse effects.

ACE = angiotensin-converting enzyme; ARBs = angiotensin II-AT₁ receptor blockers; CCBs = calcium channel blockers; DRI = direct renin inhibitor; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

Table 2

List of cardiovascular drugs and associated angioedema.

Cardiovascular drugs	Class	Oral adverse effects	First author (Refs. #)
Captopril, enalapril and lisinopril (antihypertensives)	ACE inhibitors	Angioedema (class effect)	Maier [53]; Garcia-Pavia et al. [55]
Telmisartan, candesartan, valsartan, olmesartan (antihypertensives)	Angiotensin II-AT ₁ receptor blockers	Angioedema	Lo [59], Irons and Kumar [60]; Nykamp and Winter [61]; Yusuf et al. [62]
Aliskiren (antihypertensive)	Direct renin inhibitor	Angioedema	Ali [9]
Metoprolol and propranolol (antihypertensives)	Beta-adrenergic blockers	Angioedema	Krikorian et al. [67]; Márquez-Saavedra et al. [68]
Amlodipine and nicardipine (antihypertensives)	Calcium channel blockers	Angioedema	Southward et al. [70]; Pierce et al. [71]
Amiodarone (antiarrhythmic)	Potassium channel blocker- Class III antiarrhythmic	Facial angioedema	Lahiri et al. [6]; Burches et al. [73]
Furosemide (antihypertensives)	Loop diuretic	Facial angioedema	Domínguez-Ortega et al. [74]

ral regions are the most common sites of involvement [50]. ACE inhibitors-induced angioedema is unaccompanied by hives, and is caused by bradykinin accumulation because of the inhibition of enzymatic degradation of tissue bradykinin [51]. In addition, cardiovascular drugs-induced angioedema (Table 2) could occur with the use of ARBs, renin inhibitor, beta-blockers, CCBs and diuretics [52]. Among these cardiovascular pharmacological interventions, ACE inhibitors are the most frequently reported class of drugs causing angioedema (Fig. 1).

Angioedema occurs in 0.1–0.5% of patients taking ACE inhibitors like captopril, enalapril, lisinopril, etc. [53]. The reason behind why a few individuals, but not all, on ACE inhibitor therapy develop angioedema is not precisely understood. It was suggested that patients developing angioedema during ACE inhibitor therapy might be those with a congenital or acquired impairment in the

activity of kininase I, which degrades bradykinin, resulting in significant accumulation of bradykinin once ACE (also called as kininase II) activity is blocked [54]. ACE inhibitors-induced angioedema usually appears during the first week of treatment [55]. It was however suggested that angioedema might occur at any time during the long-term use of ACE inhibitor like enalapril [56]. Of note, continuing the use of ACE inhibitors in spite of angioedema incidence could result in a markedly increased rate of angioedema recurrence with serious morbidity [57]. Therefore, ACE inhibitors therapy should be stopped if angioedema develops, while alternative therapy might be considered.

ARBs have previously been proposed to be an alternative class of drugs for hypertension management in those patients having a past history of angioedema incidence with ACE inhibitors. This is because of a theoretical advantage of ARBs having no direct

Table 3

List of cardiovascular drugs causing oral adverse effects such as dysgeusia and gingival enlargement.

Cardiovascular drugs	Class	Oral adverse effects	First author (Refs. #)
Captopril (antihypertensive)	ACE inhibitor	Taste disturbance/ dysgeusia	Coulter [78]; Boyd [79]
Losartan, eprosartan, candesartan and valsartan (antihypertensives)	Angiotensin II-AT ₁ receptor blockers	Taste disturbance/ dysgeusia	Heeringa and van Puijenbroek [85]; Castells et al. [86]; Tsuruoka et al. [87]
Amlodipine and nifedipine (antihypertensives)	Calcium channel blockers	Taste disturbance/ dysgeusia	Sadasivam and Jhaj [88]
Midodrine (vasopressor and antihypotensive agent)	Alpha-adrenoceptor agonist	Taste disturbance/ dysgeusia	Young and Mathias [89]
Clopidogrel (antiplatelet agent)	Oral thienopyridine class	Reversible loss of taste (ageusia)	Cave et al. [8]
Phenytoin (anti-arrhythmic drug)	Sodium channel blocker and a Class-I anti-arrhythmic drug	Gingival enlargement	Chacko and Abraham [92]
Nifedipine, amlodipine, verapamil, felodipine, nicardipine and nitrendipine (antihypertensives)	Calcium channel blockers	Gingival enlargement	Sam and Sebastian [97]; Lafzi et al. [98]; Bhatia et al. [99]; Mehta et al. [100]; Lombardi et al. [101]; Maguin et al. [103]; Brown et al. [104]

action on bradykinin accumulation. However, it is important to note that losartan, an ARB, in hypertensive patients, increased bradykinin levels, which were suggested to be the result of a reduced metabolism by ACE and neutral endopeptidase [58]. Campbell et al. [58] suggested that increased bradykinin levels might represent a class effect of ARBs that could contribute to angioedema during an ARB therapy. For instance, there are reports supporting the incidence of angioedema with ARBs like telmisartan, candesartan, valsartan and olmesartan [59–62]. Of note, in patients with vascular disease or high-risk diabetes mellitus, telmisartan had lower rates of angioedema as compared to ramipril (0.1% vs. 0.3%) [62].

The precise mechanism involved in ARB-induced angioedema remains obscure since bradykinin was believed not to be affected during ARB therapy. However, as discussed above, bradykinin level is increased during ARB therapy [58]. It was proposed that a secondary stimulation of unblocked angiotensin-II AT₂ receptors might produce increased tissue bradykinin, which could result in angioedema during ARB therapy [61].

Another category of the drug acting on renin-angiotensin-aldosterone system is aliskiren, a direct renin inhibitor, approved by the US FDA for the management of hypertension [1,63]. Like ACE inhibitors and ARBs, the use of aliskiren is also associated with an incidence of angioedema [9]. These classes of medications (ACE inhibitors, ARBs and the renin inhibitor) should be discontinued if symptoms of angioedema ensue. All three drug classes are associated with an incidence of angioedema, while the relative risks were suggested to be lower for adults taking ARBs (hazard ratio 1.16, 1.00 to 1.34) than for those taking ACE inhibitors (3.04, 2.81 to 3.27) or aliskiren (2.85, 1.34 to 6.04) [64]. Physicians might therefore not be deterred from recommending an ARB as an alternate to patients experiencing angioedema with an ACE inhibitor because of the benefits on blood pressure control and albuminuria reduction in selected patients [65] like hypertensive diabetics. However, patients intolerant to either an ACE inhibitor or a renin inhibitor (experiencing angioedema) beginning with an ARB therapy should be monitored carefully and be provided counseling for the possibility of incidence of angioedema again.

Beta adrenergic blockers inhibit the renin-angiotensin system by inhibiting renin secretion [66]. Evidence supports the incidence of angioedema with beta-blockers like metoprolol and propranolol [67,68]. A retrospective, observational, inception cohort study, of patients 18 years or older who had initiated the use of an ACE inhibitor, an ARB, aliskiren, or a β -blocker, determined the cumulative incidence and incidence rate of angioedema during a maximal 365-day follow-up period [69]. The cumulative incidences per 1000 persons were 1.79 cases for ACE inhibitors, 0.62 cases for ARBs, 1.44 cases for aliskiren, and 0.58 cases for beta-blockers. In addition,

the incidence rates per 1000 person-years were 4.38 cases for ACE inhibitors, 1.66 cases for ARBs, 4.67 cases for aliskiren and 1.67 cases for beta-blockers [69]. This study concluded that ACE inhibitors or aliskiren were associated with an approximately 3-fold higher risk for angioedema as compared to beta-blockers while the risk for angioedema was lower with ARBs than did ACE inhibitors or aliskiren [69].

Other cardiovascular drugs reported to possibly induce angioedema include calcium channel blockers like amlodipine and nicardipine [70,71], antiplatelet agent like clopidogrel [72], amiodarone, an antiarrhythmic agent (causing facial angioedema) [6,73], and furosemide (causing facial angioedema) [74].

6. Taste disturbance-dysgeusia

Taste perception significantly contributes to sense of well-being and satisfactory life of a person, while dysgeusia (a distortion of the sense of taste) is a kind of uneasiness and discomfort during food intake. Dysgeusia could certainly affect the quality of life since the sense of taste is an essential component of overall health of an individual. Taste disturbance could therefore hamper the life quality of a person by influencing appetite, body weight and psychological well-being [75] that might require discontinuation of drug administration. Drug-induced taste disorders might involve different mechanisms, including dysfunction of taste buds or neurons involving the ion channels [76]. Few cardiovascular drugs are known to cause taste disturbance as one of adverse reactions (Table 3); however, the precise mechanism involved in it is obscure.

It has been previously suggested that 36% of antihypertensive and antihyperlipidemic drugs produce untoward changes in chemosensory perception, which could adversely affect the quality of life [77]. The clinical use of ACE inhibitors like captopril is associated with taste disturbance [78,79]. This may not be a class effect since taste disturbance was rarely observed with other ACE inhibitors such as lisinopril and benazepril [80,81]. Likewise, no enalapril-related dysgeusia has been reported in high-risk hypertensive patients [82]. Captopril is the one among ACE inhibitors that has been well-reported to cause taste disturbance. Taste impairment due to captopril has been suggested to be reversible and usually self-limited to 2–3 months, while weight loss might be associated with the loss of taste [83]. Although the precise mechanism involved is unknown, it was proposed that the inhibition of ACE by the drug might affect the zinc of the ACE protein in salivary gland cells, which might subsequently cause taste alteration [84].

Like captopril, ARBs also cause taste disturbance. Losartan was reported to be associated with reversible dysgeusia [85]. Likewise, there is an evidence of incidence of dysgeusia and burning mouth syndrome induced by eprosartan [86]. Tsuruoka et al. [84] reported

Table 4

List of cardiovascular drugs and associated oral adverse effects such as scalded mouth syndrome, cheilitis, glossitis and pemphigus like symptoms.

Cardiovascular drugs	Class	Oral adverse effects	First author (Refs. #)
Captopril, enalapril and lisinopril (antihypertensives)	ACE inhibitors	Scalded mouth syndrome	Vlasses et al. [106]; Savino and Haushalter [107]
Simvastatin (cholesterol-lowering agent)	HMG-CoA reductase inhibitor	Cheilitis	Mehregan et al. [108]
Nicorandil (antianginal)	Potassium channel activator	Glossitis	Farah et al. [110]
Enalapril (antihypertensive)	ACE inhibitor	Glossitis	Gavras [111]
Lisinopril, captopril, fosinopril and quinapril (antihypertensives)	ACE inhibitor	Pemphigus like symptoms	Baričević et al. [113]; Kaplan et al. [114]; Ong et al. [115]

that candesartan, an ARB, subclinically reduced the taste sensitivity after a repeated dosing in healthy subjects. The authors suggested, since similar events were reported for losartan and valsartan in case reports, taste disturbance might be a class effect of ARBs [84]. The taste disturbance-induced by candesartan was potentially similar to that of valsartan [87]. The mechanism involved in ARBs-induced taste disturbance remains to be elucidated. Of note, dysgeusia with losartan but not with ACE inhibitors occurred in the same patient, suggesting that ARBs and ACE inhibitors could cause this effect through different mechanisms [86].

Among CCBs, nifedipine and amlodipine were reported to be associated with an induction of dysgeusia [88]. Other drugs which might be noted here are midodrine, an alpha-adrenoceptor agonist, and clopidogrel, an oral thienopyridine class antiplatelet agent. The use of midodrine (a vasopressor and antihypotensive agent) might be associated with taste and smell disturbance while such association is likely to be dose-dependent [89]. Clopidogrel is indicated for secondary prevention in patients with widespread atherosclerosis and coronary artery disease. Reversible loss of taste (ageusia) has been reported as a side effect of clopidogrel [8].

7. Gingival enlargement

Gingival enlargement or gingival overgrowth is a preferred term for initially employed terms such as gingival hyperplasia (refers to an increased number of cells) or gingival hypertrophy (refers to an increase in the size of individual cells) [90]. Phenytoin and a variety of CCBs are known to produce gingival overgrowth (Table 3) as an adverse effect [90,91].

Phenytoin is a sodium channel blocker and a class-I anti-arrhythmic drug. It has number of therapeutic uses ranging from epileptic disorders to cardiac arrhythmia. Around 50% of patients on chronic therapy are likely to develop gingival overgrowth [92]. It might take 2–3 months to notice the overgrowth and 12–18 months to reach its maximal severity while the anterior teeth are more commonly involved as compared to posterior teeth with more involvement on the buccal surface [92]. In phenytoin-induced gingival overgrowth, the fundamental disturbance occurs in the gingival fibroblast where phenytoin and its metabolites have a direct action leading to a subsequent increase in collagen production [92]. Of note, gingival fibroblasts are able to metabolize phenytoin, determining the susceptibility of the patient to gingival enlargement induced by phenytoin [92].

Gingival enlargement is also a common adverse effect of some CCBs, characterized by an increase in the gingival mass and volume ranging from mild to severe [93]. It was suggested that patients treated with CCBs exhibited gingival hyperplasia similar to that of phenytoin cases [94]. The microscopic appearance of gingival enlargement associated with CCBs might not be obviously distinguished from those caused by phenytoin [93]. Nifedipine is the most important one among CCBs that was reported to cause gingival enlargement [95–97]. Other CCBs which have been shown to cause gingival enlargement are amlodipine [98,99], verapamil [100], felodipine [101,102], nicardipine [103], and nitrendipine

[104]. Cessation of CCBs and a timely shift to other class of anti-hypertensive agents might be needed to prevent the gingival deterioration. Overall, the pathogenesis of drug-induced gingival enlargement has not been precisely understood although some putative mechanisms exist in the literature.

8. Scalded mouth syndrome

Scalded mouth syndrome may be associated with a burning pain of oral soft tissues. A few case reports of scalded mouth syndrome have been reported with ACE Inhibitors (Table 4). This condition however was suggested to be a rare adverse effect of ACE inhibitors [105]. A scalded sensation of the oral mucosa during the treatment with captopril or enalapril was initially reported [106]. Thence, a case study reported that a hypertensive patient treated with lisinopril developed a burning sensation in lips and buccal mucosa while the symptoms were noted to be similar to that of scalded mouth syndrome associated with the use of ACE inhibitors like captopril and enalapril as previously reported [107]. This reaction to ACE inhibitors appeared dose-related whereas the reaction was reported to be subsided with a decreased dosage or drug discontinuation [107]. The possible mechanism involved in ACE inhibitors-associated scalded mouth syndrome is not known.

9. Cheilitis and glossitis

Cheilitis is an inflammation of the lips that can be manifested as dryness, itching, burning, erythema, fissuring and edema. The inflammation might occur in the perioral skin around the mouth and the vermilion border. Simvastatin, a cholesterol-lowering agent, has been reported to possibly induce cheilitis (Table 4) in patients with hyperlipidemia [108]. Of note, the rash resolved after drug discontinuation and subsequent treatment with topical moisturizers and topical corticosteroids [108]. Unpublished evidence indicates that phenytoin might also cause cheilitis [109]. Not much clinical data however is available to highlight the association of cardiovascular drugs and cheilitis.

Glossitis is an inflammation and soreness of tongue that may be associated with depapillation of the dorsal surface of tongue. Few evidences support the correlation of glossitis with cardiovascular drugs (Table 4). There have been reports of tongue ulceration and glossitis associated with the use of nicorandil [110]. Glossitis associated with upper respiratory tract infection has also been reported with the use of enalapril [111].

10. Pemphigus

Pemphigus is a group of bullous diseases affecting the oral mucosa and the skin. It is caused by antibody-mediated autoimmune reaction to desmogleins, desmosomal transmembrane glycoproteins [112]. Cardiovascular drugs-induced pemphigus-like lesions of oral mucosa has been reported in few studies (Table 4). ACE inhibitor, lisinopril was reported to induce pemphigus in a hypertensive patient by developing blisters and ulcerations on oral

mucosa [113]. Of note, immunofluorescence analysis revealed no autoantibodies, but histological study suggested an allergic reaction [113]. Pemphigus has also been reported with other ACE inhibitors such as captopril, fosinopril and quinapril [114,115].

11. Adverse correlation between oral diseases and cardiovascular diseases

Several studies have shown the adverse association between oral disease conditions and cardiovascular diseases like atherosclerosis and coronary heart disease. Oral infection and inflammatory condition like periodontitis are considered a risk factor for vascular endothelial dysfunction (VED) in patients with coronary artery disease [116]. Periodontitis is an oral infection characterized by gradual destruction of tooth supporting tissues [117]. Chronic periodontitis can alter vascular response and increase the expression of pro-inflammatory cytokines and adhesion molecules, resulting in induction of VED [117]. The VED refers to an impairment in the endothelium-dependent vasorelaxation that can occur as a result of downregulation or inactivation of endothelial nitric oxide synthase (eNOS) and subsequent reduction in the generation of endothelium-derived relaxing factor (NO, nitric oxide), leading to deregulation of vascular homeostasis [118,119]. NO has vasodilatory, antithrombotic, anti-oxidant and anti-inflammatory properties in vessels. The reduced generation of NO during VED could lead to cardiovascular abnormalities. The VED is a key event in the pathogenesis of cardiovascular disorders such as atherosclerosis, hypertension and coronary artery disease [119–121].

It was suggested that those with periodontitis had 25% increased risk of coronary heart disease as compared to those with minimal periodontal disease [122]. In addition, poor oral hygiene has also been associated with an increased incidence of coronary heart disease [122]. Worthy of note that periodontitis has been associated with VED in coronary artery disease patients through a decrease in NO bioavailability [116]. Likewise, periodontitis has been shown to be associated with VED in healthy subjects as well as hypertensive patients through a decrease in NO bioavailability, which could lead to cardiovascular diseases [123]. It has been suggested that periodontal infection and the succeeding increase in the levels of inflammatory markers might be associated with myocardial infarction and peripheral vascular disease [124]. A recent study demonstrated that pathological periodontal pockets were related with raised diastolic blood pressure in obese adolescents [125]. These evidences strongly support the adverse correlation between periodontal oral diseases and cardiovascular diseases.

Cardiovascular drugs are indeed not reported to directly cause periodontitis. However, cardiovascular drugs-induced xerostomia might develop a burning or scalded sensation and poor oral hygiene, make the patients prone to have dental caries, oral infections and periodontal disease [126]. Xerostomia may therefore be linked with gum disease and tooth loss. Xerostomia is also adversely associated with dysgeusia, cheilitis, inflammation of the tongue and buccal mucosa, oral candidiasis and salivary gland infection [127]. Xerostomia could cause a decrease in normal salivary cleansing mechanisms and buffering capacity of saliva. Medications-induced xerostomia might be associated with compromised chewing, speaking and tasting, and increased risk for caries and periodontal disease. An increase in inflammatory gingival diseases, dental caries and rapid tooth destruction might partially be a consequence of xerostomia [128]. Adding to this, a recent study suggested that diuretics-associated xerostomia and altered salivary composition might have an impact on the incidence of dental caries, periodontal diseases and mucosal lesion formation [25]. Taken together, cardiovascular drugs-associated oral complications (Fig. 1) could adversely affect their cardiovas-

cular therapeutic outcomes. It is therefore indispensable to have awareness of incidence of oral adverse reactions during cardiovascular therapies, and healthcare professionals must find an alternate therapy if such reactions occur in patients in order to have optimal cardiovascular therapeutic outcomes.

12. Concluding remarks

Good oral health is foreseeable to get away from secondary cardiovascular complications since available evidences correlate oral disease like periodontitis with cardiovascular diseases. A plethora of evidences support the fact that many cardiovascular drugs could cause oral adverse reactions such as xerostomia, lichen planus, aphthous ulcers, angioedema, dysgeusia, gingival enlargement, scalded mouth syndrome, cheilitis, glossitis and pemphigus, affecting the oral physiology and health. It is therefore expected that cardiovascular drugs-associated oral adverse effects could unfavorably affect their cardiovascular therapeutic outcomes. The physician must therefore be well aware of such oral complications induced by cardiovascular drugs, and counsel patients to notify if such complications are experienced by them during the cardiovascular therapy. This could certainly ensure the physician to timely recommend an alternate cardiovascular medication in order to have better cardiovascular therapeutic outcomes.

Conflict of interest

No conflict of interest has been declared.

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