Clinical Experience With IV Angiotensin II Administration: A Systematic Review of Safety

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Objective: Angiotensin II is an endogenous hormone with vasopressor and endocrine activities. This is a systematic review of the safety of IV angiotensin II.

Data Sources: PubMed, Medline, Scopus, and Cochrane.

Study Selection: Studies in which human subjects received IV angiotensin II were selected whether or not safety was discussed.

Data Extraction: In total, 18,468 studies were screened by two reviewers and one arbiter. One thousand one hundred twenty-four studies, in which 31,281 participants received angiotensin II (0.5–3,780 ng/kg/min), were selected. Data recorded included number of subjects, comorbidities, angiotensin II dose and duration, pressor effects, other physiologic and side effects, and adverse events.

Data Synthesis: The most common nonpressor effects included changes in plasma aldosterone, renal function, cardiac variables, and electrolytes. Adverse events were infrequent and included headache, chest pressure, and orthostatic symptoms. The most serious side effects were exacerbation of left ventricular failure in patients with congestive heart failure and bronchoconstriction. One patient with congestive heart failure died from refractory left ventricular failure. Refractory hypotensive shock was fatal in 55 of 115 patients treated with angiotensin II in case studies, cohort studies, and one placebo-controlled study. One healthy subject died after a pressor dose of angiotensin II was infused continuously for 6 days. No other serious adverse events attributable to angiotensin II were reported. Heterogeneity in study design prevented meta-analysis.

Conclusion: Adverse events associated with angiotensin II were infrequent; however, exacerbation of asthma and congestive heart failure and one fatal cerebral hemorrhage were reported. This systematic review supports the notion that angiotensin II has an acceptable safety profile for use in humans. (*Crit Care Med* ; XX:00–00)

Key Words: aldosterone; angiotensin II; mean arterial pressure; renin-angiotensin system; safety

Angiotensin II (ATII) is a naturally occurring octapeptide hormone component of the renin-angiotensin-aldosterone system (RAAS) and is a potent vasoconstrictor (1). ATII has important roles in cardiovascular, neurologic, and

renal physiology, including maintenance of blood pressure, thirst sensation, response to the baroreceptor reflex, determination of renal blood flow and glomerular filtration rate, and electrolyte and free water homeostasis (2). ATII has also been implicated as a contributor to pathophysiology in certain conditions. Effects on myocardial structure, particularly adverse remodeling in the setting of congestive heart failure, which are mediated through a variety of receptors and mechanisms, are well described (3).

Since 1941 (4), ATII has been administered to humans in studies of vascular resistance and hypertension and has been given to healthy subjects for up to 11 days (5, 6). In the mid-1960s, IV ATII was widely administered to pregnant women in an attempt to identify those at risk for preeclampsia (7, 8). IV ATII has also been administered to patients with a broad range of medical conditions, including cardiovascular, renal, hepatic, and pulmonary diseases, endocrine and metabolic disorders, and traumatic injuries and shock. ATII has also been administered to children with cancer (9), septic shock (10), and congenital cardiac shunts (11).

ATII has been studied in combination with catecholamines, antihypertensives, anesthetics and analgesics, prostaglandins, indomethacin, and corticosteroids. IV ATII safely restored mean arterial pressure in patients with catecholamine-refractory hypotension following angiotensin converting enzyme (ACE) inhibitor overdose (12–14). A number of case reports and studies reported the successful use of ATII in the treatment of vasopressor-resistant hypotensive septic shock (10, 15–18). A randomized, placebo-controlled pilot study evaluated the use of ATII infusion in high-output shock and showed a decrease in norepinephrine doses in patients receiving ATII (19).

IV ATII has been shown to exacerbate only two underlying diseases, asthma (20) and congestive heart failure (21). In patients with mild asthma, IV ATII has the capacity to worsen bronchospasm induced by methacholine (22) but not by histamine (23); previous studies, however, have documented safe use in patients with chronic obstructive pulmonary disease (24). ATII was noted to exacerbate left ventricular failure when administered to three patients with acute congestive heart failure (21).

Further interest in the use of IV ATII to treat a variety of conditions is likely to grow. To date, there has been no comprehensive documentation of adverse effects associated with administration of exogenous ATII to humans. This systematic review describes the nature, severity, and prevalence of side effects reported in the literature.

METHODS

Search Method
We performed a comprehensive literature search on PubMed, Medline, Scopus, and Cochrane to identify studies that involved IV infusion of ATII in human subjects, initially using the key terms, "IV administration," "IV injection," or "IV infusion" combined with "ATII." Further searches without the "IV"

criterion (i.e., "ATII," filtered to exclude animal and in vitro studies) were conducted to ensure that the search was complete; search results were reviewed and references with non-IV use were discarded. Accepted articles were limited to primary studies of human participants written in the English language. Articles were added to the citation manager, and duplicates and review articles were discarded. Two reviewers (D.M.C., D.Y.) assessed satisfaction of inclusion criteria by abstract review prior to retrieving the full-length article. An additional reviewer (L.W.B.) assessed for appropriateness of including the article in the analysis.

Inclusion and Exclusion Criteria
Studies in which human subjects received IV administered ATII were included whether or not side effects or complications were noted. Side effects were defined as measureable physiologic effects that were unintended or incongruous with the pressor effects of ATII. Adverse events (AEs) were those referred to as such by the authors or described as untoward effects, complications, or symptoms reported by subjects. Exclusion criteria were intentionally minimal and included lack of human subjects, non-IV dosing, or insufficient data on the effect of ATII. Either of two synthetic forms with similar biological activity (6), ile5-ATII identical to the human sequence or val5-ATII amide based on the bovine sequence, was used in most of the studies cited herein; the source or sequence was not identified in others. Studies of other analogs were excluded.

A number of subjects identified by comparisons of authors, chronology, baseline characteristics, and treatments were apparently reported in more than one article but have been counted only once in summaries of number of subjects exposed.

Analysis
After abstract review, full-text articles were retrieved for all relevant studies and analyzed for the physiologic effects, AEs and serious AEs of ATII. Studies were grouped according to the target organ system. Two separate reviewers (D.M.C., D.Y.) extracted the number of subjects, dosages of ATII, any concurrent drug administration, the type of study, and patient comorbidities. A third reviewer (L.W.B.) verified the information.

RESULTS

Study Characteristics
The initial search yielded 18,468 studies. After application of exclusion criteria, 1,124 studies were suitable for analysis (complete reference list in **Supplemental Content 1**, http://links.lww.com/CCM/C617). These studies, published from 1941 to 2016, encompassed a total of 31,281 subjects who were administered ATII IV at infusion rates ranging from 0.05 (25) to 3,780 ng/kg/min (26). The majority of subjects received less than or equal to 30 ng/kg/min or a bolus injection of a few micrograms. The highest reported doses were administered in the following settings: one patient with pancreatic cancer (3,780 ng/kg/min) (26); 32 adults with sepsis, systemic inflammatory response

syndrome, or liver failure (maximum, 1,600 ng/kg/min; mean, 550 ng/kg/min) (17); two children with septic shock (doses of 160 and 800 ng/kg/min, respectively) (10); seven normal volunteers (100 ng/kg/min) (27); six children with cancer (up to 80 ng/kg/min) (9); and 43 pregnant women (up to 64 ng/kg/min) (7). The duration of infusion was generally minutes to hours although one study applied continuous infusion of ATII at pressor doses for up to 11 days (5). Approximately 10% of studies entailed infusion of ATII into a brachial, coronary, or hepatic artery; these studies are not included in this report.

Studies were categorized according to the primary organ system of interest, including cardiovascular (471 studies, 13,993 subjects), endocrine (226 studies, 3,605 subjects), renal (211 studies, 5,924 subjects), reproductive systems/pregnancy (71 studies, 3,278 subjects), gastrointestinal (80 studies, 3,509 subjects), pulmonary (15 studies, 167 subjects), neurologic (26 studies, 460 subjects), hematologic and immune (10 studies, 117 subjects), and other organ systems (three studies, 43 subjects). Eleven studies reported use of ATII with chemotherapy in 185 patients with solid tumors.

Frequency of Physiologic and Side Effects of ATII

Following the availability of synthetic ATII, studies in the early 1960s documented the following rapid physiologic changes with IV administration: increased systemic blood pressure, increased pulmonary arterial and wedge pressures (without change in ventilatory function), reduced heart rate and cardiac output, decreased peripheral blood flow, decreased renal blood flow and glomerular filtration rate, reduction in sodium and water excretion, and increased plasma aldosterone (5, 28–34). These studies also established that patients with cirrhosis and ascites were less sensitive to the pressor effects of ATII and had a paradoxical renal response of natriuresis and diuresis compared with healthy subjects (5, 33).

Among all studies, the most commonly cited physiologic effect of ATII was elevation of blood pressure, which was reported in the majority of studies. The acute pressor effect of ATII is shown for 34 representative studies that illustrate relationships between ATII dose and the magnitude of the pressor response (**Supplemental Content 2**, http://links.lww.com/CCM/C618). Doses eliciting a blood pressure increase of at least 5% ranged from 0.5 to 75 ng/kg/min. The most commonly cited nonpressor effects of ATII included altered renal function, increased plasma aldosterone and other changes in RAAS, other endocrine perturbations, and alterations of electrolyte balance. Increased plasma aldosterone was reported in 182 studies using ATII doses from 1 to 20 ng/kg/min; comprehensive references and details for representative studies that illustrate dose-response relationships are in **Supplemental Content 3** (http://links.lww.com/CCM/C619).

Effects of ATII by Organ System

Discussions of ATII activities specifically related to the cardiovascular, endocrine pulmonary, renal, hematologic, immunological, and neurologic systems, as well as discussions relating to oncology and pregnancy are provided in **Supplemental Content 4** (http://links.lww.com/CCM/C620).

Summary of AE Data

The majority of studies analyzed herein were not prospectively designed to collect safety data. Accordingly, of the 1,124 studies included in this analysis, 982 studies did not mention safety and 75 studies variably reported that there were no complications, AEs, side effects, or patient-reported subjective feelings or symptoms. Eight studies reported ATII dose reductions or discontinuations due to excessive pressor responses. The remaining 59 studies reported the AEs listed in **Tables 1** and **2**. The most common symptoms (reported in ≥ 2 studies) were headache, sensation of chest pressure/tightness, dyspepsia/nausea, bradycardia, and orthostatic hypotension/dizziness. One occurrence of headache was characterized as severe (32). Patients with mild asthma reported cough or chest tightness (20). ATII was noted to exacerbate the left ventricular failure when administered to three patients with acute congestive heart failure (21). Frequent or severe gastrointestinal AEs occurred only when ATII was coadministered with chemotherapy (9, 35).

Among 192 pregnant teenaged girls monitored for ATII sensitivity during pregnancy, 72 developed preeclampsia including two who had complications at delivery (one stillbirth with placental abruption and one seizure following delivery of a healthy infant) (36). These events occurred 6 and 12 days after the last ATII infusion, respectively. No AEs or pregnancy complications were reported for the 120 girls who remained normotensive during pregnancy.

A placebo-controlled study of ATII in the treatment of severely ill patients with catecholamine-resistant shock reported the following AEs in the ATII group ($n = 10$) but not in the placebo group ($n = 10$): alkalosis (four patients); hypertension (two patients); atrial fibrillation (two patients); and wheezing (one patient) (19). The 30-day mortality rate was similar for the ATII and placebo groups (50% vs 60%; $p = 1.00$).

In an early study of the effects of prolonged ATII infusion, a death in a 36-year-old healthy subject after 6 days continuous infusion of a pressor dose of ATII (1.5 μg/min to maintain blood pressure at approximately 150/100 mm Hg) occurred following a cerebral hemorrhage during straining at stool (5). The subject experienced sodium retention over the first 5 days of ATII infusion (net +265 mEq) followed by "escape" on day 6 with sodium excretion of 127 mEq/d compared with 2 mEq/d on day 2. A few minutes before the event, blood pressure was 180/100 mm Hg. One patient with preinfusion symptoms of acute heart failure expired after he experienced a decline in cardiac output, which was not restored despite the initiation of IV norepinephrine (21). Upon initiation of ATII infusion, this patient experienced no pressor effect, a decline in cardiac output of 12%, and a decrease in systemic vascular resistance of 9.6%.

The only other deaths reported after ATII administration were associated with preexisting septicemia or shock, or

TABLE 1. Reported Adverse Events by Study–Healthy Volunteers

Author	Subjects (N)[a]	Adverse Event, Verbatim (n, If Reported)	Concomitant Medications
Physiology studies	242 subjects		
Bradley and Parker (4)	Convalescent males (3)	Pressure in the head (occasional complaint)	
Breithaupt-Grogler et al (1997)[b]	Males (24)	Mild headache, dizziness when upright (in some); otherwise "well tolerated"	BAY 10–6734 (ARB)
Brod et al (1969)[b]	Males (15)	Occipital headache (2)	
		Shortness of breath (1)	
		Precordial oppression (4)	
Broughton Pipkin et al (1981)[b]	Male (1), female (1)	Marked retrosternal chest pain, with a sensation of chest tightness and heaviness (2)	Prostaglandin E2
Cevese et al (2001)[b]	Males (6), females (2)	Dizziness, nausea, weakness (8)	Urapidil
Dagher et al (1966)[b]	Males (5)	Marked headache with flushing of the face and severe anxiety (1)	
Fuchs et al (2000)[b]	Males (13)	Extrasystoles (discontinued ATII dosing)	Candesartan or losartan (ARB)
Goldberg et al (1996)[b]	Males (8)	Indigestion, upper respiratory infections, mild trauma to a vein (4)	Enalapril (angiotensin converting enzyme inhibitor) or losartan (ARB)
Gossman et al (2000)[b]	Males (8)	Headache (one; discontinued from study)	
Hausdorf et al (1987)[b]	Males (13), females (17)	Transient feeling of oppression (1)	
Johnson et al (1962)[b,c]	Males (10)	Orthostatic hypotension (one; following discontinuation of ATII infusion)	
Karnezis et al (1988)[b]	Males (8)	Chest tightness or headache (3)	Fenoldopam (dopamine-1 receptor agonist)
Lim et al (2007)[b]	Males (10), females (3)	Mild headache (1)	Valsartan (ARB)
Murphy et al (1984)[b]	Males (6)	Reversible bradycardia	Nifedipine (CCB)
Plavsic and Lambic (1964)[b]	Male (1), females (4)	Headache	
		Vomiting (1)	
Sluiter et al (1988)[b]	Males (12), crossover felodipine:placebo	Events with felodipine:placebo, all also received ATII:	Felodipine (CCB)
		Headache (10:2)	
		Flushing (10:2)	
		Warm feeling (5:2)	
		Palpitations (1:1)	
		Orthostatic dizziness (3:1)	
Stangier et al (2001)[b]	Males (48)	Head discomfort, lightheadedness, a sensation of chest pressure, and palpitations	Telmisartan (ARB)
Ueda et al (1998)[b]	Males (8)	Nonspecific erythematous rash (1)	Lacidipine (CCB)
Yu et al (1961)[b]	NT males (11), females (5)	Severe headache and general discomfort (2)	

(*Continued*)

TABLE 1. (*Continued*). Reported Adverse Events by Study–Healthy Volunteers

Author	Subjects (*N*)[a]	Adverse Event, Verbatim (*n*, If Reported)	Concomitant Medications
Studies in healthy pregnancy	(309 subjects)		
Abdul-Karim and Assalin (1961)[b]	Healthy pregnancy, various stages (29), and nonpregnant (5)	Throbbing temporal and occipital headache, dizziness, dyspnea, chest oppression, palpitation, abdominal pain, and low backache (nonpregnant subjects only)	
Adair et al (1996)[b]	Healthy pregnancy, 24–34 wk (10)	Minor dyspepsia (10)	Fish oil capsules (Omega-3 700, Solgar)
Broughton Pipkin et al (1982)[b]	Healthy pregnancy, second trimester (22)	Bradycardia	
Gant et al (36)	NT pregnancy (120), pregnancy-induced hypertension (72), nonpregnant (10)	Grand mal seizure 90 min after delivery (1); stillbirth at wk 36 (1); both events occurred in subjects with hypertension at delivery	
Morris et al (1978)[b]	Healthy pregnancy, 29–32 wk (26)	Premature delivery at 35 or 36 wk (2)	
Schwartz and Retzke (1971)[b]	Healthy pregnancy (9) and nonpregnant (6)	Headache (at highest dose)	
		Low backache (at highest dose)	
		Dizziness (at highest dose)	

ARB = angiotensin II receptor type 1 blocker, ATII = angiotensin II, CCB = calcium channel blocker, NT = normotensive.

[a]Another 48 studies in healthy subjects (total *N* = 751) explicitly reported that no adverse events (AEs)/side effects/complications (or similar terms) were observed, stated that procedures/treatments were safe/well tolerated, or reported AEs associated with other treatments used in the study that were not concomitant with ATII infusion. These studies (number of subjects who received ATII) were: Chalon et al (1999) (*N* = 4)b; Chiodera and Coiro (1991) (*N* = 14)[b]; Chiodera et al (1994) (*N* = 27)b; Chiodera et al (1998a) (*N* = 6)b; Chiodera et al (1998b) (*N* = 7)b; Chiodera et al (1998c) (*N* = 14)b; Chiodera et al (2000) (*N* = 24)b; Coiro 1989 (*N* = 7)b; Coiro 1991 (*N* = 7)b; Coiro et al (1994) (*N* = 7)b; Coiro et al (1998) (*N* = 8)b; degli Uberti et al (1990) (*N* = 7)b; degli Uberti et al (1991) (*N* = 6)b; Derad et al (1998) (*N* = 10)b; Eadington et al (1991a) (*N* = 6)b; Egan et al (1991) (*N* = 10)b; Fraser et al (1965) (*N* = 2)b; Gachalyi and Kaldor (1978) (*N* = 15)b; Goldsmith et al (1988) (*N* = 7)b; Haefeli et al (1993) (*N* = 6)b; Jones and Sanchez-Ramos (1990) (*N* = 14)b; Luther et al (2006) (*N* = 14)b; Maillard 2000a (*N* = 16)b; McGibney et al (1983) (*N* = 4)b; McVeigh et al (1990) (*N* = 8)b; Nadler et al (1983) (*N* = 17)b; Ogihara et al (1995) (*N* = 8)b; Oney and Kaulhausen (1982a) (*N* = 15)b; Phillips et al (1985) (*N* = 10)b; Ramin et al (1994) (*N* = 10)b; Ribstein et al (2001) (*N* = 42)b; Richards et al (1992) (*N* = 16)b; Rosenfeld et al (1998) (*N* = 17)b; Sannerstedt et al (1963) (*N* = 10)b; Schachinger 2004 (*N* = 30)b; Schachinger et al (2006) (*N* = 6)b; Schneider et al (2012) (*N* = 10)b; Schneider-Helmert (1983) (*N* = 2)b; Shenker et al (1988) (*N* = 13)b; Stanciu et al (1981) (*N* = 8)b; Tham et al (1993) (*N* = 10)b; Troughton et al (2001) (*N* = 8)b; Vincent et al (1985) (*N* = 6)b; Volpi 1996a (*N* = 8)b; Volpi et al (1996b) (*N* = 14)b; Wilkinson et al (2002) (*N* = 6)b; Yamamoto (1975) (*N* = 30)b; and Zuspan et al (1971) (*N* = 11)b.

[b]Complete citations for all sources referenced in this table are found in the supplementary material (Supplemental Content 1, http://links.lww.com/CCM/C617).

[c]The authors also reported that subcutaneous infiltration of ATII in two subjects caused "no local reaction of tissue."

BAY 10–6734 is also known as "embusartan." *N* represents number of subjects exposed to ATII; *n* represents number of subjects experiencing the AE.

occurred months after ATII was infused alongside chemotherapy in patients with inoperable cancer (35, 38). Among patients with one or more categories of distributive shock diagnosed (or inferred based on reported clinical information), 55 deaths occurred (16, 17, 19, 39–44). However, the reported deaths were not attributed to use of ATII.

DISCUSSION

Overall, 31,281 participants have been exposed to IV ATII in the studies reviewed including healthy normotensive subjects, normotensive and preeclamptic pregnant women, subjects with hypertension, congestive heart failure, diabetes, solid tumors, and other comorbidities, critically ill patients, and children. Excluding subjects with refractory shock and oncology patients receiving ATII with chemotherapy, there have been two deaths and fewer than 300 subjects with AEs reported.

There were two deaths not linked to sepsis, shock, or cancer. One case involved a cerebral hemorrhage in a 36-year-old healthy volunteer receiving a continuous infusion of ATII for 6 days with associated sodium retention and sustained hypertension. The other case involved fulminant left ventricular failure in a patient with preexisting acute decompensated heart failure. Since these studies, both published in 1965, studies in healthy subjects have generally used infusions of much shorter duration. In one study of five healthy volunteers, a continuous infusion of ATII at 2 ng/kg/min was maintained for 66 hours with additional incremental dose challenges on days 1 and 3; with that, sodium and potassium balances were stable and no AEs were reported (6). Beyond the cerebrovascular event and the left ventricular failure, there is no documentation of exogenous ATII association with serious AEs or morbidities, although exacerbation of existing asthma or congestive heart failure remains a potential risk. Two adverse outcomes were reported during pregnancy, placental abruption and eclampsia, but both occurred well after both patients received ATII infusions (6 and 12 d, respectively, postinfusion) and were thus

TABLE 2. Reported Adverse Events by Study–Patients With Medical Conditions

Author	Medical Condition (*N*)[a]	Adverse Event, Verbatim (*n*, If Reported)	Concomitant Medications
Physiology and efficacy studies	> 736 subjects		
Finnerty et al (30)	Shock (13), HT volunteers (3), and NT volunteers (17)	Postural hypotension (6) (not considered a side effect by authors)	None specified
Derrick (1962a)[b]	Shock (9) and NT volunteers (32)	Fatal cerebral vascular accident during shock (1)	Norepinephrine (2) and "massive doses" of chlorpromazine in patient with liver failure
		Fatal toxic hepatitis with acute liver necrosis (1)	
Wedeen and Zucker (1963)[b]	Nonhemorrhagic shock (15)	Transient nodal tachycardia (1)	Norepinephrine
Smulyan et al (1964)[b]	Shock due to myocardial infarction (3)	Reduced cardiac output (3)	Norepinephrine
Cohn and Luria (1965a)[b]	Hypotension, various etiologies (28)	Progressive left ventricular failure[c] (3)	None specified
		Dyspnea, cyanosis (1)	
		Dyspnea, agitation, confusion (1)	
		Progressive fall in blood pressure, death (1)	
Singh and Malhotra (1966)[b] and Singh and Malhotra (1967)[b]	Noncardiogenic shock (30)	Supraventricular (1) or ventricular (3) tachycardia	None specified
		First degree A-V block (6)	
		P-wave changes (7)	
		Ischemic changes in ST segments (8), with T wave inversion (3/8)	
		Bradycardia and nodal rhythm (1)	
		Headache (5)	
		Flushing of face (2)	
		Tachyphylaxis (8)	
		Thrombophlebitis (1)	
		Metasensitivity (1)	
Love et al (1971)[b]	Orthostatic hypotension (4)	Headache (1)	None specified
Chawla et al (19)[d]	Patients with high-output shock (10 received ATII)	Acidosis (2)	Norepinephrine
		Alkalosis (4)	
		Worsening respiratory failure (1)	
		Wheezing (1)	
		Hypertension (2)	
		Hypotension (2)	
		Atrial fibrillation (2)	
		Decreased urine output (3)	
		Worsening multiple organ system failure (2)	
Laragh et al (32)	Benign HT (1), nephrosis (1), and healthy volunteers (4)	Nausea and vomiting (1)	None specified
		Severe headache (1)	
		Precordial pain (2)	

(Continued)

TABLE 2. (*Continued*). Reported Adverse Events by Study–Patients With Medical Conditions

Author	Medical Condition (*N*)[a]	Adverse Event, Verbatim (*n*, If Reported)	Concomitant Medications
Peart and Brown (1961)[b]	HT (21)	Slight headache (1)	None specified
Wood (1961)[b]	HT (12) and NT (8) males	Headache, dyspnea, chest discomfort, nausea, or abdominal cramps in NT but not HT subjects	None specified
Brown and Peart (1962)[b]	HT (21)	Slight headache (1)	None specified
		Abdominal pain (1)	
Cumming (11)	Infants and children with intracardiac shunts and healthy controls (> 200)	Bradycardia	None specified
		Transitory nodal rhythm	
Mangioni and Morandini (1967)[b]	Pregnancy (third trimester) with HT/toxemia (10) or NT (14)	Nausea and headache (three patients with toxemia)	None specified
Perloff et al (1967)[b]	Uncomplicated aortic stenosis (12)	Ventricular ectopic beats, occasional mild headache	None specified
Krovetz et al (1968)[b]	Children 5–14 yr old with suspected left ventricular dysfunction (24), and healthy children (11)	Nausea and headache	None specified
Smyth et al (1969)[b]	HT (7) and healthy NT volunteers (6)	Mild febrile reaction (one NT; pyrogens in catheter suspected)	None specified
Dahn et al (1969)[b]	Leg ischemia (8)	Electrocardiogram abnormalities and possible atypical myocardial infarction (1)	Digitalis
Hansteen and Lorentsen (1972)[b]	Lower limb atherosclerosis and foot ischemia (11)	Angina pectoris (1)	None specified
Mehrotra et al (1974)[b]	Essential (15) or renal (21) HT and healthy volunteers (26)	Heaviness in the chest (1)	None specified
		Headache (4)	
Bernasconi et al (1991)[b]	Essential HT (12) and healthy NT volunteers (11)	Mild cough (one healthy volunteer); slight increases of serum aspartate and alanine aminotransferases (one healthy volunteer)	Cilazepril
Nesbit and Levagood (1961)[b]	Various conditions (13)	Vertigo and mild frontal headache (1)	None specified
Ames et al (1965)[b]	Cirrhosis (11) and healthy volunteers (7)	Cerebral hemorrhage (fatal, one)	None specified
		Occasional palpitations, transient headache, or extrasystoles	
		Orthostatic hypotension following discontinuation of ATII infusion	
Bisht et al (1965)[b]	Cirrhotic (13) or non-cirrhotic (14) liver disease and healthy volunteers (50)	Mild burning sensation in the epigastrium (1)	Phenergan
Millar et al (20)	Mild asthma (8)	Cough or chest tightness (5)	None specified

(*Continued*)

TABLE 2. (*Continued*). Reported Adverse Events by Study–Patients With Medical Conditions

Author	Medical Condition (*N*)[a]	Adverse Event, Verbatim (*n*, If Reported)	Concomitant Medications
Surgical studies	73 subjects		
Arens and Adriani (1963)[b]	Surgery with general anesthesia (14)	Anginal pain with myocardial ischemia after excessive ATII dose (1) Nodal rhythm (4)	Cyclopropane or ether and scopolamine + morphine or levohyoscyamine
Kelly (1965)[b]	Prior aortic valve replacement surgery (20)	Mild hypotension (1)	None specified
Vincent et al (37)[e]	Elective cesarean delivery (29)	Hypotension with sinus bradycardia (1) or transient sinus tachycardia (1)	Buvicaine (spinal); fentanyl or morphine
Wallace et al (1967)[b]	Cardiac surgery (10)	Reduced stroke volume without effect on cardiac output	Sodium pentothal, succinylcholine, halothane, nitrous oxide
Oncology studies	105 subjects		
Fujii et al (9)	Children with inoperable or recurrent tumors (6)	Headache (2) (avoided if pressure raised slowly) Chest discomfort (2) Nausea and vomiting (4) Bone marrow suppression (3)	2–8 chemotherapy agents
Kato et al (1993)[b]	Recurrent tumors after radiation therapy (41)	Nausea (1) Severe headache (1) Oral mucositis and esophagitis Myelosuppression	Radiation therapy
Nagamitsu et al (38)	Solid tumors (10)	Mild headache (1)	Styrene maleic acid neocarzinostatin copolymer, lipiodol
Sato et al (35)	Inoperable and/or recurrent cancer (32)	Headache, shoulder dullness, or breast discomfort (avoided if pressure was elevated gradually over 2–3 min)	Chemotherapy (adriamycin + vincristine + carboquone or 5-fluorouracil + mitomycin C)
Tomura et al (1993)[b]	Brain tumors (8) and healthy volunteers (8)	Headache (one brain tumor patient)	[15]O for PET scanning

ATII = angiotensin II, HT = hypertensive, NT = normotensive.

[a]Another 27 studies in subjects with medical conditions (total subjects, 742) explicitly reported that no adverse events (AEs)/side effects/complications (or similar terms) were observed, stated that procedures/treatments were safe/well tolerated, or reported AEs associated with other treatments used in the study that were not concomitant with ATII infusion. Indicated *N* values include healthy controls in some studies. These studies (number of subjects who received ATII) were Berman et al (1971) (*N* = 10)[b]; Burke et al (2001) (*N* = 9)[b]; Cokkinos and Voridis (1976) (*N* = 12)[b]; Deheneffe and Bernard (1974a) (*N* = 51)[b]; Deheneffe and Bernard (1974b) (*N* = 40)b; Deheneffe et al (1976) (*N* = 6)[b]; Del Greco and Johnson (1961)b (40) (*N* = 21); Del Greco (1962) (*N* = 2)[b]; Derrick (1962b) (*N* = 36)[b]; Eadington et al (1991b) (*N* = 18)[b]; Erkkola and Pirhonen (1992) (*N* = 15)[b]; Fukui et al (2000) (*N* = 1)[b]; Henriksen and Wisborg (1975) (*N* = 9)[b]; Henriksen et al (1985) (*N* = 10)[b]; Jose and Taylor (1969) (*N* = 47)[b]; Kane and Gillespie (1970) (*N* = 27)[b]; Kuchel et al (1964) (*N* = 18)[b]; Mediskou et al (2011) (*N* = 40)[b]; Mendelsohn et al (1972) (*N* = 25)[b]; Millar et al (1995) (*N* = 7)[b]; Morgan (1967) (*N* = 251)[b]; Morris et al (1994) (*N* = 11)[b]; Nicholls et al (1976) (*N* = 8)b; Radice et al (1975) (*N* = 29)b; Tran et al (2005) (*N* = 11)b; Ueda et al (1964) (*N* = 26)b; and Yunge and Petros (2000) (*N* = 2)[b].

[b]Complete citations for all sources referenced in this table are found in the supplementary material (Supplemental Content 1, http://links.lww.com/CCM/C617).

[c]Three of 13 subjects with congestive heart failure before infusion of ATII.

[d]Placebo group (N = 10): Acidosis (3); worsening respiratory failure (3); hypotension (1); decreased urine output (1); worsening acute kidney injury (2); and worsening multiple organ system failure (3). No subjects in the ATII group experienced worsening acute kidney injury and no subjects in the placebo group experienced acidosis, wheezing, hypertension, or atrial fibrillation.

[e]Ephedrine group (*N* = 25): Sinus tachycardia with hypotension (2); sinus tachycardia with hypotension (n1); ventricular bigeminy with hypertension (1). Of the newborns, two of 29 in the ATII group and three of 25 in the ephedrine group had 1-min Apgar scores < 7.

N represents number of subjects exposed to angiotensin II; *n* represents number of subjects experiencing the adverse event.

unlikely to be related to ATII. Reports of other AEs were limited. Among the relatively few studies that reported AEs, transient headache (26 studies) and abnormal chest sensations (10 studies) were reported most frequently. A period of orthostatic hypotension following discontinuation of ATII infusion was reported in several studies, suggesting that dose tapering might minimize symptoms.

Our review is limited by the heterogeneity of study design, which precluded formal meta-analysis or calculation of integrated AE rates. Studies differed in objectives; inclusion/exclusion criteria, comorbidities, and baseline characteristics; ATII amino acid sequence, dose, and duration; endpoints; and the collection of AE data. Most studies were designed to understand the physiologic changes induced by exogenous ATII and did not prospectively collect safety data. Hence, the data reported herein are obtained from a limited subset of included studies, which could represent a reporting bias. Additionally, there was no standard terminology for patient-reported symptoms.

Most of the studies used one of two synthetic forms of ATII, an amide derivative of the bovine amino acid sequence or an acetate salt of the human sequence. The human form showed greater pressor activity than the bovine form in one comparative study (45), but pressor and aldosterone-stimulating activities were similar in other limited comparisons (46, 47). No studies have directly compared the safety of the two forms in humans. Finally, although multiple broad search terms were used, there is a possibility that we may have missed relevant articles, including those in languages other than English.

ATII administered IV equilibrates rapidly in the circulation and has a half-life in plasma of approximately 1 minute or less (48, 49). Pharmacodynamics is such that blood pressure increases within minutes, is sustained at a fixed infusion rate, and returns to preinfusion values within minutes after cessation of the infusion (50). As such, direct links between dosages and changes in organ system responses could not be obtained across all studies.

In general, dosages of 1–10 ng/kg/min in normotensive or hypertensive subjects were required to elicit systemic pressor responses of 10–30 mm Hg. The magnitude of the pressor response was variable between subjects for a given dose but was dose dependent when individuals were administered successive incremental doses. In the physiologic studies, ATII was typically infused for a few minutes to a few hours in both normotensive and hypertensive subjects. In studies evaluating hypotensive subjects, much larger therapeutic dosages (50–1,600 ng/kg/min) were administered for 1–7 days to achieve hemodynamic stabilization and included administration of other vasoconstrictors (norepinephrine, vasopressin). Safety risks under these two radically different scenarios are likely to be very different. The only placebo-controlled study designed to assess safety as well as efficacy in severely ill patients found a reduced norepinephrine requirement, low frequency of AEs, and similar mortality rates (19).

These findings have important implications for clinical practice. ATII has demonstrated the ability to restore arterial pressure and reduce the need for potentially harmful doses of catecholamines in patients with refractory septic shock, improve natriuresis and diuresis in patients with liver failure, rescue subjects following ACE inhibitor overdose, and enhance chemotherapy delivery to solid tumors. Although a discussion of the efficacy of ATII is beyond the scope of this analysis, it should be noted that among patients included in this report with septic shock, catecholamine-resistant shock, ACE inhibitor overdose, and anesthesia-induced hypotension, outcomes seem to have been changed in a number of cases (10, 12–19, 21, 37, 51).

To our knowledge, ATII formulated for clinical use is currently available for research purposes only and is not an approved therapy for any indication. (Angiotensin amide was previously marketed by Ciba-Geigy under the trade name Hypertensin for "states of shock and circulatory collapse.") A phase 3 study assessing the safety and efficacy of ATII in catecholamine-resistant hypotension is ongoing (NCT02338843, www.clinicaltrials.gov). Where current literature falls short is in establishing a safe therapeutic range, with minimal AEs, for the potential clinical applications of ATII.

In summary, ATII has multiple potential clinical applications, with the recent focus being its use as a rescue vasopressor in catecholamine-resistant high-output shock. Establishing the dose range and tolerability of ATII is of fundamental importance, and the data included herein indicate that IV ATII may be safe in a variety of clinical circumstances. Further prospective trials are needed to more completely establish the appropriate dosing and duration of therapy.

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REFERENCES

1. Basso N, Terragno NA: History about the discovery of the renin-angiotensin system. *Hypertension* 2001; 38:1246–1249
2. Struthers AD, MacDonald TM: Review of aldosterone- and angiotensin II-induced target organ damage and prevention. *Cardiovasc Res* 2004; 61:663–670
3. Weber KT: Extracellular matrix remodeling in heart failure: a role for de novo angiotensin II generation. *Circulation* 1997; 96:4065–4082
4. Bradley SE, Parker B: The hemodynamic effects of angiotonin in normal man. *J Clin Invest* 1941; 20:715–719
5. Ames RP, Borkowski AJ, Sicinski AM, et al: Prolonged infusions of angiotensin II and norepinephrine and blood pressure, electrolyte balance, and aldosterone and cortisol secretion in normal man and in cirrhosis with ascites. *J Clin Invest* 1965; 44:1171–1186
6. Oelkers W, Schöneshöfer M, Schultze G, et al: Effect of prolonged low-dose angiotensin II infusion on the sensitivity of adrenal cortex in man. *Circ Res* 1975; 36(6 Suppl 1):49–56
7. Conti C, Tranquilli AL, Garzetti GG, et al: Modulation of vascular reactivity after acute calcium antagonist administration in pregnant women moderately sensitive to angiotensin infusion. *Boll Soc Ital Biol Sper* 1994; 70:243–248
8. Oney T, Kaulhausen H: The value of the angiotensin sensitivity test in the early diagnosis of hypertensive disorders in pregnancy. *Am J Obstet Gynecol* 1982; 142:17–20

9. Fujii Y, Hongo T, Masui H, et al: Angiotensin-induced hypertension chemotherapy in children with advanced solid tumors. *Acta Paediatr Jpn* 1991; 33:381–383

10. Yunge M, Petros A: Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child* 2000; 82:388–389

11. Cumming GR: Acute hemodynamic effects of angiotensin II. Preliminary report. *Can Med Assoc J* 1963; 88:827–832

12. Jackson T, Corke C, Agar J: Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; 341:703

13. Newby DE, Lee MR, Gray AJ, et al: Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; 40:103–104

14. Trilli LE, Johnson KA: Lisinopril overdose and management with intravenous angiotensin II. *Ann Pharmacother* 1994; 28:1165–1168

15. Ryding J, Heslet L, Hartvig T, et al: Reversal of 'refractory septic shock' by infusion of amrinone and angiotensin II in an anthracycline-treated patient. *Chest* 1995; 107:201–203

16. Thomas VL, Nielsen MS: Administration of angiotensin II in refractory septic shock. *Crit Care Med* 1991; 19:1084–1086

17. Whiteley SM, Dade JP: Treatment of hypotension in septic shock. *Lancet* 1996; 347:622

18. Wray GM, Coakley JH: Severe septic shock unresponsive to noradrenaline. *Lancet* 1995; 346:1604

19. Chawla LS, Busse L, Brasha-Mitchell E, et al: Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): A pilot study. *Crit Care* 2014; 18:534

20. Millar EA, Angus RM, Hulks G, et al: Activity of the renin-angiotensin system in acute severe asthma and the effect of angiotensin II on lung function. *Thorax* 1994; 49:492–495

21. Cohn JN, Luria MH: Studies in clinical shock and hypotension. II. Hemodynamic effects of norepinephrine and angiotensin. *J Clin Invest* 1965; 44:1494–1504

22. Millar EA, Nally JE, Thomson NC: Angiotensin II potentiates methacholine-induced bronchoconstriction in human airway both in vitro and in vivo. *Eur Respir J* 1995; 8:1838–1841

23. Ramsay SG, Clayton RA, Dagg KD, et al: Effect of angiotensin II on histamine-induced bronchoconstriction in the human airway both in vitro and in vivo. *Respir Med* 1997; 91:609–615

24. Jezek V, Schrijen F: Haemodynamic reaction to exercise and increased afterload in the detection of right heart failure in pulmonary diseases. *Cor Vasa* 1980; 22:272–280

25. Radice M, Folli G, Giani P, et al: Latent myocardial contractile impairment in patients with angina pectoris. *Acta Cardiol* 1975; 30:333–341

26. Louis WJ, Doyle AE: The effects of varying doses of angiotensin on renal function and blood pressure in man and dogs. *Clin Sci* 1965; 29:489–504

27. Goldsmith SR, Dodge-Brown D, Pentel P: Effects of infused norepinephrine and angiotensin-II on vasopressin levels in humans. *Am J Med Sci* 1988; 295:513–516

28. Depasquale NP, Burch GE: Angiotensin II, digital blood flow, and the precapillary and postcapillary blood vessels of man. *Ann Intern Med* 1963; 58:278–292

29. Depasquale NP, Burch GE: Effect of angiotensin II on the intact forearm veins of man. *Circ Res* 1963; 13:239–245

30. Finnerty FA Jr, Massaro GD, Chupkovich V, et al: Evaluation of the pressor, cardiac, and renal hemodynamic properties of angiotensin II in man. *Circ Res* 1961; 9:256–263

31. Gill JR Jr, Barbour BH, Slater JD, et al: Effect of angiotensin II on urinary dilution in normal man. *Am J Physiol* 1964; 206:750–754

32. Laragh JH, Angers M, Kelly WG, et al: Hypotensive agents and pressor substances. The effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. *JAMA* 1960; 174:234–240

33. Laragh JH, Cannon PJ, Bentzel CJ, et al: Angiotensin II, norepinephrine, AND renal transport of electrolytes and water in normal man and in cirrhosis with ascites. *J Clin Invest* 1963; 42:1179–1192

34. Segel N, Harris P, Bishop JM: The effects of synthetic hypertensin of the systemic and pulmonary circulations in man. *Clin Sci* 1961; 20:49–61

35. Sato H, Sato K, Sato Y, et al: Induced hypertension chemotherapy of cancer patients by selective enhancement of drug delivery to tumor tissue with angiotensin II. *Sci Rep Res Inst Tohoku Univ Med* 1981; 28:32–44

36. Gant NF, Daley GL, Chand S, et al: A study of angiotensin II pressor response throughout primigravid pregnancy. *J Clin Invest* 1973; 52:2682–2689

37. Vincent RD Jr, Werhan CF, Norman PF, et al: Prophylactic angiotensin II infusion during spinal anesthesia for elective cesarean delivery. *Anesthesiology* 1998; 88:1475–1479

38. Nagamitsu A, Greish K, Maeda H: Elevating blood pressure as a strategy to increase tumor-targeted delivery of macromolecular drug SMANCS: Cases of advanced solid tumors. *Jpn J Clin Oncol* 2009; 39:756–766

39. Cohn JN, Luria MH: Studies in clinical shock and hypotension. 3. Comparative effects of vasopressor drugs and dextran. *Arch Intern Med* 1965; 116:562–566

40. Del Greco F, Johnson DC: Clinical experience with angiotensin II in the treatment of shock. *JAMA* 1961; 178:994–999

41. Nassif AC, Nolan TR, Corcoran AC: Angiotensin II in treatment of hypotensive states. *JAMA* 1963; 183:751–754

42. Singh S, Malhotra RP: Comparative study of angiotensin and noradrenaline in hypotensive states (shock). *J Assoc Physicians India* 1966; 14:639–645

43. Tristani FE, Cohn JN: Studies in clinical shock and hypotension. VII. Renal hemodynamics before and during treatment. *Circulation* 1970; 42:839–851

44. Udhoji VN, Weil MH: Circulatory effects of angiotensin, levarterenol and metaraminol in the treatment of shock. *N Engl J Med* 1964; 270:501–505

45. Kono T, Taniguchi A, Imura H, et al: Relative biological activities of Asn1-,Val5-angiotensin II, Ile5-angiotensin II and Sar1-angiotensin II in man. *Life Sci* 1985; 37:365–369

46. Boyd GW, Adamson AR, Arnold M, et al: The role of angiotensin II in the control of aldosterone in man. *Clin Sci* 1972; 42:91–104

47. Oelkers W, Brown JJ, Fraser R, et al: Sensitization of the adrenal cortex to angiotensin II in sodium-deplete man. *Circ Res* 1974; 34:69–77

48. Donato L, Coli A, Pasqualini R, et al: Metabolic clearance rate of radioiodinated angiotensin II in normal men. *Am J Physiol* 1972; 223:1250–1256

49. Magness RR, Cox K, Rosenfeld CR, et al: Angiotensin II metabolic clearance rate and pressor responses in nonpregnant and pregnant women. *Am J Obstet Gynecol* 1994; 171:668–679

50. Vittorio TJ, Lang CC, Katz SD, et al: Vasopressor response to angiotensin II infusion in patients with chronic heart failure receiving beta-blockers. *Circulation* 2003; 107:290–293

51. Ramin SM, Ramin KD, Cox K, et al: Comparison of prophylactic angiotensin II versus ephedrine infusion for prevention of maternal hypotension during spinal anesthesia. *Am J Obstet Gynecol* 1994; 171:734–739