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Insuffisance cardiaque aiguë: vers une optimisation de la prise en charge aux urgences

Acute heart failure : towards an optimization of management in the Emergency Department

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THÈSE DE DOCTORAT
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Résumé en français

Chaque année en France, 160000 patients sont hospitalisés pour un épisode insuffisance cardiaque aiguë (ICA), dont 65% après un passage aux urgences. La prise en charge en phase initiale de ces épisodes fait l'objet de recommandations d'experts, notamment européennes et américaines, et repose sur un traitement médicamenteux par diurétiques et vasodilatateurs dérivés nitrés) et la mise en place éventuelle d'une ventilation non invasive (VNI). Il est possible de débuter ces traitements dès la phase préhospitalière à bord d'une ambulance médicalisée ou de les initier aux urgences. Au terme de la prise en charge par le médecin urgentiste (à bord de l'ambulance médicalisée et/ou aux urgences), le patient va, selon son tableau clinique et son terrain, rentrer à domicile ou être hospitalisé dans un service de soins intensifs, de cardiologie ou de médecine interne ou gériatrie. Plusieurs points de cette prise en charge sont à ce jour mal définis. Premièrement, l'intérêt des traitements médicamenteux initiaux et leur posologie optimale n'ont jamais été validés de manière claire et apparaissent d'ailleurs dans les recommandations avec un rang IC et IB IIaB pour les diurétiques et IIbB pour les dérivés nitrés. Deuxièmement, l'intérêt d'une mise en place de VNI en préhospitalier, préconisée par les recommandations européennes, n'a lui non plus jamais été démontré. Enfin, alors que chaque étape entre le domicile du patient et son hospitalisation fait l'objet d'une décision d'orientation, il semble important de préciser s'il existe un parcours de soins bénéfique. Ces trois points ont fait l'objet de ce travail.

Nous avons tout d'abord réalisé une analyse secondaire de l'étude ELISABETH afin d'évaluer l'association entre la dose de diurétiques et de dérivés nitrés administrées dans les quatre premières heures et le pronostic à 30 jours. Parmi les 502 patients, ni la dose totale de dérivés nitrés, ni la dose totale de diurétiques n'ont montré d'association significative avec le nombre de jours vivant hors de l'hôpital (ratios ajustés 1.17 (0.82–1.67) et 1.45 (0.90–2.33) pour les dérivés nitrés et 0.88 (0.63–1.23) et 0.76 (0.58–1.00) pour les diurétiques), mais une tendance se dégageait en faveur d'une forte dose de dérivés nitrés et d'une faible dose de diurétiques.

Nous avons ensuite évalué, dans une analyse du registre espagnol EAHFE, l'effet d'une initiation préhospitalière de VNI par rapport à une initiation intra hospitalière sur le pronostic à court terme des patients chez qui un traitement par VNI était préconisé. Parmi les 487 patients transportés aux urgences par une ambulance médicalisée et ayant bénéficié de VNI au cours de leur prise en charge initiale, l'initiation de VNI en préhospitalier semblait associée à une plus faible survenue du critère combiné associant mortalité toute cause ou reconsultation pour ICA à 30 jours (odd-ratio ajusté 0.66 (0.42-1.05), 0.69 (0.43-1.11) ou 0.67 (0.43-1.04)).

Nous avons finalement décrit, dans une troisième étude prospective observationnelle, les parcours de soin de patients hospitalisés dans 24 hôpitaux en France. Parmi les 3677 patients, le fait d'avoir été hospitalisé dans un service de cardiologie (soins intensifs ou cardiologie conventionnelle) était associé, de manière significative et après appariement sur un score de propension, à une réduction de la mortalité intra-hospitalière (OR 0.61 [0.44–0.84], p = 0.002). Ces trois études ont permis de mettre en évidence la nécessité d'une collaboration entre urgentiste et cardiologue dans la prise en charge des épisodes d'ICA et laissent envisager l'intérêt d'un traitement personnalisé adapté à chaque patient.

Mot clés : insuffisance cardiaque aiguë ; diurétiques ; dérivés nitrés ; ventilation non invasive ; parcours de soins.

Summary in English

Each year in France, 160,000 patients are hospitalized for an episode of acute heart failure (AHF), with 65% being admitted after an emergency department visit. The initial management of these episodes is subject to expert recommendations, notably European and American guidelines, and is based on pharmacological treatment with diuretics and vasodilators (nitrate derivatives) and the possible implementation of non-invasive ventilation (NIV). These treatments can be initiated in the pre-hospital phase in a medicalized ambulance or in the emergency department. Following the management by the emergency physician (either in the ambulance or at the hospital), depending on the patient's clinical presentation and background, they will either return home or be hospitalized in an intensive care unit, cardiology ward, internal medicine, or geriatrics department. Several aspects of this care remain poorly defined. First, the efficacy and optimal dosing of the initial pharmacological treatments have never been clearly validated and appear in recommendations with a grading of IC and IB IIaB for diuretics and IIbB for nitrates. Second, the benefit of pre-hospital NIV, as recommended by European guidelines, has also never been demonstrated. Lastly, while each step between the patient's home and their hospitalization involves a triage decision, it seems important to determine whether a beneficial care pathway exists. These three points are the focus of this study.

We first conducted a secondary analysis of the ELISABETH study to evaluate the association between the doses of diuretics and nitrates administered in the first four hours and the 30-day prognosis. Among the 502 patients, neither the total dose of nitrates nor the total dose of diuretics showed a significant association with the number of days alive and out of the hospital (adjusted ratios 1.17 (0.82–1.67) and 1.45 (0.90–2.33) for nitrates and 0.88 (0.63–1.23) and 0.76 (0.58–1.00) for diuretics), but a trend was observed favoring high doses of nitrates and low doses of diuretics.

Then, we assessed, through an analysis of the Spanish EAHFE registry, the effect of pre-hospital initiation of NIV versus in-hospital initiation on the short-term prognosis of patients for whom NIV was indicated. Among the 487 patients transported to the emergency department by a medicalized ambulance and receiving NIV during their initial care, pre-hospital NIV initiation appeared to be associated with a lower incidence of the composite outcome of all-cause mortality or rehospitalization for AHF within 30 days (adjusted odds ratio 0.66 (0.42-1.05), 0.69 (0.43-1.11), or 0.67 (0.43-1.04)).

Lastly, we described, in a third prospective observational study, the care pathways of patients hospitalized in 24 hospitals across France. Among the 3,677 patients, hospitalization in a cardiology department (either intensive care or conventional cardiology) was significantly

associated, after propensity score matching, with a reduction in in-hospital mortality (OR 0.61 [0.44–0.84], p = 0.002).

These three studies highlighted the necessity of collaboration between emergency physicians and cardiologists in managing AHF episodes and suggest the potential benefit of personalized treatment tailored to each patient.

Key words: acute heart failure; diuretics; nitrates; noninvasive ventilation; care pathway

Liste des abréviations

AHA : American Heart Association

BiPAP : Bilevel positive airway pressure

CPAP : Continuous positive airway pressure

ESC : European Society of Cardiology

FEVG : Fraction d'éjection du ventricule gauche

FiO_2 : Fraction inspire d'oxygène

IC : Intervalle de confiance

ICA : Insuffisance cardiaque aiguë

ICC : Insuffisance cardiaque chronique

IDM : Infarctus du myocarde

ISDN : Isosorbide dinitrate

IV : Intra-veineux

NTG : Nitroglycérine

OR : Odd-ratio

PaO_2 : Pression partielle artérielle en oxygène

PPC : Pression positive continue

SAMU : Service d'aide médicale urgente

SGLT : Sodium – Glucose coTransporter

SMUR : Service mobile d'urgence réanimation

SpO_2 : Saturation pulsée en oxygène

USIC : Unité de soins intensifs de cardiologie

VNI : Ventilation non invasive

I. INTRODUCTION

La prise en charge d'un patient pris en charge par le médecin urgentiste, en préhospitalier et aux urgences nécessite d'une part de mettre en place le traitement adapté au tableau clinique et à la pathologie du patient et d'autre part d'organiser, de manière non programmée, un parcours de soin débutant au domicile et allant si nécessaire jusqu'à une hospitalisation dans un service hospitalier.

Parmi les motifs de consultation fréquents aux urgences, l'insuffisance cardiaque aiguë est un exemple de prise en charge complexe. La présentation clinique des patients est variée et souvent intriquée avec celles de pathologies sous-jacentes ou associées, rendant le diagnostic syndromique et étiologique potentiellement complexe. De plus, malgré de nombreuses recommandations de diverses sociétés, le traitement à mettre en place n'est pas consensuel et varie fortement, laissé souvent à l'appréciation du clinicien. Enfin, le parcours de soin est lui aussi fluctuant. Alors qu'il s'agit d'une pathologie relevant de la cardiologie, le caractère polypathologique des patients et/ou leur âge élevé engendre souvent une orientation vers un service de médecine ou de gériatrie.

Aujourd'hui en France, on dénombre environ 160000 hospitalisations par an pour insuffisance cardiaque aiguë.(1) Dans 65% des cas, cette hospitalisation a lieu après une consultation aux urgences.(2) Environ 8% des patients décèdent au cours de l'hospitalisation et 20% d'entre eux sont réhospitalisés dans l'année qui suit.(1–3) Ces consultations et hospitalisations itératives, ainsi que les symptômes souvent présents à bas bruit au quotidien, impactent de manière importante la qualité de vie de ces patients. Dans ce contexte, il apparait donc nécessaire d'optimiser la prise en charge initiale de ces patients, en préhospitalier et aux urgences.

1. INSUFFISANCE CARDIAQUE AIGUË : DEFINITION, TABLEAUX CLINIQUES

1.1 Insuffisance cardiaque

L'insuffisance cardiaque est un syndrome clinique (dyspnée, asthénie, œdèmes des membres inférieurs) résultant d'une élévation anormale des pressions de remplissage des cavités cardiaques et /ou d'une baisse du débit cardiaque, secondairement à une ou plusieurs anomalies structurelles ou fonctionnelles. Ces anomalies sont généralement myocardiques (ischémie, hypertrophie, dilatation), mais peuvent aussi être valvulaires ou rythmiques.(4,5) En cas d'insuffisance cardiaque chronique (ICC), la pathologie est catégorisée en fonction de la fraction d'éjection du ventricule gauche (FEVG) :

- FEVG ≤ 40% : ICC à FEVG diminuée (HFrEF en anglais)
- FEVG de 41 à 49% : ICC à FEVG légèrement diminuée (HFmrEF)
- FEVG ≥ 50% : ICC à FEVG préservée (HFpEF).

Cette distinction détermine le traitement de fond des patients.

1.2 Insuffisance cardiaque aiguë

L'insuffisance cardiaque aiguë (ICA) correspond à une apparition ou une aggravation rapide des symptômes d'insuffisance cardiaque. Elle survient chez des patients ayant une ICC (décompensation aiguë d'insuffisance cardiaque) ou chez des patients n'en ayant pas jusque-là (ICA de novo).

Les symptômes de l'ICA sont liés à deux états physiopathologiques distincts :

L'hypoperfusion : en cas de diminution importante du débit cardiaque, les apports tissulaires en oxygène deviennent insuffisants, ce qui entraîne une dysfonction d'organes.

La congestion : il s'agit d'une accumulation de liquide dans le secteur extracellulaire, secondaire à plusieurs mécanismes notamment une activation neuro-hormonale.

La majorité des patients présentent principalement des signes de congestion (œdèmes des membres inférieurs ou des lombes en position déclive, dyspnée, hypoxémie, crépitants à l'auscultation pulmonaire). Celle-ci se fait soit par redistribution vasculaire, soit par rétention hydrosodée. Ces deux mécanismes sont souvent intriqués et résultent tous deux d'une activation neuro-hormonale.(6) La redistribution vasculaire est un passage d'une partie du volume sanguin des secteurs splanchnique et périphérique vers la circulation pulmonaire. La rétention hydrosodée est une réabsorption excessive d'eau et de sodium au niveau rénal. Le tableau est désigné par « surcharge hydrosodée » et s'accompagne généralement d'une prise de poids.

Tableaux cliniques

Typiquement, quatre tableaux différents d'ICA sont décrits, selon leurs mécanismes et leurs présentations cliniques (4) :

- ✓ **Décompensation aiguë d'insuffisance cardiaque (50-70% des cas)**

Ces épisodes surviennent généralement dans un contexte de surcharge hydrosodée, et sont plutôt d'apparition progressive. La présentation clinique est congestive, mais y sont parfois associés des signes d'hypoperfusion.

- ✓ **Œdème aigu pulmonaire**

Ces épisodes surviennent de manière rapide, par redistribution vasculaire, chez des patients qui sont ou non insuffisants cardiaques chroniques (dans ce cas, plutôt une dysfonction diastolique). La présentation clinique est congestive, surtout au niveau pulmonaire (crépitants). Il s'y associe souvent une détresse respiratoire aiguë. Le débit cardiaque est généralement conservé, il n'y a donc pas de signes d'hypoperfusion.

- ✓ **Insuffisance ventriculaire droite isolée**

Ce tableau survient dans un contexte de défaillance cardiaque droite (à la suite d'une ischémie du cœur droit) ou d'hypertension artérielle pulmonaire précapillaire (embolie pulmonaire). La présentation clinique est une congestion périphérique (œdèmes des membres inférieurs, turgescence jugulaire etc) et des signes d'hypoperfusion par diminution du débit du ventricule gauche.

- ✓ **Choc cardiogénique**

Ce tableau survient dans un contexte de dysfonction myocardique sévère, de manière aiguë (infarctus du myocarde, myocardite), ou progressive (ICC sévère). La présentation clinique est congestive avec des signes d'hypoperfusion qui sont souvent au premier plan.

2. PRINCIPES DU TRAITEMENT

Le traitement du patient en ICA fait l'objet de différentes recommandations de sociétés savantes, notamment Européenne (European Society of Cardiology, ESC) et Américaine (American Heart Association / American College of Cardiology / Heart Failure Society of America, AHA/ACC/HFSA) qui sont mises à jour régulièrement, intégrant les résultats de recherches récentes.(4,5) De nombreux consensus ou opinions d'experts sont aussi publiés à ce sujet.(6–8)

Ce traitement est d'une part symptomatique (selon les cas, traitement de l'hypoxémie, de la dyspnée voire d'un état de choc) et d'autre part étiologique (traitement de la congestion, diminution de la précharge et de la postcharge par vasodilatation). Il est par ailleurs nécessaire de rechercher et de traiter un potentiel facteur déclenchant ayant conduit à la décompensation d'une insuffisance cardiaque chronique équilibrée. Ces facteurs déclenchants sont : syndrome coronaire aigu, autre pathologie myocardique aiguë (myocardite), cause mécanique : valvulaire, péricardique (tamponnade), poussée hypertensive, fibrillation atriale ou autre arythmie cardiaque, infection, embolie pulmonaire, mauvaise observance du traitement médicamenteux ou du régime hyposodé, iatrogénie, trouble métabolique : anémie, dysthyroïdie. Ils peuvent être isolés, associés ou absents. La recherche et le traitement des facteurs déclenchant ne seront pas développés dans ce travail.

Nous allons développer ici les principaux modes de traitement à la phase initiale de l'insuffisance cardiaque aiguë sans choc cardiogénique : l'utilisation de diurétiques, de dérivés nitrés, et de la ventilation non invasive.

2.1 Diurétiques de l'anse

Les diurétiques, et principalement les diurétiques de l'anse, sont aujourd'hui considérés comme la pierre angulaire du traitement de l'ICA. Le registre américain ADHERE rapporte que près de 90% des patients hospitalisés pour ICA en bénéficient.(9) Il existe trois principales molécules de diurétiques de l'anse : le furosémide, qui est le plus largement utilisé, le torsemide et le bumetanide.

2.1.1 Données pharmacologiques

Au niveau rénal, les diurétiques de l'anse bloquent la réabsorption de sodium, de chlore et de potassium, et induisent la sécrétion de rénine. Au niveau vasculaire systémique, ils entraînent une vasodilatation. Ils activent par ailleurs la synthèse de prostaglandines (effet vasodilatateur systémique et des artérioles rénales afférentes).(10–16)
Un traitement par diurétiques de l'anse peut entraîner différents effets secondaires : Une dégradation de la fonction rénale (Celle-ci n'est toutefois pas associée à un mauvais pronostic si elle survient en cas de bonne réponse aux diurétiques, elle est alors qualifiée de « pseudo-dégradation de fonction rénale »), des troubles hydroélectrolytiques (hyponatrémie et/ou hypokaliémie avec risque d'arrêt cardiaque par trouble du rythme), et/ou une activation neuro-hormonale.(17–22)

2.1.2 Preuve de l'efficacité

Depuis une soixantaine d'années, le traitement de l'ICA par des diurétiques de l'anse s'est imposé comme une évidence, fort de son mécanisme décongestif, et de son efficacité dans l'insuffisance cardiaque chronique.(23) Toutefois, aucun essai contrôlé randomisé contre placebo ou contre une autre classe thérapeutique n'a jamais été menée, et aujourd'hui, seuls la posologie, le mode d'administration et les traitements adjuvants sont évalués.(24) Une analyse du registre américain ADHERE a comparé 56484 patients hospitalisés pour ICA recevant ou non des diurétiques de l'anse IV, et a trouvé que les diurétiques amélioraient la dyspnée et la surcharge mais augmentaient la durée d'hospitalisation, la durée de séjour en réanimation et la mortalité.(25)

2.1.3 Posologie et mode d'administration

Peu d'études ont comparé différentes doses de diurétiques de l'anse administrées au moment d'un épisode d'ICA. Une analyse secondaire de l'étude ESCAPE, en 2007, retrouvait une association entre des doses élevées quotidiennes de diurétiques et la mortalité à 6 mois. La dose médiane de diurétique était de 400mg/j.(26) Une analyse du registre américain ADHERE, en 2008, a trouvé qu'une dose ≥ 160 mg au cours des 24 premières heures était associée à un plus fort taux de mortalité intra-hospitalière, un plus fort taux d'hospitalisations prolongées, à des séjours en soins intensifs plus longs et davantage d'effets secondaires rénaux.(27) Une analyse du registre ALARM-HF n'a pas trouvé de différence en termes de mortalité intra hospitalière entre des doses > ou < 1mg/kg de diurétiques.(28) Enfin, en 2019, une analyse post-hoc de l'étude DIUR-HF, trouvait que les patients recevant ≥ 125 mg par jour de furosémide avaient un taux plus élevé de mortalité ou réhospitalisation pour ICA et une réponse aux diurétiques plus faible.(29) Ces quatre analyses sont plutôt en faveur de doses « peu élevées ».
Entre 2008 et 2009, l'étude DOSE-AHF a randomisé 308 patients insuffisants cardiaques chroniques, prenant entre 80 et 240 mg de furosémide au quotidien en quatre bras différents : dose totale sur 24h équivalente à leur dose quotidienne (faible dose) ou dose totale sur 24h équivalente à 2,5 fois leur dose quotidienne (forte dose) et administration en bolus IV toutes les 12 heures ou en IV continu sur 24 heures. Les résultats montraient une perte de poids et une perte hydrique significatives et une tendance non significative de meilleure régression des symptômes par échelle visuelle analogique pour le traitement par forte dose.(30) La synthèse des études portant sur la posologie des diurétiques de l'anse dans l'ICA est présentée dans le tableau 1 en annexe.

A l'inverse de la dose, le mode d'administration des diurétiques de l'anse a été largement étudié. Les premières études interventionnelles randomisées, sur de petits nombres de patients, étaient plutôt en faveur d'un traitement en IV continu, avec le constat d'une meilleure diurèse chez les patients traités en continu.(31–34) Cependant, l'étude DOSE-AHF n'a pas trouvé de différence en termes d'amélioration des symptômes, de modification de la créatinine ou dans les critères de jugements secondaires.(30) De même, une méta-analyse récente de la Cochrane Database n'a pas trouvé de différence entre les deux modes d'administration.(35) Aucun mode d'administration ne semble donc prévaloir sur l'autre. La synthèse des études portant sur le mode d'administration des diurétiques de l'anse est présentée dans le tableau 2 en annexe.

2.1.4 Stratégie thérapeutique guidée par la réponse et notion de résistance

La réponse aux diurétiques se définit par la quantité de déplétion hydrosodée provoquée par l'administration du traitement. Elle est associée à une meilleure évolution à moyen et long terme.(17,36,37) A l'inverse, une congestion résiduelle en fin d'hospitalisation pour ICA est de mauvais pronostic.(38) Plusieurs critères sont utilisés pour évaluer la réponse aux diurétiques : amélioration de la congestion clinique, perte de poids, diurèse et natriurèse, biomarqueurs (peptides natriurétiques), et hémoconcentration.(17,39–55) Pour obtenir une réponse suffisante tout en limitant la survenue d'effet secondaires, il a été proposé d'adapter la posologie administrée sur l'évolution des éléments sus-cités.(39,56–58) Dans ce contexte, une stratégie d'adaptation a été préconisée par des groupes d'experts.(10,12) Celle-ci est en cours d'évaluation dans plusieurs études multicentriques.(59,60)

La résistance aux diurétiques est définie par « l'échec à l'obtention d'une décongestion avec une faible concentration urinaire en sodium malgré l'utilisation des doses maximales recommandées de diurétiques ».(11) Pour pallier cette résistance aux diurétiques, il existe plusieurs possibilités : majoration des doses, ajout d'une seconde molécule (diurétique thiazidique ou acétazolamide) ou encore ajout de sérum salé hypertonique. (10,12,61–68)

2.1.5 Recommandations

Les recommandations des principales sociétés savantes de cardiologie, européenne (ESC) et américaines (AHA), concernant les diurétiques de l'anse ont peu évolué ces 20 dernières années. Le niveau de recommandation pour leur utilisation est passé de IB à IC à l'ESC et de IC à IB à l'AHA. Elles s'appuient principalement sur des avis d'experts et depuis 2013 sur l'étude DOSE-AHF qui n'avait toutefois pas de bras placebo.(12,30) La synthèse de l'évolution des recommandations sur les diurétiques dans l'ICA est présentée dans le tableau 6 en annexe.

2.2 Vasodilatateurs

Les traitements vasodilatateurs, généralement IV, sont eux aussi utilisés dans l'ICA depuis de nombreuses années et notamment en cas d'hypertension artérielle, au vu de leur effet hypotenseur. Le terme « vasodilatateur » implique un effet physiologique et regroupe différents types de molécules : Les molécules à action vasodilatatrice directe, qui agissement sur les parois vasculaires, comme les dérivés nitrés et les molécules qui agissement via l'activation d'un récepteur, comme les peptides natriurétiques.(69)
Les vasodilatateurs les plus utilisés sont les dérivés nitrés. Ceux-ci figurent actuellement dans les recommandations de l'ESC et de l'AHA.(4,5) Il existe trois principales molécules de dérivés nitrés injectables, dont l'utilisation semble varier selon le pays : la nitroglycérine (NTG), l'isosorbide dinitrate (ISDN) et le nitroprusside.(70)

2.2.1 Notions pharmacologiques

Les dérivés nitrés entraînent une relaxation des cellules musculaires lisses des parois vasculaires. A faible dose ils agissement principalement au niveau veineux et à forte dose ils agissent au niveau artériel, y compris sur les artères coronaires. Dans l'ICA, leur action permet la réduction des pressions de remplissage des ventricules droit et gauche, l'augmentation de la perfusion coronaire et la diminution d'une potentielle régurgitation mitrale, tout ceci aboutissant à une augmentation du débit cardiaque.(71). L'administration de dérivés nitrés peut entraîner plusieurs effets secondaires : céphalées, hypotension artérielle, nausées et activation neuro-hormonale.(72,73)

2.2.2 Preuve de l'efficacité

Les dérivés nitrés étaient initialement utilisés dans l'infarctus aigu du myocarde (IDM) du fait de leur action vasodilatatrice coronaire. Les premières études portant sur leur efficacité dans l'insuffisance cardiaque aiguë ont donc été menées dans des contextes post-IDM.(74–76) Celles-ci retrouvaient une meilleure action hémodynamique à court terme, sans différence sur la mortalité. Deux études ont randomisé des patients en ICA hors contexte d'IDM entre un traitement par dérivés nitrés et un autre traitement. Beltrame et al n'ont pas trouvé de différence en termes de PaO_2/FiO_2 ou de nécessité de ventilation mécanique entre des patients recevant du

furosémide et de la morphine et des patients recevant de la nitroglycérine et du N-acetyl-cystéine.(77) Levy et al ont mis en place un protocole avec nitroglycérine chez des patients avec ICA hypertensive. Les patients bénéficiant de ce protocole semblaient avoir moins de complications cardiovasculaires et nécessiter moins d'intubation, toutefois aucun test de comparaison statistique n'a été réalisé avec le groupe contrôle.(78) Par la suite, plusieurs études rétrospectives ont trouvé un meilleur pronostic chez les patients ayant reçu des dérivés nitrés lors d'un épisode d'ICA.(79,80) Enfin, deux études ont testé une stratégie de traitement intensif par dérivés nitrés sublinguaux et transdermiques. La première, réalisée entre 2006 et 2008 chez 128 patients, a trouvé une meilleure diminution du BNP dans le groupe avec vasodilatation intensive par rapport aux soins usuels, et une tendance non significative à moins d'hospitalisation en soins intensifs, sans impact sur la mortalité ou les réhospitalisations.(81) La seconde, réalisée entre 2007 et 2018 chez 788 patients, ne retrouvait pas de différence de mortalité ou de réhospitalisation à 180 jours par rapport aux soins usuels. La pression artérielle baissait plus rapidement dans le groupe de vasodilatation intensive, mais après trois jours les valeurs étaient comparables dans les deux groupes.(82) Ces études sont plutôt en faveur d'une utilisation des dérivés nitrés. La synthèse des études portant sur l'efficacité des vasodilatateurs dans l'ICA est présentée dans le tableau 3 en annexe.

2.2.3 Posologie et mode d'administration

Tout comme pour les diurétiques de l'anse, l'administration des dérivés nitrés IV peut se faire soit en continu, soit par bolus. Dans ce dernier cas, les boli sont répétés à court intervalle, afin de maintenir une concentration plasmatique suffisante. L'administration par bolus permettrait de limiter l'accoutumance aux dérivés nitrés et ne semble pas, malgré les doses plus importantes administrées, provoquer davantage d'hypotension.(83,84) Concernant la posologie, l'équipe de Cotter et al a comparé l'administration d'une forte dose d'ISDN dans deux essais randomisés. Dans le premier, 110 patients recevaient soit de l'ISDN en boli forte dose soit du furosémide forte dose et de l'ISDN faible dose en IV continu.(85) Dans la seconde, 40 patients bénéficiaient soit d'ISDN en boli forte dose, soit de ventilation non invasive et d'ISDN en continu faible dose.(86) Dans les deux études, une forte dose d'ISDN prévenait la survenue d'infarctus du myocarde et la nécessité d'intubation.

Par ailleurs, les dérivés nitrés existent sous d'autres formes galéniques.(87) Les patches transdermiques sont utilisés dans l'angor instable à visée vasodilatatrice coronaire, et dans

l'insuffisance cardiaque chronique. La forme sublinguale (en comprimés ou en spray) est utilisée dans le syndrome coronaire aigu. Ces formes ont été évaluées, de manière moindre, dans l'ICA.(81,82,88) Toutefois, leur biodisponibilité moins certaine et leur présentation moins pratique pour une éventuelle titration que la forme IV n'en font pas la forme de premier choix dans les épisodes d'ICA. La synthèse des études portant sur la posologie des dérivés nitrés dans l'ICA est présentée dans le tableau 4 en annexe.

2.2.4 Recommandations

Sur les vingt dernières années, l'utilisation de vasodilatateurs, notamment des dérivés nitrés, a été recommandée par l'ESC et l'AHA en cas d'ICA et en l'absence d'hypotension. Toutefois, la force de ces recommandations a progressivement diminué, passant de IB à IIbB pour les européennes et de IIaC à IIbB pour les Américaines. Plusieurs évolutions sont à noter : le nésiritide, apparu au début des années 2000, a disparu des dernières recommandations, probablement en raison d'une survenue trop fréquente d'hypotensions. Par ailleurs l'utilisation en cas de rétrécissement valvulaire, notamment aortique, était initialement déconseillé ; elle est maintenant recommandée suite à une étude ayant montré une efficacité du nitroprusside sur la fonction cardiaque de 25 patients avec rétrécissement aortique sévère.(89)
Concernant la posologie recommandée, elle n'a pas changé. Il est préconisé une utilisation par titration, et l'ESC préconise :
- nitroglycérine début 10-20 µg/min et augmenter jusque 200 µg/min
- ISDN bolus initial puis 1mg/h et augmenter jusque 10mg/h
- nitroprusside 0.3 µg/kg/min et augmenter jusque 5 µg/kg/min

La synthèse de l'évolution des recommandations sur les vasodilatateurs dans l'ICA est présentée dans le tableau 7 en annexe.

2.3 Ventilation non invasive

Lorsque l'apport d'oxygène est insuffisant à remonter la SpO2 du patient, ou lorsque celui-ci présente une hypercapnie et/ou des signes de détresse respiratoire, le traitement consiste en l'apport d'une pression positive d'un mélange air/oxygène afin d'améliorer la ventilation et les échanges gazeux. Historiquement, cet apport de pression se faisait chez des patients intubés et restait limité aux services de réanimation. Le développement, dans les années 1980s, d'interfaces non invasives a permis d'une part de le diffuser dans les services d'urgence, de SMUR et les unités de soins intensifs de cardiologie (USIC), et d'autre part d'en faire bénéficier un plus grand nombre de patients qui n'auraient pas forcément été éligibles à l'intubation.

2.3.1 Principes de la VNI et effets physiologiques

Lorsqu'un patient bénéficie de ventilation mécanique, on lui apporte une pression de gaz supplémentaire à celle induite par ses efforts ventilatoires. Dans le cadre de la ventilation dite « non invasive », il existe plusieurs possibilités :

- Pression positive continue (PPC ou CPAP en anglais). : la pression apportée est constante pendant tout le cycle respiratoire.
- Pression positive à deux niveaux : il est apporté d'une part une pression positive continue de fond, présente notamment au moment de l'expiration et qui est appelée « pression expiratoire positive » (PEP) et d'autre part une pression supplémentaire au moment de l'inspiration, appelée « aide inspiratoire » (AI), dont le déclenchement est provoqué par l'effort inspiratoire du patient. Ce mode à deux niveaux est appelé « BiPAP ».(90)

L'application d'une PPC va recruter les alvéoles collabées, lutter contre la pression hydrostatique capillaire pulmonaire, augmenter la compliance pulmonaire, diminuer la résistance des voies aériennes et augmenter les échanges gazeux et la P_aO_2 et donc diminuer le shunt intra pulmonaire. Au niveau hémodynamique, l'augmentation de la pression intrathoracique secondaire à la PPC diminue le retour veineux et donc la précharge des ventricules ainsi que la post charge du ventricule gauche, ce qui permet d'augmenter le volume d'éjection systolique et le débit cardiaque. L'application d'une AI va réduire le travail des muscles respiratoires et améliorer le volume courant.(91–95)

2.3.2 Preuve de l'efficacité

Dès les années 1980s et au début des années 2000s, plusieurs essais contrôlés de petite taille ont été menés chez des patients en ICA et ont conclu à une efficacité de la VNI par rapport à une oxygénothérapie simple, pour diminuer plus rapidement les symptômes de détresse respiratoire aiguë, améliorer plus rapidement les gaz du sang et pour certaines réduire la nécessité d'intubation et/ou la mortalité.(96–104)

En 2008, l'étude 3CPO a inclus et randomisés 1069 patients en ICA à recevoir une oxygénothérapie standard, une VNI par PPC ou une VNI paf BiPAP. La dyspnée et les gaz du sang après 1 heure de traitement étaient à nouveau améliorés chez les patients bénéficiant de VNI par rapport à l'oxygène seul, mais il n'y avait pas de différence de mortalité.(105)

Toutefois, les méta-analyses sur données regroupées ayant utilisé les patients de cette étude ont trouvé que la VNI réduisait la mortalité et le taux d'intubations.(106,107) La synthèse des études portant sur l'efficacité de la VNI dans l'ICA est présentée dans le tableau 5 en annexe.

2.3.3 Intérêt de l'aide inspiratoire

Plusieurs auteurs ont comparé entre eux les deux modes ventilatoires avec ou sans aide inspiratoire : PPC et BiPAP dans l'ICA. Aucune des études n'a trouvé de différence en termes de taux d'intubation ou de mortalité.(108–112)

2.3.4 Recommandations

Les recommandations de l'European Society of Cardiology (ESC) préconisent l'utilisation de la VNI en cas de détresse respiratoire, afin d'éviter l'intubation. Le niveau de recommandation était initialement IIaA et est passé à IIaB en 2008 avec la publication de l'étude 3CPO.(105) L'utilisation de ventilation invasive ou non invasive n'apparait pas dans les recommandations américaines de l'American Heart Association (AHA). La synthèse de l'évolution des recommandations sur la VNI dans l'ICA est présentée dans le tableau 8 en annexe.

3. PARCOURS DE SOINS

Lorsqu'un patient est pris en charge à l'hôpital pour un épisode d'ICA, la question de son orientation se pose au médecin urgentiste, à plusieurs reprises, en préhospitalier ou aux urgences :

3.1 Quel mode de transport vers l'hôpital ?

Plusieurs études se sont intéressées à l'impact du mode d'arrivée des patients consultant pour ICA aux urgences sur le pronostic à moyen terme. Dans des analyses ancillaires des études ASCEND-HF et EURODEM, le fait d'arriver aux urgences par ambulance semblait ou était associé à une plus grande mortalité à 30 et 180 jours.(113,114) De même, dans une étude prospective sur 12600 patients, ceux transportés par ambulance avaient un taux de mortalité à 7 jours plus élevé.(115) Ces résultats peuvent s'expliquer par le fait que les patients transportés par ambulance sont plus graves ou plus comorbides que ceux arrivant par leurs propres moyens et que cette différence était mal contrebalancée par les ajustements statistiques. Par ailleurs, il n'était pas précisé si des traitements ont été administrés au cours du transport, ce qui est possible dans les systèmes avec ambulances médicalisées ou dans certains systèmes de « paramedics ».(116) Une petite étude observationnelle française analysant le parcours de soin de 119 patients en ICA n'a quant à elle pas retrouvé de différence pronostique entre les patients arrivés par transport médicalisé et les autres.(117)

3.2 Quel service d'accueil ?

L'accueil des patients transportés par le SMUR et admis directement en USIC est une pratique que l'on peut rencontrer en France, en particulier dans les zones à forte densité hospitalière comme l'Ile de France. Cette stratégie permet d'éviter une attente parfois prolongée aux urgences, à l'origine d'un potentiel retard de prise en charge et/ou de l'inconfort du patient.(118) Dans les autres pays, la grande majorité des patients semblent être transportés aux urgences pour une première évaluation pour la plupart des pathologies. Il existe toutefois peu de littérature à ce sujet.

3.3 Quelle orientation à l'issue de la prise en charge aux urgences ?

Le choix d'orientation (retour à domicile ou hospitalisation) après diagnostic et initiation du traitement aux urgences implique deux types de risques : 1° si le patient rentre à domicile à tort, il peut ne pas avoir reçu un traitement suffisant, et donc ne pas s'améliorer voire s'aggraver ce qui le conduira à reconsulter aux urgences, à dégrader sa qualité de vie et/ou dans le pire des cas à mourir ; 2° à l'inverse, si le patient est hospitalisé à tort, il risque de souffrir des complications liées à une hospitalisation (complications de décubitus, dénutrition, perte de lien social), d'engendrer des coûts inutiles et/ou d'occuper un lit qui pourrait bénéficier à un autre patient. Plusieurs auteurs et sociétés savantes ont souligné l'importance de ce choix. (119–124)
Le taux de patients rentrant à domicile après consultation aux urgences varie en fonction du pays et du système de soins, allant de 16% (Etats-Unis) à 36% (Canada).(121) Après 3 mois, environ 60% d'entre eux auront reconsulté ou seront décédés.(125) Il semble que ces taux de mortalité et de reconsultation soient plus élevés que ceux des patients ayant été réhospitalisés.(126–128) La raison de ces taux plus élevés de décès et de reconsultation pourrait être la difficulté de jugement des médecins urgentistes vis-à-vis de la possibilité de retour à domicile. Dans une étude rétrospective avec définition d'un risque a posteriori, 14% et 11% des patients à haut et très haut risque étaient rentrés à domicile après les urgences alors que 66% de ceux à faible risque avaient été hospitalisés.(129)
Dans ce contexte, différents outils ont été construits afin de sélectionner les patients pouvant rentrer à domicile de manière sûre, c'est-à-dire avec un faible risque de complications entraînant le décès et/ou la nécessité de reconsulter aux urgences.(122) Plusieurs scores ont été créés, les premiers incluant principalement des biomarqueurs et paramètres vitaux comme la pression artérielle, les suivants étant plus complexes.(120) Parmi eux, le « Ottawa Heart Failure Risk Scale », le « Emergency Heart Failure Mortality Risk Grade » ou encore le « Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF » (MEESSI-AHF).(115,130–136)
Les recommandations ESC de 2021 indiquent qu'en cas de symptômes modérés et en l'absence de dysfonction rénale, d'élévation du taux de troponine ou de NT-proBNP, le patient pourrait rentrer à domicile après administration d'une faible dose de diurétiques et une adaptation du traitement de fond et être surveillé en ambulatoire.(4)

3.4 Quel service d'hospitalisation ?

Les patients hospitalisés lors d'un épisode d'ICA ne le sont pas toujours en service de cardiologie : en raison d'un nombre limité de places d'hospitalisation et de l'existence de pathologies intriquées induisant la nécessité d'une prise en charge plus globale, ils sont parfois orientés vers un service de médecine interne ou de gériatrie. Si le patient présente des critères de gravité, l'orientation se fait vers un service de soins intensifs ; ces critères sont précisés dans les recommandations de l'ESC.(4) A l'inverse, aucun critère d'orientation vers un service de cardiologie conventionnelle plutôt que de médecine interne ou de gériatrie n'existe et la décision se prend plutôt au cas par cas.

Dans plusieurs études, le pronostic des patients semblait meilleur en cas d'hospitalisation en cardiologie ou identique mais avec un niveau de gravité initiale plus important pour les patients orientés vers la cardiologie.(137,138) La prise en charge des patients ne semble pas être différente en phase initiale : une analyse ancillaire de l'étude REALITY-AHF n'a pas trouvé de différence de traitement initié aux urgences lorsque le médecin responsable était un urgentiste ou un cardiologue.(139) En revanche, les patients hospitalisés en cardiologie semblent bénéficier davantage de l'introduction d'un traitement de fond conforme aux recommandations.(137)

Afin de réduire le nombre de patients hospitalisés, tout en permettant l'évaluation de l'efficacité du traitement initial et la mise en place du traitement de fond, une alternative a été proposée : les unités d'observation ou de courte hospitalisation. Ces unités sont dédiées aux patients en ICA ou rattachées au service des urgences.(140,141) L'admission en unité d'observation ainsi que le retour à domicile au décours ou le transfert vers un autre service d'hospitalisation se font alors selon certains critères proposés par Peacock et al.(124,140) Dans une analyse du registre espagnol EAHFE, la présence d'une unité de courte hospitalisation dans l'hôpital où le patient consulte pour ICA induisait un taux d'hospitalisation plus important mais réduisait le taux de décès à 30 jours et de reconsultation parmi les patients étant rentrés chez eux après passage aux urgences.(141)

4. TEMPORALITE DE LA PRISE EN CHARGE

Dans plusieurs pathologies aiguës, il a été montré qu'une réduction du temps entre l'apparition des symptômes et l'initiation des traitements améliorait le pronostic.(142,143) Dans l'ICA, ce principe semble moins évident, puisque les symptômes apparaissent plus ou moins progressivement et leur début ne peut être daté précisément comme c'est le cas pour une douleur thoracique ou un déficit neurologique. Plusieurs études se sont toutefois intéressées au délai entre l'arrivée du patient et l'initiation du traitement. L'étude REALITY-AHF observationnelle a trouvé qu'une initiation de diurétiques moins de 60 minutes après l'arrivée aux urgences « door-to-furosemide time » permettait de réduire la mortalité intra-hospitalière.(144) Chez les patients du registre ADHERE, l'initiation de nesiritide aux urgences plutôt qu'en service d'hospitalisation réduisait la durée d'hospitalisation et le risque de transfert en soins intensifs et l'initiation d'un traitement vasoactif quel qu'il soit permettait, si elle avait lieu dans les 6 premières heures, de réduire la mortalité intra hospitalière par rapport à une initiation plus tardive.(27,145) Ces résultats sont donc en faveur d'une initiation rapide du traitement.

Un des moyens d'initier rapidement le traitement est de le débuter avant même l'arrivée à l'hôpital, dès la prise en charge préhospitalière. La présence d'un médecin dans les ambulances de nombreux systèmes préhospitaliers et la possibilité d'administrer certains traitements par du personnel paramédical sous l'égide de protocoles dans de nombreux autres permettent en pratique débuter VNI et traitement médicamenteux dès le domicile du patient.(146–152) Dans les années 1990, une étude rétrospective trouvait que l'administration d'un traitement par furosémide, nitroglycérine et/ou morphine en préhospitalier diminuait la mortalité intra hospitalière.(146) De même dans l'étude SEMICA-2, une analyse de patients issus du registre espagnol EAHFE transportés par ambulances médicalisées, les patients recevant en préhospitalier au moins deux traitements parmi VNI / oxygène / nitroglycérine / diurétiques IV avaient une mortalité à 7 jours moins élevée que ceux n'en recevant qu'un seul ou aucun.(147) Quand on regarde chaque traitement séparément, c'est uniquement l'administration de nitroglycérine qui avait un impact significatif et ces résultats se confirment dans des études dédiées chez les patients du même registre : l'administration en préhospitalier de diurétiques IV n'avait pas d'impact sur les critères de jugements, par contre les patients ayant reçu de la nitroglycérine IV avait une mortalité moins élevée que ceux n'en recevant pas, contrairement aux patients n'en ayant reçu qu'aux urgences.(153,154) A ce jour, et bien qu'en 2015 un groupe de travail se positionnait en faveur d'une administration des traitements médicamenteux en préhospitalier, celle-ci, il n'est pas recommandé par l'ESC ou l'AHA et seule l'utilisation de la VNI est préconisée par l'ESC en cas de signe de détresse respiratoire aiguë.(4,7)

5. SUIVI DES RECOMMANDATIONS

Pour une pathologie ou une situation donnée, les recommandations des sociétés savantes ou des organismes publiques de santé ont pour but de colliger les données récentes sur le sujet afin d'harmoniser les pratiques de tous les praticiens, et que tout patient concerné, où qu'il se trouve, ait accès à la même prise en charge fondée sur la preuve.(155) Bien que basées principalement sur des opinions d'experts, les recommandations sur la prise en charge de l'ICA qui préconisent une décongestion par diurétiques, une diminution de la précharge et de la post charge par vasodilatateurs et la recherche puis le traitement d'un potentiel facteur déclenchant semblent plutôt de bon sens. Pourtant, ces recommandations ne semblent que partiellement suivies : dans plusieurs registres de patients hospitalisés pour ICA, le taux de traitement reçu est relativement bas, notamment pour les dérivés nitrés.(156–158) Dans une étude prospective ayant porté sur quelques patients dans plusieurs centres en France, le traitement recommandé était initié dans 34% des cas et la recherche d'un facteur précipitant (syndrome coronaire aigu) réalisé dans 81% des cas mais traité le cas échéant uniquement dans 22% des cas, ce qui résultait en un suivi global des recommandations dans seulement 16% des cas.(159) Plusieurs raisons peuvent expliquer un suivi incomplet des recommandations, en dehors d'une potentielle méconnaissance desdites recommandations. En premier lieu, il peut s'agir de la survenue d'effets secondaires, tels qu'une dégradation de la fonction rénale ou une hypotension, ou alors même de la peur de leur survenue. Dans une étude prospective observationnelle sur le traitement de sortie de patients hospitalisés pour ICA, si le patient sortait avec une congestion résiduelle ou avec une faible dose de traitement neuro-hormonal, la raison avancée par le médecin était, dans 27% des cas, la survenue d'une insuffisance rénale.(160) Les autres raisons invoquées étaient la résistance au traitement ou une mauvaise observance, un compromis clinique avec tolérance d'une part d'œdème chronique, une hypotension ou une hypoalbuminémie. Au-delà de ça, on peut ajouter le fait, comme abordé précédemment, que les recommandations restent floues sur les indications et les temps d'administration des traitements, les posologies exactes et les associations éventuelles avec la VNI. Enfin, ces recommandations sont parfois discordantes de la réalité des patients, rendant leur application difficile ou inadaptée.(161,162) En France, l'étude ELISABETH a eu pour but d'implémenter un protocole de prise en charge des patients consultant aux urgences pour ICA dans le respect des recommandations, et, en la comparant aux soins usuels, d'évaluer son impact sur le devenir des patients dans 15 services d'urgences, ainsi que de renforcer, en cas de résultat positif, le niveau de preuve des recommandations de l'ESC.(163) La mise en place du protocole permettait un meilleur suivi des recommandations.(164) L'étude ELISABETH est présentée dans les annexes.

6. PROBLEMATIQUES

Au vu des éléments que nous venons de développer, plusieurs questions émergent. Premièrement, la place et la posologie des deux principaux traitements de la congestion (diurétiques et dérivés nitrés) n'ont jamais été validées de manière robuste et font désormais débat. Deuxièmement, il semble important de préciser s'il existe un bénéfice à la mise en place de la VNI dès la prise en charge en préhospitalier. Troisièmement, alors que les choix d'orientation du patient lors de sa prise en charge initiale ont été analysés un à un, peu d'études ont regardé l'impact du parcours de soins dans sa globalité.

II. IMPACT DES DOSES INITIALES DE DIURETIQUES ET DERIVES NITRES

Comme décrit dans l'introduction, les deux traitements médicamenteux de la congestion recommandés dans l'ICA sans choc cardiogénique sont les diurétiques de l'anse et les dérivés nitrés. Cependant, aucune étude n'a pu confirmer leurs bénéfices ni leur modalité d'administration optimales avec un bon niveau de preuve. Aujourd'hui, l'indication de ces deux traitements apparait comme un prérequis et ne semble jamais remise en question dans la littérature traitant de ce sujet.(4,5) Concernant la dose à administrer en phase aiguë, les études sont là aussi peu nombreuses. Pour les diurétiques, des études rétrospectives ayant montré qu'une forte dose - avec chaque fois une définition différente - pouvait avoir des effets délétères, il était préconisé depuis 20 ans de débuter par la plus petite dose efficace (20 à 40 mg d'équivalent furosémide ou la dose quotidienne chez les patients avec traitement au long cours), mais cette stratégie n'a jamais été testée, prospectivement ou même rétrospectivement.(26,27,29) A l'inverse, les recommandations américaines préconisent désormais une forte dose de diurétiques (au moins deux fois la dose quotidienne) à la suite des résultats de l'étude DOSE-AHF. Cette étude n'incluait cependant que des patients prenant au moins 80 mg de furosémide au quotidien, ses résultats paraissent donc difficilement généralisables.(30) Pour les dérivés nitrés, les quelques études ayant comparé une faible dose et une forte dose étaient en faveur d'une forte dose.(85,86) Pourtant les recommandations recommandent là aussi de débuter par la plus faible dose efficace.(4,5) Dans ce contexte, nous avons cherché à savoir s'il y avait une dose optimale pour ces deux traitements administrés en phase précoce.

L'étude ELISABETH, citée plus haut, avait comparé un groupe « soins usuels » et un groupe interventionnel dans lequel la prise en charge suivait un protocole didactique basé sur les recommandations ESC de 2016 en termes de bilan étiologique et traitement médicamenteux (40 mg de furosémide ou dose quotidienne et titration de dérivés nitrés IV de 3mg toutes les 5 minutes pendant 1 heure jusqu'à obtention d'une pression artérielle systolique < 100 mmHg). L'étude n'avait pas montré de différence significative sur le critère de jugement (nombre de jours vivant en dehors de l'hôpital) entre les deux groupes mais les doses de traitements elles-mêmes n'avaient pas directement été étudiées.(164)
Nous avons donc réanalysé, dans une première étude de ce travail de thèse, les données des patients de l'étude ELISABETH et regardé l'association entre la dose de diurétiques de l'anse et de dérivés nitrés administrées dans les quatre premières heures et le pronostic à 30 jours.

Association of early doses of diuretics and nitrates in acute heart failure with 30 days outcomes: ancillary analysis of ELISABETH study

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Aims **The optimal dose of diuretics and nitrates for acute heart failure treatment remains uncertain. This study aimed to assess the association between intravenous nitrates and loop diuretics doses within the initial 4 h of emergency department presentation and the number of days alive and out of hospital (NDAOH) through 30 days.**

Methods **This was an ancillary study of the ELISABETH stepped-wedge cluster randomized trial that included 502 acute heart failure patients 75 years or older in 15 French emergency departments. The primary endpoint was the NDAOH at 30 days. The total dose of intravenous nitrates and loop diuretics administered in the initial 4 h were each categorized into three classes: 'no nitrate', '> 0–16', and '> 16 mg' for nitrates and '< 60', '60', and '> 60 mg' for diuretics. Secondary endpoints included 30-day mortality, 30-day hospital readmission, and hospital length of stay in patients alive at 30 days. Generalized linear mixed models were used to examine associations with the endpoints.**

Results **Of 502 patients, the median age was 87 years, with 59% women. The median administered dose within the initial 4 h was 16 mg (5.0; 40.0) for nitrates and 40 mg (40.0; 80.0) for diuretics. The median NDAOH at 30 days was 19 (0.0–24.0). The adjusted ratios of the NDAOH were 0.88 [95% confidence interval (CI): 0.63–1.23] and 0.76 (95% CI: 0.58–1.00) for patients that received 60 and > 60 mg, respectively, compared with patients that received 40 mg or less of diuretics. Compared with patients who did not receive nitrates, the adjusted ratios of the NDAOH were 1.17 (95% CI: 0.82–1.67) and 1.45 (95% CI: 0.90–2.33) for patients who received 1–16 and > 16 mg, respectively. There was no significant association with any of the secondary endpoints.**

Conclusion **In this ancillary analysis, there was no significant association between different doses of diuretics and nitrates with the NDAOH at 30 days. Point estimates and CIs may suggest that the optimal doses are less than 60 mg of diuretics, and more than 16 mg of nitrates in the first 4 h.** *European Journal of Emergency Medicine* **XXX: XXXX–XXXX**

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Introduction

Medical treatment for acute heart failure (AHF) comprises two main therapeutic classes: diuretics, particularly loop diuretics, to reduce fluid overload, and intravenous (i.v.) vasodilators, notably nitrates, to mitigate cardiac preload and afterload [1,2].

For the past years, the European Society of Cardiology (ESC) guidelines as well as expert's consensus have recommended a low-dose approach to diuretics (a bolus of 20–40 mg of furosemide or equivalent in diuretics naive patients, or the preexisting daily oral dose in patients on an ambulatory diuretics regimen), along with a continuous intravenous (i.v.) infusion of nitrates starting at 10 µg/min of nitroglycerin or 1 mg/h of isosorbide dinitrate [2–5]. The American Heart Association (AHA) guidelines also suggest a titration regarding loop diuretics and i.v. nitrates doses [1]. This low-dose strategy is grounded in experts' opinions due to concerns over adverse events associated with higher doses [6–8]. Despite these recommendations, no clinical benefit of any dosing regimen has been demonstrated in AHF patients. In 2008, the DOSE-AHF trial compared two loop diuretics doses in AHF patients and found better early outcomes in the high-dose group. This study, however, included only patients who were already taking at least 80 mg per day of furosemide at home [9]. More recently, studies found contradictory results about the impact of these drugs on outcomes [10–12]. Furthermore, the strength of recommendations for i.v.

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vasodilators in AHF have been downgraded from class I to IIb over the years with the utility of i.v. vasodilators even questioned in the last ESC guidelines [2,13].

The ELISABETH stepped-wedge randomized trial recruited 502 patients in 15 French emergency departments (EDs) with AHF and found that an early intervention that improved physician's adherence to guidelines was not associated with 30-day hospital discharge or mortality. Within the intervention group, median furosemide doses were significantly lower (40 vs. 60 mg) and median i.v. nitrate doses were higher (27 vs. 4 mg) in the first 4 h compared with the control group [14]. However, the potential clinical benefits of dosing within this range remain unknown.

Aims

This ancillary study of the ELISABETH trial sought to investigate the association between i.v. nitrate and loop diuretics doses administered within the initial 4 h after ED presentation and the number of days alive and out of hospital (NDAOH) through 30 days, the risk of 30-day mortality and the risk of hospital readmission.

Methods

This constituted a secondary analysis of the ELISABETH trial, which was a prospective stepped-wedge cluster randomized interventional study. The trial aimed to compare a guidelines-based care bundle with usual care in the initial management of patients 75 years and older presenting to the ED with AHF. The guidelines-based care bundle encompassed early administration of i.v. nitrate boluses, a moderate dosage of i.v. loop diuretics, and the management of precipitating factors such as acute coronary syndrome, infection, or atrial fibrillation. In the control group, management was left to the discretion of the treating emergency physician. The study included and analyzed a total of 502 patients between December 2018 and September 2019 in 15 French EDs. Follow-up extended for a period of 30 days. Comprehensive details regarding the ELISABETH study's protocol and findings have been previously published [14,15].

Ethics

The ELISABETH trial was approved by an institutional review board (Comité de Protection des Personnes SOOM 2, Toulouse Academic Hospital, France). and written informed consent was sought for all patients. The investigation conformed with the principles outlined in the Declaration of Helsinki [16].

Data collection

During the ELISABETH study, the treatment administered to each patient in the ED was recorded, especially the total dose of i.v. nitrates and loop diuretics administered within the initial 4 h after inclusion. All the participating EDs used furosemide so there was no converting issue regarding the diuretics dose.

Additional variables that were likely to influence outcomes were also collected for the purpose of being included in the subsequent multivariable analysis: inclusion center, study design parameters (randomization group: intervention/control, cluster size and inclusion period), age, sex, comorbidities (chronic heart failure, and coronaropathy), baseline clinical parameters (oxygen saturation and systolic blood pressure), and troponin levels.

Considering the data distribution and the nonrespect of log linearity, the values for troponin and oxygen saturation were transformed into two categories – above or below the median value.

Study endpoints

The primary endpoint was the same as in ELISABETH study: NDAOH during the 30-day period after the ED visit.

Secondary endpoints consisted of 30-day all-cause mortality, hospital readmission within 30 days, and hospital length of stay in patients alive at 30 days.

Statistical analysis

The association between the total dose of each administered drug within the first 4 h and the NDAOH at 30 days was evaluated using a generalized linear mixed model with a negative binomial distribution (log link). The model included: the inclusion center as a random effect, and the total given dose and adjustment factors (age, chronic heart failure, coronaropathy, inclusion oxygen saturation, inclusion systolic blood pressure, and troponin concentration) as fixed effects.

The total doses of nitrates and loop diuretics were each categorized into three classes: no nitrate; >0–16, and >16 mg for nitrates and <60; 60 (most frequent dose), and >60 mg for diuretics.

The association between the total dose of each administered drug within the first 4 h and the secondary endpoints was evaluated using a generalized linear mixed model with a Bernoulli distribution (logit link). The model included: the inclusion center as a random effect and clinical baseline parameters as a fixed effect.

For 30-day mortality and hospital readmission, the total dose of diuretics was categorized into three classes: no diuretics, >0–40, and >40 mg.

Management of missing data

The NDAOH was available for all patients. For categorical outcome variables (death, hospital readmission) comorbidities, and the total doses of treatments, missing values were considered as not having the event or the comorbidity or as not having received the medication.

Only patients who survived to 30 days were included in the analysis of hospital length of stay. Missing values of hospital length of stay were not replaced, analyses were performed on available data. The length of stay was considered 0 days for patients who were not hospitalized.

In the case of the biological parameters (troponin and oxygen saturation) missing values were handled using multivariate imputation by chained equations (MICE) in R software. Fifteen imputed datasets were generated, and prediction models were developed for each dataset. Model parameter estimates were subsequently combined following Rubin's rules. Multiple imputation was executed for each analysis after transforming quantitative variables into categorical variables based on the original.

All statistical analyses were conducted by a qualified statistician employed at the URC-Est research coordinating center utilizing SAS software (version 9.4; SAS Institute Inc., Cary, North Carolina, USA) and R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) software.

Results

A total of 502 patients from the ELISABETH study were included in the analysis. The median age of the patients was 87 years (81.0; 91.0), 59% being women, and 54% having a history of chronic heart failure. During the initial 4 h, 259 patients (51.6%) received treatment with i.v. nitrates, with a median dose of 16 mg (5.0; 40.0), and 466 patients (93%) were treated with loop diuretics, with a median dose of 40 mg (40.0; 80.0). During the 30-day follow-up period, 45 (9%) patients died, and 59 (11.7%) were readmitted to the hospital. The median NDAOH in the total population was 19 (0.0–24.0). The median hospital length of stay was 8 days (5; 18).

Baseline characteristics, treatments administered, and endpoints can be found in Table 1.

Compared with patients that did not receive any nitrates, there was no association between the total dose of nitrate and the NDAOH: adjusted ratios were 1.17 [95% confidence interval (CI): 0.82–1.67] and 1.45 (95% CI: 0.90–2.33) for patients that received 1–16 and >16 mg, respectively. Point estimates, however, are in favor of larger doses of nitrates.

Compared with patients who received less than 60 mg of loop diuretics, there was no association between the total dose of diuretics and the NDAOH: adjusted ratios were 0.88 (95% CI: 0.63–1.23) and 0.76 (95% CI: 0.58–1.00) for patients that received 60 and >60 mg, respectively. Point estimates, however, tend toward a detrimental effect of higher doses.

The associations between the total dose of each drug and the primary endpoint are detailed in Table 2.

There was no statistically significant association of any dose of nitrates or diuretics with the secondary endpoints (Tables 3 and 4).

Table 1 Baseline characteristics

Variables	$N = 502$	Available
Age, median (IQR), years	87.0 (81.0; 91.0)	502
Sex, *n* (%)		
Women	298 (59.4)	502
Men	204 (40.6)	
Comorbidities, *n* (%)		
Chronic pulmonary disease	85 (16.9)	502
Chronic heart failure	269 (53.7)	501
Chronic kidney disease	122 (24.3)	502
Diabetes	146 (29.1)	502
Myocardial infarction	171 (34.1)	502
Vital signs at randomization, mean ±SD		
Heart rate, beats/min	86.5 ± 23.6	502
Oxygen saturation, %	90.9 ± 6.8	471
Respiratory rate, /min	26.0 ± 7.0	460
Systolic blood pressure, mmHg	151.4 ± 28.4	502
Temperature, ° C	36.7 ± 0.6	501
Medication at randomization, *n* (%)		
ACE inhibitor	142 (28.3)	502
ARB	120 (23.9)	502
Antibiotics	43 (8.6)	502
Anticoagulant	243 (48.4)	502
Antiplatelet	191 (38.0)	502
β-blockers	288 (57.4)	502
Diuretics	351 (69.9)	502
Nitrates	30 (6.0)	502
Laboratory results, median (IQR)		
BNP, ng/L	602.0 (284.5; 1114.5)	232
NT-proBNP, ng/L	4440 (2220; 8870)	260
Creatinine, mg/L	11.4 (8.8; 15.5)	500
C-reactive protein, mg/L	13.6 (5.0; 45.6)	391
Hemoglobin, mean±SD, g/dL	12.2 ± 1.9	499
Leukocytes, G/L	8.5 (6.6; 11.3)	500
Procalcitonin, µg/L	0.1 (0.1; 0.2)	99
Troponin, µg/L	0.0 (0.0; 0.1)	428
pH, mean ±SD	7.4 ± 0.1	386
PaCO2, mmHg	39.0 (34.0; 46.0)	386
PaO2, mmHg	72.0 (63.0; 90.0)	386
Bicarbonates, mean±SD, mmol/L	25.1 ± 4.8	371
Randomization, *n* (%)		502
Intervention group	199 (40)	
Control group	303 (60)	
Loop diuretics		
Given in the ED	469 (93.4)	502
Total dose in first 4 h in those who received it	40.0 (40.0; 80.0)	468
Total dose in first 4 h in the whole population	40.0 (40.0; 80.0)	501
i.v. nitrates		
Given in the ED	265 (52.9)	501
Total dose in first 4 h in those who received it	16.0 (5.0; 40.0)	261
Total dose in first 4 h in the whole population	1.0 (0.0; 18.0)	497
Endpoints		
Number of days alive and out of hospital, median (Q1–Q3)	19 (0.0–24.0)	502
30 days all-cause mortality, *n* (%)	45 (9.0)	502
30 days all-cause hospital readmission, *n* (%)	59 (11.7)	502
Hospital length of stay, median (Q1–Q3), days	8 (5; 18)	451

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic protein; ED, emergency department; IQR, interquartile range; i.v., intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Discussion

In this secondary analysis of a stepped-wedge cluster randomized controlled trial that compared a comprehensive care bundle intervention to usual care in AHF episodes of patients aged 75 or older, there was no statistically significant impact of the total administered dose of nitrates

Table 2 Association between the total dose in the initial 4 h and primary endpoint

Total dose during initial 4 h	Number of days alive and out of hospital, median (Q1–Q3) (minimum–maximum)	Unadjusted difference (95% CI)	Adjusted difference (95% CI)[a]	Unadjusted ratio (95% CI)	Adjusted ratio (95% CI)[a]
i.v. nitrates					
No nitrates ($n=243$)	18.0 (0.0–24.0) (0.0–30.0)	0	0	1	1
1–16 mg ($n=131$)	18.0 (0.0–24.0) (0.0–29.0)	0.2 (–3.8 to 4.3)	2.1 (–3.0–7.2)[b] 2.8 (–2.4 to 8.0)[c]	1.02 (0.77–1.34)	1.17 (0.82–1.67)
>16 mg ($n=128$)	21.0 (5.0–24.0) (0.0–30.0)	1.5 (–2.8 to 5.8)	5.8 (–2.4–13.9)[b] 6.3 (–2.0 to 14.6)[c]	1.10 (0.84–1.45)	1.45 (0.90–2.33)
Loop diuretics					
0–40 mg ($n=278$)	21.0 (5.0–24.0)(0.0–30.0)	0	0	1	1
60 mg ($n=80$)	19.5 (0.0–24.0) (0.0–29.0)	–1.2 (–6.0 to 3.6)	–2.4 (–7.4–2.5)[b] –1.4 (–6.6 to 3.7)[c]	0.92 (0.67–1.27)	0.88 (0.63–1.23)
> 60 mg ($n=144$)	14.0 (0.0–23.0) (0.0–30.0)	–3.4 (–7.0 to 0.1)	–4.3 (–8.1 to –0.4)[b] –3.8 (–7.6 to 0.1)[c]	0.79 (0.61–1.02)	0.76 (0.58–1.00)

The combinations of adjusted differences and their CI after multiple imputations are not possible after using a generalized linear mixed model.
The size and number of events of each modality are equal to the mean size and the mean number of events found in the 15 imputed datasets.
CI, confidence interval; i.v., intravenous.
[a]Difference and ratio are adjusted on intervention, period of inclusion, cluster size (categorical variable), age, chronic heart failure, coronaropathy, oxygen saturation, systolic blood pressure, and troponin rate (µg/L) as fixed effects and center as a random effect.
[b]Minimal difference and CI, observed on the 15 imputed datasets.
[c]Maximal difference and CI, observed on the 15 imputed datasets.

Table 3 Association of the total dose in the initial 4 h with secondary endpoints: hospital length of stay (patients alive at 30 days)

Total dose during initial 4 h	Hospital LOS, median (Q1–Q3) (minimum–maximum)	Unadjusted difference (95% CI)	Adjusted difference (95% CI)[a]	Unadjusted ratio (95% CI)	Adjusted ratio (95% CI)[a]
i.v. nitrates					
No nitrates ($n=211$)	8.0 (5.0–17.0) (0.0–30.0)	0	0	1	1
> 0–16 mg ($n=121$)	8.0 (5.0–19.0) (0.0–30.0)	0.6 (–1.8 to 2.9)	–0.7 (–3.8 to 2.4)[b] –0.4 (–3.5 to 2.6)[c]	1.05 (0.86–1.27)	0.96 (0.75–1.22)
> 16 mg ($n=119$)	7.0 (5.0–16.0) (0.0–30.0)	–0.6 (–2.9 to 1.8)	–3.1 (–6.9 to 0.8)[b] –2.8 (–6.6 to 1.02)[c]	0.95 (0.77–1.17)	0.77 (0.55–1.09)
Loop diuretics					
< 60 mg ($n=257$)	7.0 (5.0–16.0) (0.0–30.0)	0	0	1	1
60 mg ($n=73$)	8.0 (5.0–20.0) (0.0–30.0)	0.9 (–1.9 to 3.6)	1.3 (–1.7 to 4.3)[b] 1.6 (–1.4 to 4.6)[c]	1.08 (0.86–1.36)	1.13 (0.89–1.45)
> 60 mg ($n=121$)	10.0 (4.0–20.0) (0.0–30.0)	1.8 (–0.5 to 4.2)	1.8 (–0.7 to 4.2)[b] 2.0 (–0.5 to 4.5)[c]	1.16 (0.96–1.40)	1.17 (0.96–1.43)

The combinations of adjusted differences and their CI after multiple imputation are not possible after using a generalized linear mixed model.
CI, confidence interval; i.v., intravenous; LOS, length of stay.
[a]Difference and ratio are adjusted on intervention, period of inclusion, cluster size (categorical variable), age, chronic heart failure, coronaropathy, oxygen saturation, systolic blood pressure, and troponin rate (µg/L) as fixed effects and center as a random effect.
[b]Minimal difference and CI, observed on the 15 imputed datasets.
[c]Maximal difference and CI, observed on the 15 imputed datasets.

or diuretics on the NDAOH through 30 days. However, noteworthy NS point estimates emerged from the analysis. Specifically, the administration of nitrates within the initial 4 h after inclusion may be associated with a more favorable outcome when the total administered dose exceeded 16 mg. Conversely, a total dose of diuretics equal or surpassing 60 mg seemed to be associated with a lower NDAOH.

In the ELISABETH study [14], patients in the intervention group did not exhibit a greater NDAOH through 30 days despite receiving higher doses of i.v. nitrates and lower doses of loop diuretics compared with the control group. This finding suggested that the dosing regimen of both drugs may not have a significant impact on the outcome. However, since the analyses were conducted based on the overarching care bundle rather than specific dose levels, this assessment necessitated validation through dedicated dose-focused analyses. The results of the present study align with this aforesaid presumption.

Nevertheless, the absence of statistically significant results does not negate the presence of NS trends that favor administering a minimum of 16 mg of i.v. nitrates and less than 60 mg of loop diuretics within the initial 4 h in patients with AHF which is in concordance with contemporary clinical practices and established guidelines [1,17].

The lack of statistical significance in these trends might be attributed to inherent limitations in the study design and a lack of power. Given that the study population stems from the ELISABETH trial, the number of participants was predetermined and not specifically calculated for the current analysis. Consequently, the sample

Table 4 Association of the total dose in the initial 4 h with secondary endpoints: 30-day mortality and hospital readmission

	Death					Hospital readmission				
Total dose during initial 4 h	Death	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	Unadjusted OR(95% CI)	Adjusted OR (95% CI)[a]	Hospital readmission	Unadjusted difference (95% CI)	Adjusted difference (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
i.v. nitrates										
No nitrates ($n = 243$)	28 (11.5)	0	0	1	1	29 (11.9)	0	0	1	1
> 0–16 mg ($n = 131$)	9 (6.9)	−4.6 (−10.6 to 1.3)	−3.9 (−9.8 to 2.0)[b] −3.1 (−9.1 to 2.7)[c]	0.57 (0.26–1.24)	0.63 (0.28–1.45)	16 (12.3)	0.0 (−7.0 to 7.0)	0.3 (−6.9 to 5.9)[b] 0.8 (−6.5 to 6.4)[c]	1.00 (0.51–1.95)	1.06 (0.52–2.15)
> 16 mg ($n = 128$)	8 (6.2)	−5.3 (−11.1 to 0.5)	−4.2 (−10.1 to 1.8)[b] −3.2 (−9.3 to 2.9)[c]	0.51 (0.23–1.16)	0.61 (0.26–1.45)	14 (10.8)	−1.7 (−8.5 to 5.2)	−1.2 (−8.3 to 5.9)[b] −0.8 (−8.0 to 6.4)[c]	0.84 (0.41–1.72)	0.90 (0.42–1.90)
Loop diuretics										
No diuretics ($n = 36$)	2 (5.6)	0	0	1	1	8 (22.2)	0	0	1	1
> 0–40 mg ($n = 242$)	17 (7.0)	1.5 (−6.7 to 9.6)	0.3 (−9.1 to 9.6)[b] 1.3 (−7.0 to 9.7)[c]	1.28 (0.28–5.83)	1.17 (0.25–5.61)	25 (10.3)	−13.2 (−28.0 to 1.7)	−10.3 (−24.3 to 3.7)[b] −9.4 (−23.0 to 4.2)[c]	0.36 (0.14–0.92)	0.45 (0.17–1.16)
> 40–500 mg ($n = 224$)	26 (11.6)	6.0 (−2.5 to 14.6)	4.9 (−2.8 to 14.6)[b] 5.6 (−4.9 to 14.2)[c]	2.23 (0.50–9.88)	2.05 (0.44–9.49)	26 (11.6)	−11.7 (−26.5 to 3.2)	−9.9 (−23.7 to 4.0)[b] −8.9 (−22.7 to 4.8)[c]	0.43 (0.17–1.07)	0.47 (0.19–1.20)

The combinations of adjusted differences and their CI after multiple imputations are not possible after using a generalized linear mixed model.
CI, confidence interval; i.v., intravenous; LOS, length of stay; OR, odds ratio.
[a]Difference and OR are adjusted on age, chronic heart failure, coronaropathy, oxygen saturation, systolic blood pressure, and troponin rate (µg/L) as fixed effects and center as a random effect. The study design is not included in the model.
[b]Minimal difference and CI, observed on the 15 imputed datasets.
[c]Maximal difference and CI, observed on the 15 imputed datasets.

size may have been insufficient, thereby undermining statistical power. Alternatively, the absence of significant findings may imply the absence of a universal optimal dose of i.v. nitrates or loop diuretics for early administration in AHF. Instead, it could signify the necessity for a patient-specific dose.

Regarding loop diuretics, the hypothesis has garnered substantial attention from experts in recent years. They propose a threshold of local renal diuretics concentration, below which treatment efficacy becomes futile, and this threshold might be individualized for each patient [18]. Within this context, the latest ESC guidelines advocate a 'sequential' therapeutic strategy, involving dose adjustments based on natriuresis [1]. Validation of this therapeutic approach is currently underway through an international randomized controlled trial [19]

Concerning i.v. nitrates, current recommendations emphasize titration of the administered dose in response to individual patient clinical feedback. However, this titration predominantly emerges from concerns over potential side effects rather than a firm belief in a specific effective dose for each patient [1].

Limitations

This study bears several limitations in addition to those inherent to the ELISABETH trial. First, initial randomization of patients focused on comprehensive care strategies rather than precise treatment dosages. Consequently, patient categories delineated by administered dose exhibited marked imbalances and potential heterogeneity. Statistical models were adjusted for confounding factors to mitigate biases, but this does not alter the numerical disparity between categories. Second, the multivariable models did not encompass various factors that might have influenced outcomes, including background treatments, other interventions administered in the ED (such as noninvasive ventilation) or treatments at discharge, and the management of precipitating factors, though these interventions have been shown to improve outcome in AHF [20].

Moreover, design parameters could not be incorporated in all models due to the limited number of events. Third, the selection of cutoff points for dose categorization was based on median dosages, a decision that holds a degree of arbitrariness. Last, missing data for outcomes were handled assuming that if the data was missing, it meant the event did not occur, which might not have been the actual case. However, a sensitivity analysis utilizing multiple imputation generated results consistent with those presented.

In conclusion, this secondary analysis of the ELISABETH trial did not find any significant association between the total dose of i.v. nitrates and loop

diuretics administered in the initial 4 h and the NDAOH at 30 days. However, the point estimates and CI may suggest that the optimal doses are less than 60 mg of diuretics, and more than 16 mg of nitrates within the initial 4 h.

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Conflicts of interest

J.G. has received a grant from the Société Française de Médecine d'Urgence (SFMU). B.D. and G.C. are directors of Heart Initiative, a nonprofit organization. A.M. is the coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. For the remaining authors, there are no conflicts of interest.

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Dans cette analyse secondaire des données de l'étude ELISABETH, les traitement reçus par les 502 patients de l'étude au cours des quatre premières heures de leur prise en charge ont été analysés.

La moitié des patients (52%) ont reçu des dérivés nitrés avec une dose médiane totale de 16 mg (5;40), et 93% d'entre eux ont reçu des diurétiques avec une dose médiane totale de 40 mg (40;80).

Ni la dose totale de dérivés nitrés, ni la dose totale de diurétiques n'ont montré d'association significative avec le critère de jugement principal (nombre de jour vivant en dehors de l'hôpital après 30 jours) : les ratios ajustés pour les dérivés nitrés étaient de 1.17 (intervalle de confiance à 95%, IC95% : 0.82–1.67) (dose totale de 1 à 16mg comparée à « pas de dérivés nitrés ») et 1.45 (IC95% : 0.90–2.33) (dose totale supérieure à 16 mg comparé à « pas de dérivés nitrés ») et les ratios ajustés pour les diurétiques étaient de 0.88 (IC95% : 0.63–1.23) (dose totale de 60 mg comparée à une dose totale inférieure à 60 mg) et 0.76 (IC95% : 0.58–1.00) (dose totale supérieure à 60 mg comparé à une dose totale inférieure à 60 mg). On note cependant que ces résultats sont plutôt en faveur d'une forte dose de dérivés nitrés et d'une faible dose de diurétiques, ce qui correspond aux pratiques actuelles.(7) De même, les doses totales de dérivés nitrés et de diurétiques n'avaient pas d'association significative avec les critères de jugement secondaires (mortalité toute cause à 30 jours, réhospitalisation dans les 30 jours et durée d'hospitalisation pour les patients vivant à 30 jours).

On peut émettre plusieurs hypothèses pour expliquer l'absence de résultat significatif. La première est qu'il s'agit d'une analyse secondaire, donc le calcul du nombre de patients nécessaire avait été fait pour sur le critère de jugement principal de l'étude ELISABTH et non pour l'analyse rapportée ici qui souffre probablement d'un manque de puissance. La seconde hypothèse est qu'il n'y a réellement pas de dose optimale universelle, mais que chaque patient a une dose efficace qui lui est propre. Ceci corrobore le principe de « stratégie guidée par la réponse », décrite dans l'introduction et qui apparait dans les dernières recommandations de l'ESC.(4)

III. IMPACT DE L'INITIATION DE LA VNI EN PREHOSPITALIER

Comme détaillé dans l'introduction, les recommandations de l'ESC préconisent, si indiqué (détresse respiratoire, fréquence respiratoire > 25 /min et/ou SpO2 < 90), l'initiation de VNI dès le préhospitalier.(4) De nombreuses études prospectives ont été menées sur ce sujet, avec des résultats en faveurs d'une amélioration sur les signes cliniques et les paramètres vitaux immédiats et d'une réduction de la mortalité.(152,165–168) Deux méta-analyses publiées en 2014 indiquent que l'application d'une PPC en préhospitalier diminue la mortalité et le risque d'intubation.(167,168) Cependant, toutes ces études comparaient des patients ayant reçu de la VNI en préhospitalier et des patients n'en ayant pas reçu du tout, ce qui n'analyse pas vraiment l'intérêt d'un début précoce par rapport à un début plus tardif une fois arrivé à l'hôpital chez les patients pour qui ce traitement est recommandé.

Alors qu'une mise en place de VNI en préhospitalier mobilise des moyens matériels et humains importants et dont la disponibilité est limitée, il nous semblait nécessaire d'évaluer l'intérêt de son initiation précoce.
Dans une seconde étude, nous avons évalué l'effet d'une initiation préhospitalière de VNI par rapport à une initiation intra hospitalière sur le pronostic à court terme des patients consultant aux urgences pour ICA chez qui un traitement par VNI était préconisé. Pour cela, nous avons analysé les données des patients transportés par ambulance médicalisée du registre espagnol EAHFE et ayant bénéficié de VNI aux urgences. Celle-ci était débutée soit en préhospitalier (et poursuivie aux urgences), soit aux urgences.

Effect of early initiation of noninvasive ventilation in patients transported by emergency medical service for acute heart failure

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Background While the indication for noninvasive ventilation (NIV) in severely hypoxemic patients with acute heart failure (AHF) is often indicated and may improve clinical course, the benefit of early initiation before patient arrival to the emergency department (ED) remains unknown.

Objective This study aimed to assess the impact of early initiation of NIV during emergency medical service (EMS) transportation on outcomes in patients with AHF.

Design A secondary retrospective analysis of the EAHFE (Epidemiology of AHF in EDs) registry.

Setting Fifty-three Spanish EDs.

Participants Patients with AHF transported by EMS physician-staffed ambulances who were treated with NIV at any time during of their emergency care were included and categorized into two groups based on the place of NIV initiation: prehospital (EMS group) or ED (ED group).

Outcome measures Primary outcome was the composite of in-hospital mortality and 30-day postdischarge death, readmission to hospital or return visit to the ED due to AHF. Secondary outcomes included 30-day all-cause mortality after the index event (ED admission) and the different component of the composite primary endpoint considered individually. Multivariate logistic regressions were employed for analysis.

Results Out of 2406 patients transported by EMS, 487 received NIV (EMS group: 31%; EMS group: 69%). Mean age was 79 years, 48% were women. The EMS group, characterized by younger age, more coronary artery disease, and less atrial fibrillation, received more prehospital treatments. The adjusted odds ratio (aOR) for composite endpoint was 0.66 (95% CI: 0.42–1.05). The aOR for secondary endpoints were 0.74 (95% CI: 0.38–1.45) for in-hospital mortality, 0.74 (95% CI: 0.40–1.37) for 30-day mortality, 0.70 (95% CI: 0.41–1.21) for 30-day postdischarge ED reconsultation, 0.80 (95% CI: 0.44–1.44) for 30-day postdischarge rehospitalization, and 0.72 (95% CI: 0.25–2.04) for 30-day postdischarge death.

Conclusion In this ancillary analysis, prehospital initiation of NIV in patients with AHF was not associated with a significant reduction in short-term outcomes. The large confidence intervals, however, may preclude significant conclusion, and all point estimates consistently pointed toward a potential benefit from early NIV initiation.

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Keywords: acute heart failure, advanced life support ambulances, emergency department, emergency medical services, mortality, noninvasive ventilation

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Introduction

Among the treatments for acute heart failure (AHF), noninvasive ventilation (NIV) in the form of continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) is widely used today. It is quick to set up, easily removable, and helps rapidly improve symptoms of acute respiratory distress [1]. Over the past two decades, the development of medicalized ambulances equipped with ventilators (also known as advanced life support ambulances) and the training of emergency physicians in both invasive and NIV techniques have allowed performing early initiation of treatment, sometimes even at the patient's residence [2,3].

The effectiveness of NIV has been the subject of numerous studies, demonstrating a reduction in intubation rates and mortality [4]. In this context, the latest recommendations of the European Society of Cardiology (ESC) advocate its use in patients with AHF experiencing respiratory distress (respiratory rate >25, SpO_2 < 90%) and recommend its initiation 'as soon as possible', especially in prehospital settings, when possible and available [5].

While the indication for NIV seems indisputable, however, the benefit of early initiation has not been conclusively demonstrated. All studies evaluating prehospital NIV compared a group with NIV initiated in the prehospital setting to a group without NIV, but none compared early initiation to later initiation [6–9]. As the use of prehospital care systems is increasing [10], it is necessary to assess the actual effectiveness of a practice involving significant human and material resources. Therefore, the objective of this study was to assess the effect of early NIV initiation (in prehospital setting) on short-term outcomes in patients treated with NIV during an episode of AHF.

Methods

This study is a secondary retrospective and exploratory analysis that utilized data from the Epidemiology of Acute Heart Failure in the Emergency department (EAHFE) registry. The EAHFE registry prospectively enrolled 24 300 patients presenting to one of 53 Spanish emergency departments (EDs) for an episode of AHF during six periods of 1–2 months between 2007 and 2019 (from EAHFE-1 to EAHFE-8 recruitment phases). AHF diagnosis was assessed by the treating physician following the ESC criteria and confirmed by natriuretic peptide measurement or echocardiography. Patients were followed up for 1–3 months after the index ED visit by a phone call. The methods and characteristics of the EAHFE registry have been published elsewhere [11–13].

The present study recruited patients from EAHFE-3 (2011, 25 EDs, 3414 patients), EAHFE-4 (2014, 27 EDs, 3233 patients), EAHFE-5 (2016, 30 EDs, 4713 patients) and EAHFE-6 (2018, 32 EDs, 4623 patients), EAHFE-7 (2019, 8 EDs, 1577 patients), and EAHFE-8 (2022, 40 EDs, 4264 patients) as data regarding prehospital care were not collected during EAHFE-1 and EAHFE-2. Patients were included if they were transported to the ED by a physician-staffed emergency medical service (EMS) ambulance. Thus, all patients could have potentially received NIV in the prehospital setting. Those who did not receive any NIV treatment during EMS transportation or ED stay were excluded. Patients were classified into two groups based on the time they first received NIV: during EMS transportation (EMS group) or in the ED (ED group).

Data collection

The primary outcome of this study was a 30-day postdischarge composite adverse event formed by all-cause in-hospital mortality (no discharge), 30-day postdischarge mortality and 30-day new ED presentation or hospitalization due to AHF. The secondary outcomes were 30-day all-cause mortality (after the ED index event), and the events included in the composite adverse event were considered. The 30-day postdischarge outcomes were analyzed in a postdischarge population, excluding patients who died in hospital.

Variables potentially associated with the time of NIV initiation or with one of the outcomes were collected, and included 2 demographic variables (age, sex), 13 comorbidities, 2 variables regarding baseline status (Barthel index and New York Heart Association class), precipitating factors of the AHF episode, vitals and treatments provided by the EMS and ED, laboratory and electrocardiogram data, and risk stratification of the AHF episode based on the Multiple Estimation of risk based on the Emergency department Spanish Score in patient with AHF (MEESSI-AHF) scale [14–16].

Statistical analysis

Categorical variables were reported as numbers (%). Quantitative variables were reported as mean (SD) or median [interquartile range (IQR)] depending on their distribution. EMS and ED groups were compared using univariate analyses: a Chi-square test (or Fisher test when appropriate) was used for categorical variables and Student's *t*-test (or Mann–Whitney test when appropriate) for quantitative variables.

To assess factors independently associated with NIV start during EMS transportation, a multivariate analysis was conducted using logistic regression. For this purpose, variables were included in the analysis if they were available during the transportation (e.g. demographic data, comorbidities, initial clinical parameters) and if there was a difference between groups in the univariate analysis under a chosen cutoff ($P < 0.2$).

The association between the NIV group (EMS or ED) and each of the outcome was assessed using logistic regressions. Several multivariate models were developed

to ensure the robustness of the results. The first (principal) model included MEESSI-AHF score, variables associated with the endpoints under the $P < 0.2$ cutoff (except those which are already part of MEESSI-AHF score), the three mostly used treatments (diuretics, intravenous nitrates, and morphine), and the admission in an ICU because they could have influenced outcomes. The second model included variables associated with the endpoints under the $P < 0.2$ cutoff, the three mostly used treatments, and the admission in an ICU. The third model included the same variables as in the first model except for the given treatments.

To address missing data, multiple imputation by chained equations was used. Fifty datasets were generated and pooled following Rubin's rules.

All tests were two-sided and considered statistically significant if $P < 0.05$. Statistical analyses were performed using R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The EAHFE Registry protocol was approved by the Ethics Committees of the Hospital Universitario Central de Asturias (Oviedo, Spain, reference numbers 49/2010, 69/2011, 166/13, 160/15, and 205/17) and Hospital Clínic de Barcelona (Barcelona, Spain, reference number 2018/0233). All participating patients gave informed consent to be included in the registry and to be contacted for follow-up. The present study was carried out in strict compliance with the principles of the Declaration of Helsinki.

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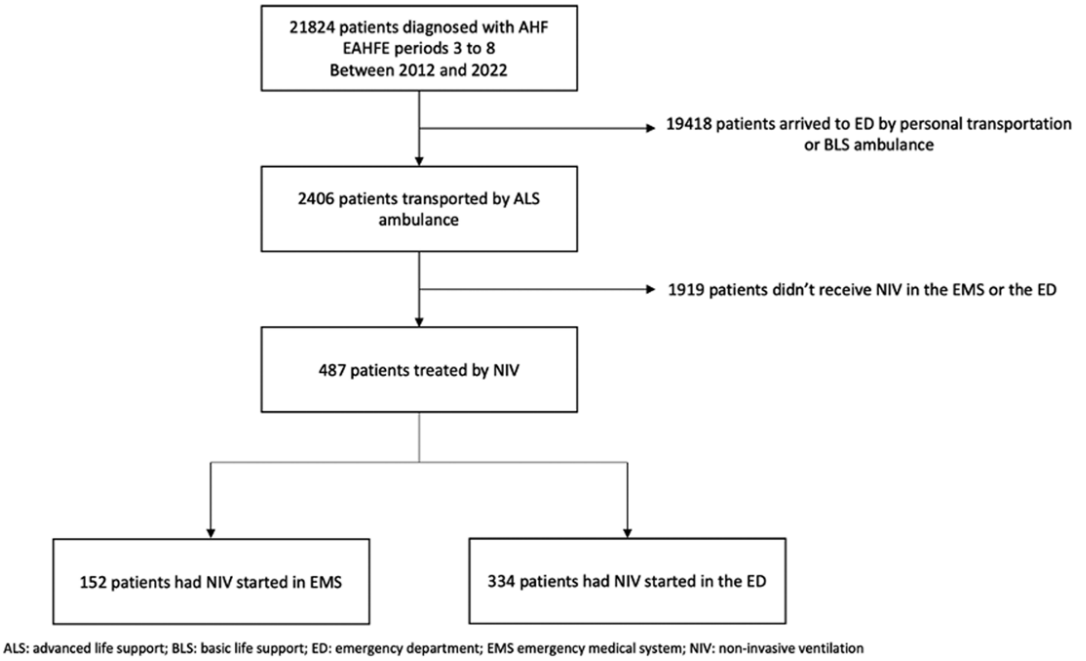
Results

In the EAHFE-3 to EAHFE-8 cohorts, 2406 patients arrived at the ED in EMS physician-staffed ambulances. Among these, 487 were treated with NIV. In 152 patients (31%), NIV was started in EMS (and continued in the ED), and in the 334 others (69%), NIV was started in the ED. The flowchart of patients is presented in Fig. 1.

Overall, the mean age was 79 (SD 10), with 48% being women, and the main precipitating factor of the AHF episode was an infection (38%). Regarding patients in the EMS group, they were younger than in the ED group (77 vs 80 years, $P = 0.008$), had more coronary artery disease (42 vs 28%, $P = 0.003$), less atrial fibrillation as a precipitating factor (8 vs 17%, $P = 0.012$), and more NYHA 4 level of dyspnea (92 vs 83%, $P = 0.012$) than those in the ED group. They received more morphine, (45 vs 21%, $P < 0.001$), diuretics (68 vs 43%, $P < 0.001$), and nitrates (46 vs 18%, $P < 0.001$) in EMS. Baseline characteristics and treatments received in the total cohort and in both groups are presented in Table 1 and factors

Fig. 1



Flowchart of patients inclusion.

Table 1 Baseline characteristics and outcomes of the whole cohort and of the two groups according to the initiation of noninvasive ventilation by emergency medical services or in the emergency department

Variables	Available	Total NIV $n=487$	NIV started in EMS $n=153$	NIV started in ED $n=334$	*P*-value
Age (years, mean, SD)	487	79 (10)	77 (11)	80 (11)	**0.008**
Sex: female (*n*, %)	486	235 (48)	78 (51)	157 (47)	0.378
Comorbidities					
Hypertension	487	412 (85)	127 (83)	285 (85)	0.510
Diabetes	487	249 (51)	81 (53)	168 (50)	0.588
Dyslipidemia	487	242 (50)	72 (47)	170 (51)	0.432
Coronary artery disease	487	158 (32)	64 (42)	94 28)	**0.003**
Chronic kidney failure	486	146 (30)	41 (27)	105 (32)	0.290
Previous stroke	487	80 (16)	22 (14)	58 (17)	0.409
Atrial fibrillation	487	172 (35)	47 (31)	125 (37)	0.151
Periph artery disease	487	64 (13)	23 (15)	41 (12)	0.403
Valvulopathy	487	110 (23)	31 (20)	79 (24)	0.406
COPD	487	144 (30)	40 (26)	104 (31)	0.262
Dementia	486	59 (12)	16 (11)	43 (13)	0.463
Known CHF	477	276 (58)	79 (52)	197 (60)	0.095
Neoplasia	487	68 (14)	22 (14)	46 (14)	0.858
Barthel index at admission (median, IQR)	394	50 (55)	45 (50)	50 (50)	0.357
NYHA class	460				**0.015**
1		7 (2)	1 (0.7)	7 (2)	
2		9 (2)	1 (0.7)	9 (3)	
3		51 (11)	10 (7)	51 (13)	
4		393 (85)	131 (92)	393 (83)	
NYHA 4		393 (85)	131 (92)	262 (83)	**0.012**
Precipitating factor					
Descendant ACS	484	51 (11)	21 (14)	30 (9)	0.120
Infection	475	179 (38)	55 (37)	124 (38)	0.756
Atrial fibrillation	487	70 (14)	13 (8)	57 (17)	**0.012**
High blood pressure	475	89 (19)	33 (22)	56 (17)	0.216
Anemia	475	17 (4)	5 (3)	12 (4)	1
Treatment inobs	475	17 (4)	6 (4)	11 (3)	0.792
Other	474	72 (15)	27 (18)	45 (14)	0.229
Parameters in EMS					
SBP (mmHg, mean, SD)	124	158 (35)	164 (37)	154 (33)	0.111
HR (bpm, mean, SD)	115	108 (30)	111 (27)	106 (33)	0.383
Respiratory rate (/min, mean, SD)	90	32 (8)	33 (8)	31 (7)	0.247
SpO_2 (%, mean, SD)	131	82 (12)	80 (14)	83 (10)	0.088
Treatment in EMS					
Oxygen	487	376 (77)	100 (65)	276 (83)	**<0.001**
Morphine	321	94 (29)	49 (45)	45 (21)	**<0.001**
Diuretics	487	248 (51)	104 (68)	144 (43)	**<0.001**
Nitrates	487	131 (27)	70 (46)	61 (18)	**<0.001**
Parameters in the ED					
SBP (mmHg, mean, SD)	476	147 (35)	149 (35)	146 (35)	0.463
HR (bpm, mean, SD)	473	98 (27)	98 (26)	98 (27)	0.798
Respiratory rate (/min, mean, SD)	408	28 (8)	27 (8)	28 (8)	0.351
SpO_2 (%, mean, SD)	476	90 (10)	93 (8)	89 (10)	**<0.001**
Low output signs	487	192 (39)	54 (35)	138 (41)	0.207
Treatment in the ED					
Oxygen	481	205 (43)	56 (37)	149 (45)	0.097
Morphine	487	201 (41)	62 (49)	121 (42)	0.445
Diuretics	487	444 (91)	142 (93)	302 (90)	0.388
Nitrates	487	254 (52)	83 (54)	171 (51)	0.532
Inotropes	417	29 (7)	10 (8)	19 (7)	0.604
Mechanical ventil	487	23 (5)	13 (8)	10 (3)	**0.011**
Lab results					
Glycemia (mg/dl, median, IQR)	484	189 (113)	223 (111)	173 (110)	**<0.001**
Creatinine (mg/dL, median, IQR)	481	1.30 (0.72)	1.24 (0.63)	1.31 (0.7)	0.089
Hemoglobin (g/dL, mean, SD)	481	12.2 (2.3)	12.3 (2.1)	12.2 (2.2)	0.710
White blood cells (median, IQR)	482	1192 (6290)	12 470 (6290)	11 750 (6300)	0.098
Kaliemia (mean, SD)	458	4.5 (0.9)	4.6 (0.9)	4.5 (0.9)	0485
NT-proBNP (median, IQR)	251	4805 (8365)	4118 (7143)	4995 (8491)	0.558
Troponin positive	369	202 (55)	68 (55)	134 (55)	0.979
ECG findings					
Sinusal	468	242 (52)	90 (60)	152 (48)	**0.014**
LBBB	468	68 (15)	17 (6)	51 (5)	0.178
LVH	468	26 (6)	9 (6)	17 (5)	0.773
Atrial fibrillation	468	168 (36)	43 (29)	125 (39)	**0.025**
MEESSI-AHF score (mean, SD)	340	−2.02 (1.20)	−2.05 (1.31)	−2.00 (1.14)	0.738
Hospital admission	487	474 (97)	149 (97)	325 (97)	1
In ICU	483	47 (10)	20 (13)	27 (8)	0.085
Primary outcome					
Composite endpoint[a]	413	158 (38)	46 (31)	126 (39)	0.0713
Secondary outcomes					
In-hospital all-cause mortality	487	71 (15)	19 (12)	52 (16)	0.360
30-day all-cause mortality	487	82 (17)	21 (14)	61 (18)	0.214
30-day postdischarge outcomes					
ED reconsultation due to AHF	406	93 (23)	25 (19)	68 (25)	0.206
Rehospitalization due to AHF	406	69 (17)	20 (15)	49 (18)	0.522
Death (all-cause)	408	21 (5)	6 (5)	15 (5)	0.722

Bold *P*-numbers denote statistical significance ($P<0.05$).
ACS, acute coronary syndrome; AHF, acute heart failure; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; ED, emergency department; EMS, emergency medical system; HR, heart rate; IQR, intenquartile range; LBBB, left bundle branch block, LVH, left ventricular hypertrophy; MEESSI-AHF, multiple estimation of risk based on the emergency department Spanish score in patient with AHF; NIV, noninvasive ventilation; NYHA, New York heart association; SBP, systolic blood pressure.
[a]Composite endpoint consisted in in-hospital mortality or all-cause death or emergency department reconsultation or hospitalization due to AHF during the 30 days following patient discharge.

independently associated with NIV initiation during EMS transportation are presented in Table 2.

The composite endpoint was met in 172 patients (36%): 46 patients from the EMS group (31%) and 126 patients from the ED group (39%). NIV initiation in EMS seemed to be associated with a lower rate of the composite endpoint: unadjusted odds ratio (OR) 0.70 (0.47–1.06) and adjusted OR (aOR) in Model 1 : 0.66 (0.42–1.05), aOR in Model 2 : 0.69 (0.43–1.11), and aOR in Model 3 : 0.67 (0.43–1.04). These unadjusted and adjusted ORs of the association between the place of NIV initiation and the composite endpoint are shown in Table 3 and represented in Fig. 2.

With respect to secondary endpoints, 82 patients (17%) died within 30 days after the index event [21 patients from the EMS group (14%) and 61 patients from the ED group (18%)] and 71 (15%) died during hospitalization [19 patients from the EMS group (12%) and 52 patients from the ED group (16%)]. Regarding the 416 patients discharged alive from hospital, 93 (23%) visited the ED

again within the next 30 days following discharge because of AHF [25 patients (19%) from the EMS group and 68 patients (25%) from the ED group], 69 (17%) were rehospitalized due to AHF [20 patients (15%) from the EMS group and 49 patients (18%) from the ED group], and 21 (5%) died [6 patients (5%) from the EMS group and 15 patients (5%) from the ED group] (Table 1). Early NIV initiation in EMS was not significantly associated with any of these secondary endpoints, although consistent estimations were always observed towards a risk reduction in all the unadjusted and adjusted ORs between 0.70 and 0.89 (Table 2).

Discussion

In this analysis of patients with AHF arriving at the ED via physician-staffed ambulances and treated with NIV, we were unable to demonstrate significant differences in short-term outcomes under the conditions of our study and analyses. Nonetheless, the initiation of NIV in the prehospital setting, compared to in the ED, appeared to be associated with a reduction in all primary and secondary outcomes, with consistent 10–30% reductions in the odds of adverse outcomes.

This study focused not on the efficacy of NIV treatment, which has already been extensively demonstrated [4], but on the benefits of prompt implementation in patients who indeed required this treatment. The concept of rapid initiation of treatment has proven effective in conditions such as myocardial infarction and stroke [17,18]. For AHF, the main drugs – diuretics and nitrates – have been studied. The early initiation of diuretics was initially emphasized [19] but later nuanced, especially when considering the prehospital aspect. In the FAST-FURO study [20], which compared patients with diuretic initiation in the prehospital setting, initiation in the ED, and no diuretic treatment, prehospital initiation did not improve short-term survival or hospitalization duration. Conversely, the prehospital initiation of nitrate derivatives had a more significant effect on mortality than initiation in the ED [21]. Regarding NIV, a study examined the initiation time, but NIV was started in the prehospital setting in both study groups, with a mere 15-min difference between groups [22]. To our knowledge, no study has compared prehospital NIV initiation with initiation in the ED.

The potential positive effect observed with prehospital initiation of NIV on the composite mortality and 30-day

Table 2 Association between patient baseline characteristics and initiation of noninvasive ventilation by emergency medical services

Variables	Adjusted OR (95% CI)	Adjusted *P*-value
Age (years, mean, SD)	0.98 (0.96–1.00)	**0.025**
Coronary artery disease	1.71 (1.13–2.60)	**0.012**
Known CHF	0.66 (0.44–1.00)	0.051
NYHA 4	2.35 (1.20–4.60)	**0.013**
Descendant ACS	1.32 (0.71–2.46)	0.373
Atrial fibrillation	0.45 (0.23–0.87)	**0.017**
LBBB	0.60 (0.32–1.10)	0.100

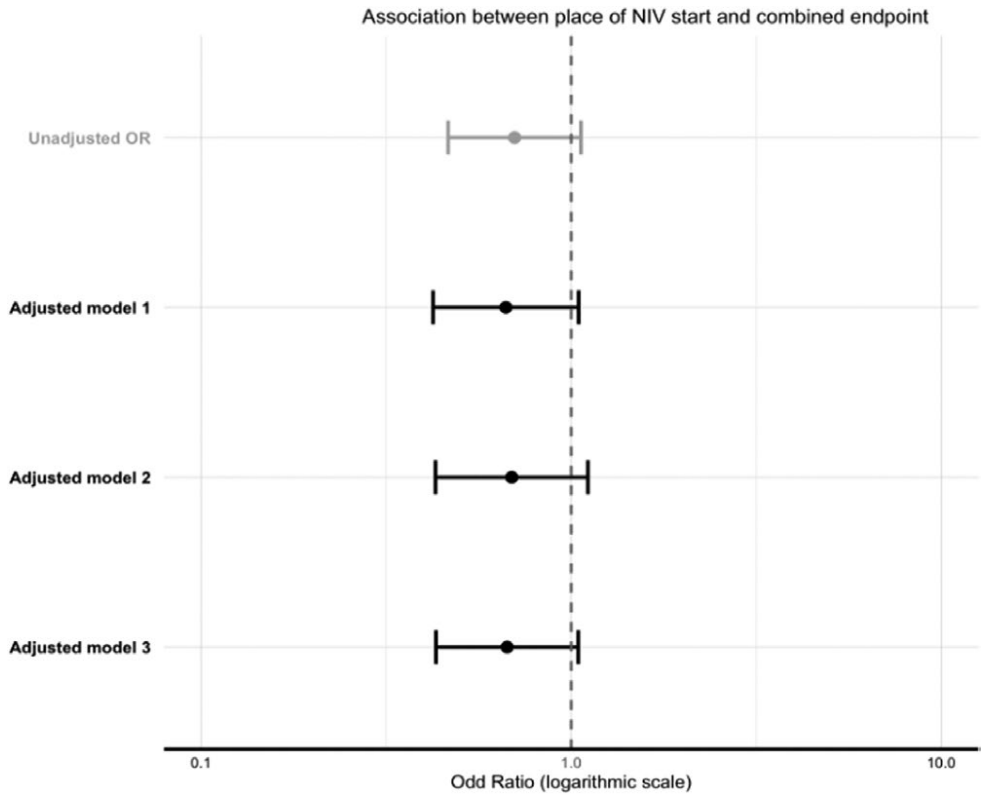
Bold *P*-numbers denote statistical significance ($P < 0.05$).
ACS, acute coronary syndrome; AHF, acute heart failure; CHF, chronic heart failure; CI, confidence interval; LBBB, left bundle branch block; NYHA, New York heart association; OR, odds ratio.

Table 3 Association between place of initiation of noninvasive ventilation and primary and secondary outcomes

Endpoint	OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	Adjusted *P*-value[a]	Adjusted OR[b] (95% CI)	Adjusted *P*-value[b]	Adjusted OR[c] (95% CI)	Adjusted *P*-value[c]
Primary endpoint								
Composite endpoint[d,e]	0.70 (0.47–1.06)	0.095	0.66 (0.42–1.05)	0.079	0.69 (0.43–1.11)	0.126	0.67 (0.43–1.04)	0.077
Secondary endpoints								
In-hospital death[f]	0.77 (0.44–1.35)	0.362	0.74 (0.38–1.45)	0.380	0.89 (0.44–1.77)	0.730	0.70 (0.37–1.35)	0.289
Death 30-day from ED presentation[g]	0.71 (0.42–1.22)	0.216	0.74 (0.40–1.37)	0.336	0.87 (0.45–1.67)	0.672	0.70 (0.38–1.29)	0.259
30-day postdischarge outcomes								
Reconsultation 30-day after discharge[h]	0.71 (0.43–1.19)	0.197	0.70 (0.41–1.21)	0.201	0.70 (0.41–1.20)	0.197	0.72 (0.43–1.22)	0.226
Rehospitalization 30-day after discharge[i]	0.82 (0.46–1.44)	0.488	0.80 (0.44–1.44)	0.454	0.80 (0.44–1.45)	0.459	0.80 (0.45–1.42)	0.442
Death 30-day after discharge[j]	0.84 (0.32–2.21)	0.717	0.72 (0.25–2.04)	0.529	0.72 (0.25–2.04)	0.536	0.80 (0.29–2.18)	0.663

AHF, acute heart failure; CHF, chronic heart failure; CI, confidence interval; ED, emergency department; HR, heart rate; LBBB, left bundle branch block; MEESSI-AHF, multiple estimation of risk based on the emergency department Spanish score in patient with AHF; NYHA, New York heart association; OR, odds ratio; SBP, systolic blood pressure.
[a]Adjustment factors included MEESSI-AHF score, factors associated with endpoint in univariate analysis except those which are already part of MEESSI score given treatments (morphine, IV nitrates, and systemic diuretics) and ICU admission.
[b]Adjustment factors included factors associated with endpoint in univariate analysis except those which are already part of MEESSI-AHF score, given treatments (morphine, IV nitrates, and systemic diuretics) and ICU admission.
[c]Adjustment factors included f factors associated with endpoint in univariate analysis except those which are already part of MEESSI-AHF score.
[d]Composite endpoint consisted in in-hospital mortality or all-cause death or emergency department reconsultation or hospitalization due to AHF during the 30 days following patient discharge.
[e]Adjustment factors are age, known CHF, Barthel index of the episode, NYHA 4, atrial fibrillation as precipitating factor, SBP, SpO_2, HR, low output signs, hemoglobin, creatinine, kaliemia, and LBBB.
[f]Adjustment factors are age, diabetes, valvulopathy, known CHF, atrial fibrillation as precipitating factor, Barthel index of the episode, NYHA 4, SBP, SpO_2, creatinine, hemoglobin, and kaliemia.
[g]Adjustment factors are age, diabetes, valvulopathy, known CHF, HBP as precipitating factor, Barthel index of the episode, SBP, HR, SpO_2, creatinine, hemoglobin, and kaliemia.
[h]Adjustment factors are chronic kidney failure, known CHF, Barthel index of the episode, atrial fibrillation as precipitating factor, creatinine, and hemoglobin.
[i]Adjustment factors are known CHF, Barthel index of the episode, atrial fibrillation as precipitating factor, and creatinine.
[j]Adjustment factors are: known CHF.

Fig. 2



Graphic representation of the unadjusted and adjusted odds ratios of the primary outcome (composite endpoint) for patients in whom noninvasive ventilation was initiated by emergency medical systems compared to those in whom noninvasive ventilation was initiated in the emergency department.

ED new consultation endpoint can be explained in various ways. The first is purely physiological: early implementation may limit hypoxia and hypercapnia, thereby reducing tissue damage and providing quicker relief to respiratory muscles, leading to better long-term recovery. The second explanation is more related to comprehensive patient management. Patients in the EMS group also received more diuretics, nitrates, and morphine in the prehospital setting, suggesting they benefited from a more sophisticated strategy and closer monitoring. The SEMICA-2 study also found that an intensive therapeutic strategy in the prehospital setting significantly reduced mortality at 7 days [23].

The physician's choice to initiate NIV in the ambulance in patients with AHF depends on several factors. Besides the obvious criteria of respiratory distress outlined in guidelines [5] and very well reflected in the present study by the strong association with NYHA class IV during the AHF episode (ED group patients appearing less severe), older age may have restrained physicians from implementing more aggressive treatment [average age 77 years (SD 11) vs 80 years (SD 11)], as well as a more challenging diagnosis, such as atrial fibrillation, which could take precedence (8 vs 17%). This decision also likely depends on the EMS physicians and their proficiency in ventilation.

Limitations

This study has several limitations. First, although EAHFE patients were prospectively recruited, the current study was conducted retrospectively, lacking power for the analyses presented here. This, however, allows patients and interventions to closely reflect real-life scenarios and the present data obtained from a low-potency analysis consistently pointed towards a potential benefit of early NIV initiation by EMS. Therefore, this hypothesis should be further explored in larger and, ideally, prospective studies. With this approach, we obtained consistent data. Second, some variables had many missing data, especially vital signs in the prehospital setting, measured at the time of the decision to initiate NIV or not. Given the high rate of missing data, these variables could not be imputed and used as adjustment factors in the analyses. Instead, they were replaced by vital signs upon arrival at the ED, even though prehospital treatment could influence these values. Thirdly, the delay in NIV initiation was dichotomized into EMS and ED without considering travel time, waiting time in the ED, or the delay in NIV initiation after medical management,

whether prehospital or in the ED. More specifically, a short travel time could have prevented NIV initiation by EMS. Fourthly, the choice of adjustment factors, although made according to common statistical rules (cutoff *P*-value <0.2), is subjective and could be erroneous. Among these factors, we did not record frailty, which is frequent in AHF patients and is a strong predictor of outcomes [24,25]. Several models, however, were tested, yielding similar results. Similarly, the outcome criteria – in-hospital and 30-day mortality and outcomes 30 days after hospital discharge – were chosen according to medical research conventions. Fifth, the ED length of stay was not available, even though it could have been influenced by NIV initiation making it a relevant outcome. Sixth, the study was run in Spain, and particularities in organization of ambulatory, EMS, hospital, and ED care to patients with heart failure could influence the results [26]. Therefore, external validation in other countries is needed. Finally, no center effect was investigated during the analysis, and thus, the possibility of prehospital NIV initiation due to service habits cannot be completely ruled out.

Conclusion

In this ancillary analysis, prehospital initiation of NIV in patients with AHF was not associated with a significant reduction in short-term outcomes. The large confidence intervals, however, may preclude significant conclusion, and all point estimates consistently pointed toward a potential benefit from early NIV initiation.

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Conflicts of interest

There are no conflicts of interest.

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Dans cette analyse des 487 patients du registre EAHFE transportés aux urgences par une ambulance médicalisée et ayant bénéficié de VNI au cours de leur prise en charge initiale, 31% d'entre eux ont reçu de la VNI dès leur transport préhospitalier et 69% d'entre eux n'en ont reçu qu'à partir de leur arrivée aux urgences.

L'initiation de VNI en préhospitalier semblait associée à une plus faible survenue du critère de jugement principal (critère combiné associant mortalité toute cause ou reconsultation pour ICA à 30 jours) : selon le modèle d'ajustement, l'odd-ratio (OR) ajusté était de 0.66 (0.42-1.05), 0.69 (0.43-1.11) ou 0.67 (0.43-1.04). De même, cette initiation en préhospitalier semblait associée, de manière non significative, à une réduction des critères de jugement secondaires (mortalité intra-hospitalière, mortalité à 30 jours et reconsultation pour ICA à 30 jours) : les odds-ratio ajustés étaient tous compris entre 0.70 et 0.89.

Ces résultats peuvent s'expliquer de plusieurs manières. D'une part, d'un point de vue physiologique, la mise en place rapide de VNI permettrait de limiter l'hypoxie et/ou l'hypercapnie et de réduire l'épuisement des muscles respiratoire pouvant avoir un effet délétère à long terme. D'un autre côté, cela peut aussi être dû à une prise en charge globale plus avancée de ces patients, puisque ceux qui ont bénéficié de VNI en préhospitalier ont aussi davantage bénéficié de dérivés nitrés et de diurétiques en préhospitalier. Dans tous les cas, les résultats de cette étude viennent appuyer les recommandations de l'ESC qui préconisent que, chez les patients avec une indication à la VNI, celle-ci doit être initiée en préhospitalier.(4)

IV. RECHERCHE DU PARCOURS DE SOINS OPTIMAL

Il a été rappelé dans l'introduction que les parcours de soins des patients présentant un épisode d'ICA est fait de différentes étapes dont chacune a été étudiée de manière séparée. Un transport vers l'hôpital par ambulance semble associé dans la littérature à un moins bon pronostic par rapport à une présentation aux urgences par ses propres moyens, tout comme le retour à domicile après passage aux urgences. Ce dernier étant nécessaire chez une partie des patients afin d'éviter un épuisement des ressource hospitalières et la survenue de complications liées à l'hospitalisation, des score pronostiques dédiés ont été créés. Concernant le service d'hospitalisation, l'étude OSCUR comparant des patients italiens hospitalisés en cardiologie ou en médecine interne trouvait que ceux hospitalisés en cardiologie étaient plus graves à l'arrivée mais la mortalité était la même entre les deux groupes.(137) Au Royaume-Uni, une analyse des parcours de plus de 6000 patients hospitalisés a trouvé un taux de mortalité au cours de l'hospitalisation et après 1 an plus élevée chez les patients hospitalisés en médecine interne que ceux admis en cardiologie.(138) L'étude française de Cluzol et al n'a pas retrouvé de différence pronostique entre les différents services d'hospitalisation.(117) Toutefois il s'agit une étude sur un faible nombre de patients qui souffre probablement d'un manque de puissance.

Contrairement à chacune de ces étapes, le parcours de soin dans sa globalité n'a pas été étudié. En pratique, la prise en charge d'un patient présentant un épisode d'ICA nécessite donc plusieurs prises de décisions successives. Il nous semble alors intéressant d'envisager des « parcours de soin - types », suivis par un certain nombre de patients, qui seraient analysés de manière globale. Dans ce cadre, la trajectoire du patient ne relèverait plus de multiples décisions, mais d'une décision unique. Dans un contexte où chaque prise de décision représente un risque d'erreur et nécessite un temps dédié, la mise en place d'un parcours de soin optimal permettrait de fluidifier la prise en charge des patients.

Dans une troisième étude, prospective observationnelle et multicentrique, nous avons suivi la trajectoire préhospitalière et hospitalière de patients pris en charge pour ICA dans 24 hôpitaux français entre 2014 et 2018 et analysé l'impact des différentes étapes de cette prise en charge sur le pronostic des patients, notamment l'impact d'une hospitalisation en cardiologie.

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Patient care pathways in acute heart failure and their impact on in-hospital mortality, a French national prospective survey

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ABSTRACT

Background: Our purpose was to describe the care pathway of patients hospitalized for acute heart failure (AHF) and investigate whether a management involving a cardiology department had an impact on in-hospital mortality.

Methods: Between June 2014 and October 2018, we included patients hospitalized for AHF in 24 French hospitals. Characteristics of the episode, patient's care pathway and outcomes were recorded on a specific assessment tool. The primary outcome was the association between patient care pathway and in-hospital mortality. The independent association between admission to a cardiology ward and in-hospital mortality was assessed through a multivariate regression model and propensity score matching.

Results: A total of 3677 patients, mean age of 78, were included. The in-hospital mortality rate was 8% (n = 287) and was associated on multivariate regression with advanced age, presence of sepsis, of cardiogenic shock, high New York Heart Association (NYHA) score and increased plasma creatinine level on admission. High blood pressure and admission to a cardiology department appeared as protective factors. After propensity score matching, hospitalization in a cardiology department remained a protective factor of in-hospital mortality (OR = 0.61 [0.44–0.84], p = 0.002).

Conclusion: A hospital course of care involving a cardiology department was associated with an increase in hospital survival in AHF patients. These finding may highlight the importance of collaboration between cardiologists and other in-hospitals specialties, such as emergency physicians, in order to find the best in-hospital pathway for patients with AHF.

Clinical Trial NCT03903198.

1. Introduction

Hospitalization for acute heart failure (AHF) is an important event in the patient's life whether it is the first presentation of heart disease or a decompensation of chronic heart failure [1,2]. While AHF may lead to a worsened quality of life, increased rates of future hospitalizations or in the worst case death, an episode of AHF may also represents an opportunity to take control of the disease and to optimize treatment [3,4].

The management of AHF will often involve numerous health care providers, from the first contact with the EMS, the initial care in the emergency department to the physician of the admitting ward. The admitting ward will not always be a cardiology department, but may instead be a geriatrics or general ward, as patients with AHF are increasingly at an advanced age and suffer from substantial comorbidities [5,6]. In fact, most of AHF patients may not even see a cardiologist during their hospitalization [7].

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Whereas the presentation characteristics and outcomes of patients hospitalized for AHF have been described numerous times, knowledge on patients' in-hospital care pathways and its influence on morbidity and mortality is limited [8–11]. To study this, a French nationwide survey was set up. As a first step of this prospective observational study, we aimed to describe the different patient care pathways from home to hospital discharge for AHF patients, the treatments received in the different steps of prehospital and in-hospital stays, as well as the outcomes in terms of survival. The primary aim of this study was to assess whether a patient in-hospital care pathway that included a cardiology department (coronary care unit or cardiology ward) decreased in-hospital mortality in AHF patients.

2. Methods

2.1. Design

Between June 2014 and October 2018, we conducted a national multicentric cohort study in 24 French hospitals. Every physician-staffed Emergency Medical Service (EMS), Emergency department (ED), Coronary Care Unit (CCU) and conventional cardiology ward agreed to participate. A cardiology ward is a hospitalization department where most of the working physicians, including chief department, are cardiologists and where patients are hospitalized for a cardiac acute or chronic pathology. It can be of any size and can include any level of technical platform. A CCU is a cardiology ward where patients' vitals are continuously monitored. A conventional cardiology ward is a cardiology ward which is not a CCU. In a given hospital, there can be both a conventional cardiology ward and a CCU. Our study is reported in accordance with the STROBE guidelines for the reporting of observational studies [12]. The study was designed in accordance to the Declaration of Helsinski and was approved by the Institutional Review Board.

2.2. Selection of participants

All patients above 18 years old that presented with a suspected diagnosis of AHF were prospectively enrolled. AHF was defined following the ESC 2012 Guidelines as the presence of congestive symptoms: cardiac dyspnea, increase of chronic edema, or cardiogenic shock. The diagnosis was established by the first physician in charge of the patient according to those guidelines. The initial treatment at admission was decided by the physician of EMS and/or ED. This treatment could be discussed between the EMS or ED physician and a cardiologist. The admission to a CCU, a conventional cardiology ward or another department was decided by the EMS or ED physician, in accordance with the cardiologist when the patient was admitted in a cardiology ward (CCU conventional). No instruction had been given by the investigator regarding admission criteria to each kind of hospitalization ward. According to French legislation, no written informed consent was required, and the protocol was approved by the national ethics committee (CNIL n°1836586 v 0). All patients were informed of the study plan. No opposition was voiced.

2.3. Data collection

Data was collected using a pre-defined assessment tool which followed the patients during their hospitalization. The tool included the baseline characteristics, medical history and previous heart failure events, the first clinical and echocardiography assessment which included the assessment of NYHA and KILLIP scores, the blood test results on admission, as well as the initiated treatments on admission, during hospitalization, and at discharge. The patient care pathways were tracked and registered: the place and time of the first medical contact, the presence of a pre-hospital physician, ED length of stay, place of hospitalization (CCU, cardiology conventional ward, general medicine ward), the kind of specialist involved, place of discharge and in-hospital mortality. The collected data were gathered for analysis by the main investigator and retained for further analysis.

2.4. Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included the complementary clinical exams and the treatments initiated during hospitalization and at discharge. We also aimed to describe the various possible steps of care during the hospitalization.

2.5. Statistical analysis

Categorical variables are expressed as numbers (%). Continuous variables are expressed as means (standard deviation, SD), or as medians [25th and 75th percentiles]. We analyzed the association between factors of interest (baseline characteristics, complementary exams, initiated treatments, and wards) and the main outcome, using a chi^2 test for the qualitative variables, a *t*-test for the quantitative variables and a non-parametric Mann-Whitney test for time variables.

Subsequently, we set up a multivariate logistic regression model to evaluate the independent association between the factors of interest and the main outcome. All the factors associated in univariate analysis with the main outcome with a p value below 0.1 were tested in the model and the selection followed a stepwise procedure.

Finally, we analyzed the association between hospitalization in a CCU and/or cardiology ward with in-hospital mortality using an adjustment with a propensity score to prevent potential confusion bias. The score was estimated using a logistic regression. The primary analyses were based on propensity score matching with a ratio 1:4 and a caliper of 0.05 standard deviation of the logit propensity score. To account for missing data, analyses were conducted using multiple imputations by chained equations with 50 imputations obtained after 10 iterations [13]. The variables considered in the imputation models were all characteristics used in the propensity score, except cardiology stay, which was not imputed. The propensity scores came from 50 independent complete imputed data sets and were averaged and used for matching according "across approach" [14]. Balance in potentials confounders were assessed by standardized mean differences which came from a complete imputed data set [15]. A conditional logistic regression was used to analyze matched data and to estimate the odds ratio (OR) for the relationship between a hospitalization in CCU/ cardiology ward and in-hospital mortality.

Sensitivity analyses were performed using other alternative methods of propensity score analysis. Here we used a matching method with a 1:1 ratio within a caliper of 0.05 standard deviation of the logit propensity score, stratification on the quintiles of the propensity score, and inverse probability of treatment weighting (IPTW). The same analyses were carried out according to the "within approach" [14].

All tests are two-tailed and the results were considered to be statistically significant when $p < 0.05$. The statistics were performed using R software version 3.3.3 (R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

Between June 2014 and October 2018, 3677 patients presenting with AHF were included in the study. The mean age was 78 years and 48% were women. Heart failure was previously known in a majority of cases. The main etiology was ischemic cardiopathy (36%) and the main precipitating factor was atrial fibrillation (26%). The clinical presentation was a cardiogenic shock in 109 patients (3%). The left ventricular ejection fraction (LVEF) was reduced (<50%) in more than half of these patients. Diuretics and beta-blockers were the most common medications present on admission. Baseline characteristics are represented in Table 1.

3.2. Patient care pathways

In more than 50% of cases the general practitioner or the EMS represented the first encounter with a health care staff. In 9% of cases the patient presented directly at the hospital. The first encounter occurred after an average (median) of one day after the onset of symptoms. Characteristics of the first encounter are presented in Table 1.

The first medical treatment was carried out by a physician-staffed EMS and/or the ED in 80% of patients. Then, only about one third of patients were transferred to the CCU. Later, 2683 (73%) patients were admitted to the CCU and/or cardiology ward. Fig. 1 demonstrates the different pathways. The overall median length of stay in-hospital was eight days. The median length of stay

Table 1
Patients characteristics.

	Total (n = 3677)	Cardiology admission (n = 2683)	No cardiology admission (n = 756)	p
Demographic and clinical data				
Female sex, (%)	1634 (48)	1084 (44.2)	423 (59.7)	<0.0001
Mean (SD) age, years	79 ± 12	76.5 ± 12.6	85 ± 9.7	<0.0001
Mean (SD) BMI, kg/m^2	27 ± 8	27 ± 7.3	24.8 ± 8.5	<0.0001
Mean (SD) Blood Pressure, mmHg				
Systolic	138 ± 31	137.6 ± 31.3	140.6 ± 31.2	0.043
Diastolic	77 ± 18	77.4 ± 18.5	76.3 ± 18.6	0.21
Mean (SD) heartbeat rate, bpm	91 ± 30	91.3 ± 32.5	89.3 ± 23.8	0.089
Previously known heart failure, (%)	2475 (69)	1750 (66.3)	559 (77.3)	<0.0001
AHF type of presentation				
Cardiac dyspnea, (%)	3209 (89)	2350 (88.)	653 (89.3)	0.65
Increase of chronic edema, (%)	799 (22)	626 (23.6)	125 (17.1)	0.0002
Cardiogenic shock, (%)	109 (3)	101 (3.8)	6 (0.8)	<0.0001
AHF hospitalization in previous year, (%)	1404 (42)	1018 (41)	302 (44.4)	0.12
Precipitating factor				
Atrial arrhythmia, (%)	772 (26)	576 (27.4)	156 (25.7)	0.44
Sepsis, (%)	723 (25)	414 (19.7)	259 (42.7)	<0.0001
High blood pressure, (%)	376 (13)	260 (12.4)	92 (15.2)	0.081
Low compliance to treatment, (%)	226 (8)	183 (8.7)	37 (6.1)	0.047
Ventricular arrhythmia, (%)	48 (1.5)	47 (2.2)	1 (0.2)	0.001
Other (%)	1152 (39)	819 (38.8)	214 (35.1)	0.11
Reduced LVEF < 50%, (%)	631 (59)	583 (62.2)	34 (38.2)	<0.0001
Mean (SD) measured LVEF, %	41 ± 15	40.8 ± 15.2	45.1 ± 15.7	0.063
Mean (SD) plasma creatinine rate, μmol/L	122 ± 69	123.9 ± 68	122.6 ± 73.8	0.71
NT-proBNP > 125 or BNP > 35 pg/mL (%)	2641 (95.6)	1950 (96.8)	520 (90.9)	<0.0001
NYHA score				
I, (%)	42 (1.5)	31 (1.6)	6 (1.)	<0.0001
II, (%)	312 (12)	192 (9.8)	86 (18.4)	
III, (%)	913 (35)	712 (36.2)	164 (35.)	
IV, (%)	1307 (51)	1034 (52.)	211 (45.)	
Pathways and lengths of stay				
First encounter				
General practitioner, (%)	1153 (34)	858 (33.)	227 (33.5)	<0.0001
Physician-staffed EMS, (%)	675 (20)	489 (19.3)	150 (22.1)	
Firemen, ambulance, (%)	318 (9)	241 (9.5)	67 (9.9)	
Relatives, (%)	248 (7)	175 (6.9)	60 (8.8)	
Nurse, (%)	179 (5)	92 (3.6)	67 (9.9)	
Cardiologist, (%)	158 (5)	152 (6)	5 (0.7)	
No call, (%)	699 (20)	530 (20.9)	102 (15)	
Physician-staffed EMS care, (%)	519 (15)	415 (16.5)	78 (10.3)	<0.0001
Median [IQR] time between first symptoms and arrival at hospital, days	2 [0–6]	2 [0–7]	1 [0–3]	0.0004
Treatment				
Diuretics (%)	423 (84.7)	1618 (83)	624 (90.8)	<0.0001
Oxygen (%)	2136 (76.6)	1484 (78.1)	531 (79.8)	0.36
NIV (%)	383 (16.1)	287 (17.9)	78 (13.6)	0.022
Nitrates (%)	584 (22.9)	433 (24.7)	120 (20.5)	0.045
Inotrope (%)	54 (2.2)	46 (2.7)	5 (0.9)	0.019

Data in the table are numbers (%) for categorical data and mean ± standard deviation or median [interquartile range] for continuous data depending on the distribution. AHF: acute heart failure, BMI: body mass index, BNP: brain natriuretic protein, b.p.m: beats per minute, CCU: coronary care unit, EMS: emergency medical service, IQR: interquartile range, LVEF: left ventricular ejected fraction, NT-proBNP: N-terminal fragment of brain natriuretic protein, NYHA: New York heart association, SD: standard deviation.

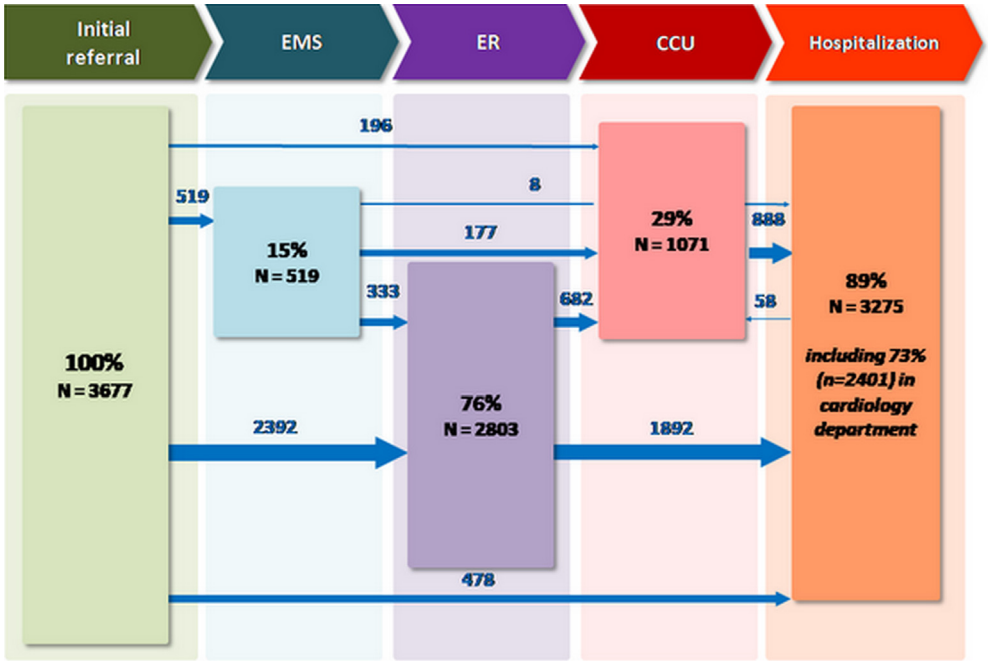

Fig. 1. Care pathways of patients with acute heart failure.

was one hour with physician-staffed EMS, eight hours in the ED, three days in CCU and seven days in a conventional ward (Fig. 1).

At discharge, two-third of the patients went back home. The remaining third were discharged to rehabilitation centers, nursing homes, and other hospitals (Table 1).

3.3. Mortality during hospitalization

The in-hospital mortality was 8% (n = 287). On univariate analysis, a significant association was found between increased in-hospital mortality and hospitalization in cardiology (CCU or conventional ward). The other factors significantly associated with in-hospital mortality are listed in Table 2.

On multivariate analysis, factors associated with increased in-hospital mortality included age (included as a continuous variable. The OR is for a one-year increase) (OR 1.02 [1.01–1.04]), an episode of sepsis (OR 1.73 [1.26–2.33]), a cardiogenic shock (OR 6.41 [3.86–10.56]), a NYHA score equal to four (as a dichotomous factor: 4 or <4) (OR 1.61 [1.17–2.22]) and an elevated creatinine rate (included as a continuous variable. The OR is for a 10 μmol/L increase) (OR 1.05 [1.03–1.06]). The presence of high blood pressure at presentation and hospitalization in a cardiology ward seemed to be protective factors ((OR 0.44 [0.25–0.78]) and OR 0.53 [0.40–0.72] respectively). Results of the multivariate analysis are presented in Table 3.

The propensity score used to determine the independent association between mortality and hospitalization in the CCU and/or cardiology department included sex, age, BMI, first encounter, cardiogenic shock, increase in edemas, High Blood Pressure (HBP) cardiopathy, sepsis, atrial fibrillation, dyslipidemia, hospitalization for AHF in the previous 12 months, previously known heart failure, being taken care of by physician-staffed EMS, emergency department visit, NYHA score, creatinine rate, abnormal BNP (>35 pg/mL) or NT-pro-BNP (>125 pg/mL), time between first symptoms, and first encounter Fig. 2. When adjusting the on propensity score, a hospitalization in the CCU or Cardiology Department was significantly inversely associated with in-hospital mortality (OR 0.61 [0.44–0.84], p = 0.002), Fig. 3.

4. Discussion

This study provides a real-life picture of the patients' care pathway before and during their hospitalization for AHF in 24 French hospitals. Very few studies have investigated the specific relation between care pathways and mortality.

Our main result clearly shows that admission to a cardiology ward or to CCU was independently and strongly associated with lower in-hospital mortality (OR 0.61 [0.44–0.84]). A national survey conducted in England and Wales in 2008–2009 found a decreasing association between length of stay in specialist services and mortality for AHF patients [7]. Nevertheless, this result was not the primary end-point of their study. Conversely, a recent analysis from the REALITY-AHF registry that included 1,682 AHF patients found no difference in in-hospital mortality between patients managed by emergency physicians and those managed by cardiologists [16].

Several hypotheses could explain this association between improved outcomes following AHF and patient care pathways involving the cardiology or CCU wards. First, this difference may result from a delay in the initiation of treatment which is known to be associated with mortality [17–20]. One could presume that the number of patients receiving appropriate treatments will be higher for those immediately taken into care by a cardiologist, as described in the REALITY-AHF registry [16]. However in this study and in our cohort, admission to the ED did not appear to be associated with mortality. Another hypothesis is that patients hospitalized in the CCU or cardiology department are more closely monitored, and thus a new cardiologic event or deterioration could be detected earlier than in a general ward. Moreover, all patients hospitalized in a cardiology unit receive early echocardiographic assessment and, likely, more targeted treatment. Patients hospitalized in cardiology department also have their long-term heart failure treatment plan revised by cardiologists, which can have a positive impact on outcome, especially if it is done at the beginning of the hospitalization. For patients with de novo heart failure this assessment constitutes the first investigation of their cardiac pathology and the first prescribed heart failure treatment. In our

Table 2
Univariate analysis on in-hospital mortality.

Variables of interest	Not deceased (n = 3390)	Deceased (n = 287)	p-trend
Female sex (%)	1506 (48)	128 (49)	0.89
Mean (SD) age, years	78 ± 12	82 ± 13	<0.0001
Mean (SD) BMI, kg/m^2	27 ± 8	25 ± 8	0.02
First encounter			
General practitioner, (%)	1061 (33)	92 (35)	<0.0001
Cardiologist, (%)	153 (5)	5 (2)	
Nurse, (%)	149 (5)	30 (11)	
No call, (%)	643 (20)	56 (21)	
Firemen, ambulance, (%)	295 (9)	23 (9)	
Relatives, (%)	236 (7)	12 (4)	
Physician-staffed EMS, (%)	627 (20)	48 (18)	
Time between first symptoms and arrival at hospital, median [IQR], days	2 [0–7]	1 [0–5]	0.03
Mean (SD) heartbeat rate, bpm	90 ± (31)	94 ± (29)	0.08
Mean (SD) Systolic blood pressure, mmHg	139 ± (31)	129 ± (30)	<0.0001
Mean (SD) Diastolic blood pressure, mmHg	77 ± (18)	73 ± (17)	0.0004
Mean (SD) LVEF, %	42 ± (15)	36 ± (16)	<0.0001
Reduced LVEF <50%, (%)	575 (58)	36 (16)	0.049
AHF type: Cardiogenic shock, (%)	76 (2)	33 (12)	<0.0001
AHF type: Cardiac dyspnea, (%)	2983 (89)	226 (81)	<0.0001
AHF type: Increase of edema, (%)	742 (22)	57 (20)	0.51
Etiology: Ischemic cardiopathy, (%)	1014 (36)	84 (35.3)	0.92
Etiology: Hypertensive cardiopathy, (%)	638 (23)	42 (18)	0.09
Etiology: Valvopathy, (%)	597 (21)	55 (23)	0.49
Etiology: Rhythmic cardiopathy, (%)	925 (33)	72 (30)	0.48
Etiology: Other, (%)	1062 (39)	67 (28)	0.15
Previously known heart failure, (%)	2283 (69)	192 (69)	0.98
Precipitating factor: sepsis (%)	633 (23)	90 (40)	<0.0001
Precipitating factor: atrial arrhythmia (%)	720 (27)	52 (23)	0.26
Precipitating factor: ventricular arrhythmia (%)	43 (2)	5 (2)	0.41
Precipitating factor: High blood pressure (%)	362 (13)	14 (6)	0.003
Precipitating factor: low compliance to treatment (%)	217 (8)	9 (4)	0.039
Precipitating factor: other (%)	1062 (39)	90 (40)	0.98
NYHA score: IV, (%)	1186 (50)	121 (65)	<0.0001
Mean (SD) admission natremia, mEq/L	138 ± 8	136 ± 11	0.14
Mean (SD) admission creatinine rate, μmol/L	120 ± 66	150 ± 88	<0.0001
NT-proBNP > 125 or BNP > 35 pg/mL (%)	2452 (95.9%)	189 (91.7%)	0.009
AHF hospitalization in the previous year, (%)	1300 (42)	104 (90)	0.52
Physician-staffed EMS care, (%)	474 (15)	45 (16)	0.56
ED admission, (%)	2569 (76)	234 (81)	0.034
Median [IQR] time before ED care, min	42 [17–99]	46 [11–108]	0.68
Contact ED physician and cardiologist, (%)	1784 (71)	140 (61)	0.001
Hospitalization in cardiology, (%)	2508 (79)	175 (64)	<0.0001
Assessment by a cardiologist, (%)	2517 (79)	180 (67)	<0.0001
Treatment: diuretics, (%)	2226 (84.6)	197 (85)	0.87
Treatment: oxygen, (%)	1952 (76)	184 (80)	0.24
Treatment: NIV, (%)	341 (15.7)	42 (21.1)	0.058
Treatment: nitrates, (%)	538 (23)	46 (22)	0.88
Treatment: inotrope, (%)	47 (2)	7 (3)	0.20

Data in the table are numbers (%) for categorical data and mean ± standard deviation or median [interquartile range] for continuous data depending on the distribution. AHF: acute heart failure, BMI: body mass index, bpm: beats per minute, CCU: coronary care unit, ED: emergency department, EMS: emergency medical service, IQR: interquartile range, LVEF: left ventricular ejected fraction, NYHA: New York heart association, SD: standard deviation.

cohort, 16% of the patients with a de novo acute heart failure were hospitalized in a non-cardiology ward and thus didn't receive this first assessment which may be even more impacting on outcome.

Table 3
Multivariate analysis.

Variables	OR [CI95%]	p
Age[a]	1.02 [1.01–1.04]	0.0004
Cardiogenic shock	6.41 [3.86–10.56]	<0.0001
Sepsis	1.73 [1.26–2.33]	0.0005
NYHA (4 vs < 4)	1.61 [1.17–2.22]	0.004
Precipitating factor: High blood pressure	0.44 [0.25–0.78]	0.005
Creatinine rate[b]	1.05 [1.03–1.06]	<0.0001
Hospitalization in CCU or cardiology ward	0.53 [0.40–0.72]	<0.0001

CCU: coronary care unit, NYHA: New York heart association.
[a] Included as a continuous variable. The OR is for a one-year increase.
[b] Included as a continuous variable. The OR is for a 10 μmol/L increase.

Furthermore, patients hospitalized in cardiology will receive targeted education during hospitalization. However, even if this last factor has an impact on compliance with at-home treatment and on long-term outcome [4], it is unknown whether it impacts in-hospital mortality.

Deciding to admit every patient with AHF to the cardiology department would be unrealistic, due to the increasing number of such patients and because of the necessity of holistic care in patients with one or more important comorbidities. Besides, objective criteria for hospitalization in the CCU or ICU have been established [21]. A more feasible option is a tighter collaboration between cardiologists and other practitioners, which could improve a patient's outcome when admitted to other wards [22]. In a recent French survey of 132 AHF patients, no association was found between hospitalization in cardiology departments and mortality because of the wide involvement of cardiologists in the management of patients hospitalized in the non-cardiology departments [23]. In our study, the cooperation between Cardiologists and Emergency Physicians appears as a protective factor for in-hospital mortality. This cooperation between specialists should be continued during the entire hospital admission and could take place as a "AHF cardiologist mobile team" as has previously been suggested [23].

Most of the previous studies describing patients hospitalized for AHF focus on the in-hospital course [8–11]. In 2016, a small cohort study in France described the prehospital and in-hospital care pathways of patients hospitalized for AHF and their treatments and outcomes depending on the departments involved in care [23]. The study was conducted in three hospitals and included only 119 patients [23]. Our study is the first to report on a national scale the step by step patient care pathways from first point of contact to hospital discharge, to associate in-hospital mortality with specific patients' pathways.

The patients' characteristics in our cohort are comparable with previous studies. The mean age was 78 years and two patients out of three had a chronic heart failure or previous history of AHF [7–11,23]. The main precipitating factors were atrial fibrillation and sepsis as previously described [8–11,23,24]. Furthermore, in-hospital mortality rate was 8%, similar to what it was in previous studies [7–9,23] except for EFICA where it was up to 27%, but that study only enrolled patients requiring admission to the ICU and CCU, where outcomes are known to be somewhat worse than the average [11]. These observations reinforce the validity of our cohort.

5. Limitations

Our study presents several limitations. First, we focused on in-hospital mortality but did not follow patients after discharge, so we could not assess either re-hospitalization or 30-days, six months or 1-year mortality, which are known to be high after an

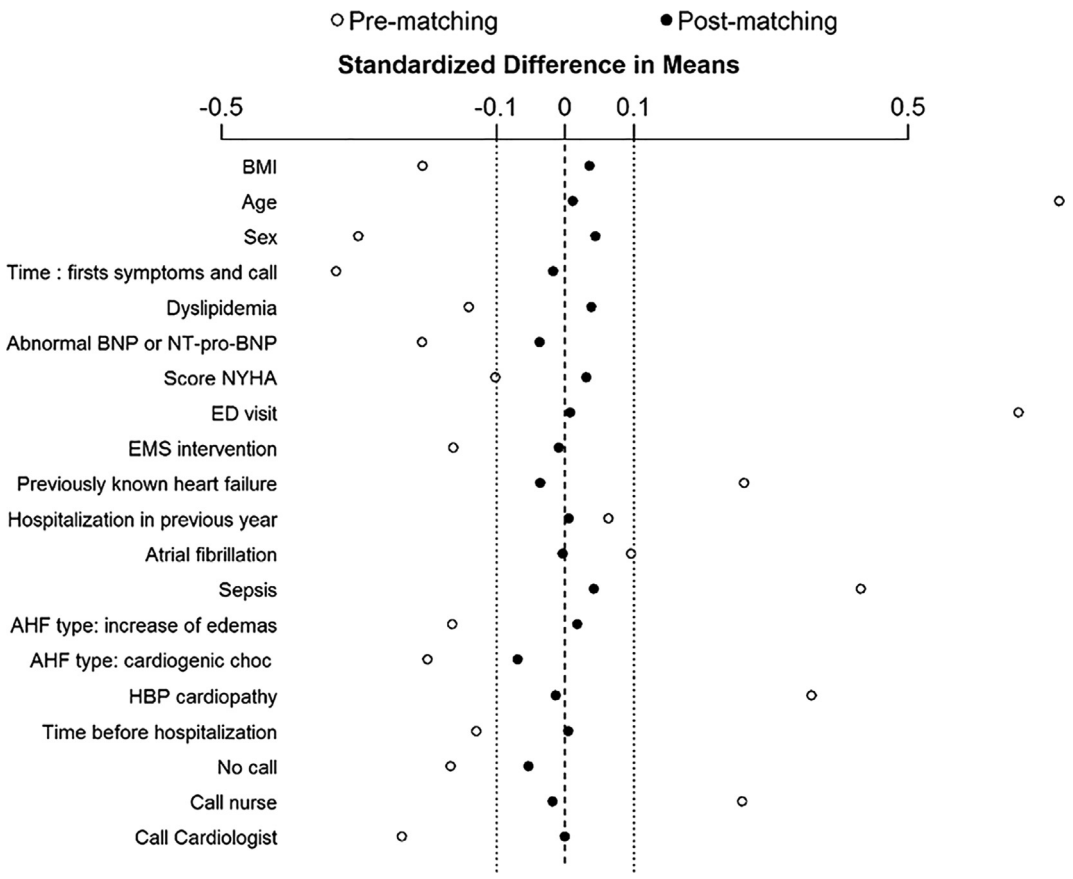

Fig. 2. Accuracy of propensity score matching. Propensity score was set up to predict in-hospital mortality. For each variable included in the propensity score, standardized difference in mean between the groups "cardiology admission" and "no cardiology admission" is given before and after matching those groups on the propensity score.

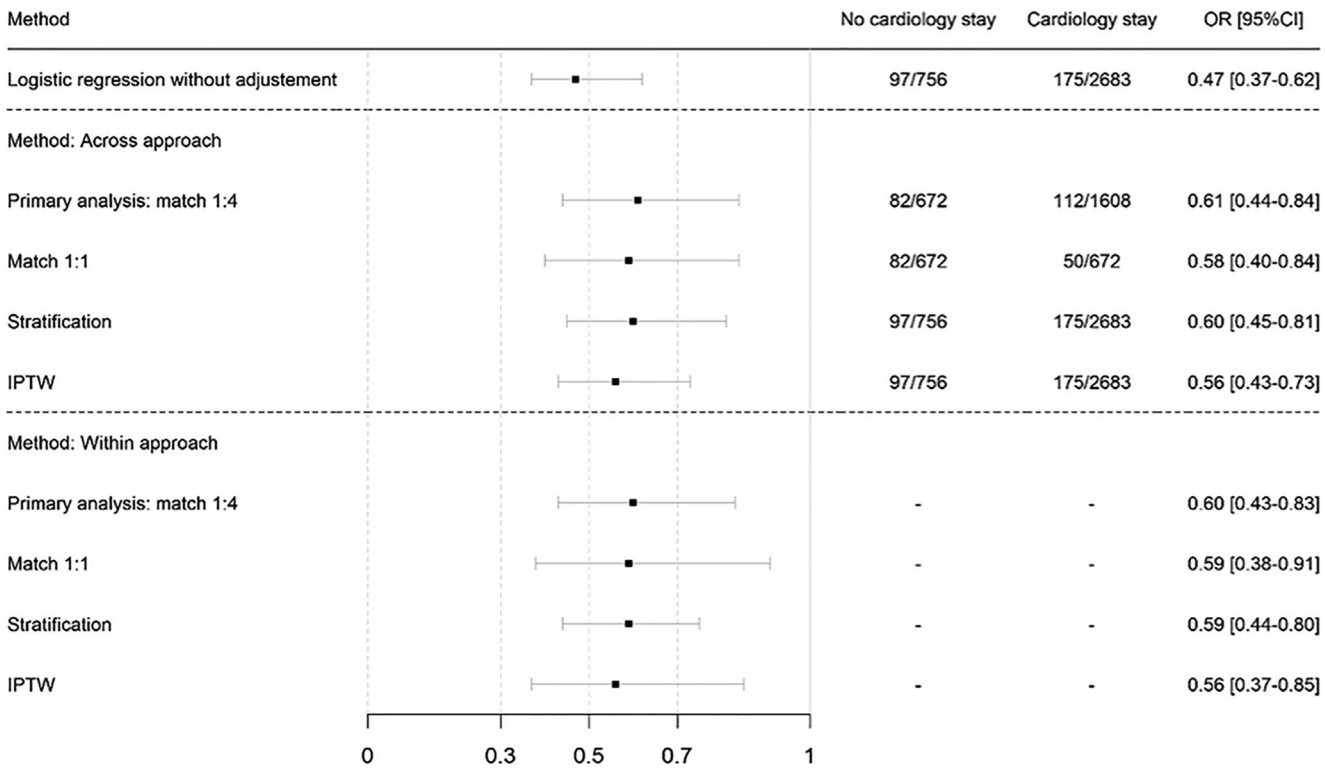

Fig. 3. Association between in-hospital mortality and hospitalization in cardiology. First rank is the odd ratio (OR) without adjustment. Second rank is the OR adjusted on propensity score using the across approach method with 4 different matching ratios. Third rank is the OR adjusted on propensity score using the within approach method (sensitivity analysis) with 4 different matching ratios.

AHF episode and are widely used as prognostic criteria [7,23,25,26]. Second, diagnosis was made by the physician on field and no independent adjudication have been made. Hence, some patients with another acute pathology than AHF can have been wrongly included in the study, explaining a low BNP or NT-proBNP rate in 4%. However, this situation also occurs in real life, which is what we aimed to describe and analyze. Third, cardiologists were part of each local board of our study, which may have led to a better management of AHF patients than the usual standard of care. However, we were still able to find a difference between patients admitted to a cardiology departments and non-cardiology departments, meaning that AHF management was not optimum for all enrolled patients.

6. Conclusion

In-hospital mortality of AHF was significantly lower when the patient care pathway involved admission to a CCU or cardiology ward. Cooperation between general-ward physicians and cardiologists should be reinforced in order to give the same specialized cardiac management to all patients.

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Dans cette étude prospective ayant eu lieu entre juin 2014 et octobre 2018, les parcours de 3677 patients en ICA ont été analysés.

Avant d'arriver à l'hôpital, 34% des patients avaient contacté leur médecin généraliste, 5% leur cardiologue et 29% avaient fait appel aux pompiers ou au SAMU. Parmi ces derniers, 9% avaient été transportés par un véhicule de secours (pompiers, ambulance) et 15% par une équipe de SMUR dont 34% ont été amenés directement en soins intensifs. A leur arrivée à l'hôpital, 76% des patients ont été vus aux urgences à la suite de quoi 92% d'entre eux ont été hospitalisés. Au total 94% des patients de l'étude ont été hospitalisés dont 29% en soins intensifs et 65% en service de cardiologie conventionnelle. Au cours de leur prise en charge hospitalière, seuls 73% des patients ont été évalués par un cardiologue. Le fait d'avoir été hospitalisé dans un service de cardiologie (soins intensifs ou cardiologie conventionnelle) était associé, de manière significative et après appariement sur un score de propension, à une réduction de la mortalité intra-hospitalière (OR 0.61 [0.44–0.84], p = 0.002).

Concernant la description du parcours de soins des patients, ces résultats permettent de brosser un portrait unique de la trajectoire des patients français en insuffisance cardiaque aiguë : la plupart des registres étant initiés par des services de soins intensifs, il y a généralement une perte d'information sur les patients ayant été hospitalisés dans d'autres services de type médecine interne ou gériatrie. Concernant l'association entre hospitalisation en cardiologie et mortalité intra-hospitalière, ce résultat peut s'expliquer par plusieurs raisons : il peut s'agir d'une prise en charge plus rapide, d'une surveillance plus rapprochée, de l'accès plus rapide à des investigations spécialisées comme échographie cardiaque, explorations de rythmologie, coronarographie et/ou de l'introduction plus rapide et plus efficiente du traitement de l'insuffisance cardiaque chronique au cours de l'hospitalisation. Ce résultat devrait être pris en compte lors du choix d'orientation des patients consultants pour insuffisance cardiaque aiguë, notamment aux urgences.

V. ANALYSE GLOBALE DES RESULTATS

Ce travail, qui porte sur la prise en charge aux urgences des patients présentant un épisode d'insuffisance cardiaque aiguë sans choc cardiogénique, s'est concentré sur trois points qui ne sont à ce jour pas consensuels et qui ont peu été étudiés : la posologie initiale des traitements médicamenteux, l'intérêt d'une initiation de ventilation non invasive en préhospitalier plutôt qu'aux urgences et le parcours de soins optimal pré et intra-hospitalier.

Concernant la posologie initiale des traitements médicamenteux, l'analyse secondaire d'un essai contrôlé randomisé par paliers qui comparait la mise en place d'un protocole de prise en charge exhaustif aux soins usuels dans des épisodes d'ICA chez des patients âgés de 75 ans ou plus n'a pas montré d'impact statistiquement significatif de la dose totale de dérivés nitrés ou de diurétiques administrée au cours des quatre premières heures de prise en charge sur le nombre de jours vivants et hors de l'hôpital pendant 30 jours. Cependant, il est apparu plusieurs tendances non significatives : une dose totale de dérivés nitrés au cours des quatre premières heures supérieure à 16 mg semblait être associée à un pronostic plus favorable. À l'inverse, une dose totale de diurétiques égale ou supérieure à 60 mg semblait être associée à un nombre de jours vivants et hors de l'hôpital plus faible.

Concernant l'initiation d'une VNI en préhospitalier, l'analyse des données de 487 patients de la cohorte espagnole EAHFE ayant été pris en charge par une ambulance médicalisée avant leur arrivée aux urgences et ayant bénéficié de VNI au moins aux urgences n'a pas montré d'association significative entre le lieu d'initiation de la VNI (préhospitalier ou hospitalier) et le pronostic à 30 jours (décès ou reconsultation aux urgences ou réhospitalisation pour ICA). Cependant, l'initiation de la VNI en préhospitalier semblait réduire la survenue du critère de jugement principal (décès, reconsultation ou réhospitalisation pour ICA à 30 jours) et des critères de jugement secondaires (mortalité intra-hospitalière, décès à 30 jours, reconsultation aux urgences à 30 jours et réhospitalisation à 30 jours).

Enfin, l'étude des parcours de 3677 patients entre leur domicile et leur sortie de l'hôpital a permis de dresser le tableau en vie réelle des trajectoires multiples des patients lors de leur épisode d'ICA. Quinze pour cent d'entre eux étaient pris en charge par le SAMU, 10% étaient admis directement en soins intensifs, 89% étaient hospitalisés, dont en soins intensifs et 73% en cardiologie. Parmi les facteurs pronostiques, les patients admis en soins intensifs et/ou cardiologie avaient une plus faible mortalité intra-hospitalière.

VI. DISCUSSION

Ce travail porte sur trois populations de patients, recrutées de manière prospective dans des services d'urgences et analysées sous le prisme de l'urgentiste. D'une part il s'agit de patients « en vie réelle », au plus proche des réalités quant à leurs caractéristiques et à leur prise en charge, au sein d'études pragmatiques ou observationnelles. D'autre part les problématiques, relevées par des médecins urgentistes, correspondent à celles qui se posent lors de la prise en charge des patients en ICA. Par ailleurs, les patients inclus dans ce travail sont nombreux : 487 + 502 + 3677 = 4666 patients, recrutés dans respectivement 53, 15 et 24 hôpitaux en France et en Espagne, ce qui offre un panel important de patients en ICA. Enfin, tous les aspects de la prise en charge du patient, une fois le diagnostic posé, y sont étudiés, permettant une vision globale de celle-ci.

o Perspectives

Au vu des résultats de ce travail, plusieurs axes d'optimisation de la prise en charge de l'insuffisance cardiaque aiguë aux urgences se profilent. Premièrement, au plan thérapeutique, il semble nécessaire, d'une part de valider de manière robuste les traitements actuellement préconisés et leurs éventuelles associations, et d'autre part d'explorer de nouvelles classes thérapeutiques, qui pourraient agir par d'autres mécanismes sur les processus de l'insuffisance cardiaque aiguë. Deuxièmement, il semble intéressant d'aider le médecin urgentiste au moment de l'orientation, que ce soit avec les outils existant ou par de nouveaux outils, afin de fluidifier la trajectoire des patients. Troisièmement, la prise en charge doit désormais se faire en fonction du profil de chaque patient, et donc être personnalisée. Enfin, il apparait indispensable d'impliquer davantage les principaux acteurs concernés par l'insuffisance cardiaque aiguë dans le processus décisionnel de ces épisodes : à la fois le médecin urgentiste et le patient lui-même.

✓ Nouvelles classes thérapeutiques

Comme nous l'avons vu dans l'introduction, les traitements médicamenteux de l'ICA, diurétiques de l'anse et dérivés nitrés, sont recommandés avec des niveaux respectifs IIaB et IIbB, en l'absence d'essais cliniques validant leur efficacité. Différentes molécules, la plupart à action vasodilatatrice (ularitide, serelaxine, hydralazine, tezosentan, cinaciguat etc), ont été

testées au cours des vingt dernières années mais aucune n'a retenu d'indication dans l'ICA.(69,72,169–171) Actuellement, deux classes thérapeutiques sont à l'étude : les inhibiteurs de SGLT-2 et les corticoïdes.

Les inhibiteurs de SGLT-2 (empagliflozine, dapagliflozine), testés initialement dans le traitement du diabète (le SGLT-2 est un cotransporteur rénal sodium-glucose), ont montré une réduction de la mortalité cardiovasculaire et du nombre d'hospitalisations dans l'insuffisance cardiaque chronique.(172–175) Dans l'ICA, plusieurs études randomisées contre placebo ont trouvé que l'ajout d'un inhibiteur de SGLT-2 au traitement standard permettait une meilleure diurèse et décongestion, voire un meilleur pronostic que dans le groupe contrôle.(176–180) Actuellement, d'autres essais cliniques sont en cours d'inclusion pour évaluer l'effet des inhibiteurs de SGLT-2 sur la décongestion et/ou le pronostic (par exemple NCT06442280, NCT04298229, NCT05392764).

Les corticoïdes, utilisés dans de nombreuses pathologies pour leur effet anti-inflammatoire, soulèvent désormais eux aussi un certain intérêt dans le traitement de l'ICA. D'une part, les glucocorticoïdes semblent avoir un effet diurétique qui potentialise l'action des peptides natriurétique en préservant la fonction rénale.(181,182) D'autre part, il existe une part d'inflammation dans les mécanismes conduisant à l'insuffisance cardiaque, aiguë comme chronique.(183) Il a d'ailleurs été trouvé qu'une élévation des marqueurs de l'inflammation, notamment la C-reactive protein (CRP) était associée à un pronostic à long terme plus sombre chez les patients en ICA.(184) Dans une analyse du registre EAHFE, les patients en ICA avec un taux de CRP > 40 mg/L et traités initialement par corticoïdes (dans l'hypothèse d'une décompensation de bronchopneumopathie chronique obstructive) semblaient avoir une mortalité à 30 jours moins élevée que ceux n'en ayant pas reçu.(185) Dans ce contexte, l'étude CORTAHF (NCT0591658), dont le recrutement est en cours, cherche à montrer que l'ajout d'un traitement par glucocorticoïdes au traitement standard de l'ICA chez les patients avec un taux de CRP > 20 mg/L sans signe infectieux permettrait une réduction à 7 jours du taux de CRP (lui-même étant associé à un mauvais pronostic à long terme).(186)

- ✓ **Aide à l'orientation et parcours de soins**

Le second élément qu'il semble essentiel d'optimiser est la bonne orientation du patient à chaque étape de sa prise en charge, tant d'un point de vue pronostique que d'un point de vue économique.(187) Comme vu précédemment, il existe différents scores pronostiques permettant d'établir, à l'issu d'une évaluation aux urgences, le risque d'évènements à court et

moyen terme et, en fonction du risque de chaque patient, de décider si celui-ci doit être ou non hospitalisé. En pratique, ces scores ne sont pas toujours faciles d'utilisation (bien que leur calcul puisse se faire en ligne, par exemple sur https://meessi-ahf.risk.score-calculator-ica-semes.portalsemes.org/ pour le score MEESSI-AHF), la mise en place d'outils plus intuitifs semble nécessaire. Une des pistes intéressantes peut être celle de programmes informatiques, avec une aide à la décision allant au-delà d'un simple calcul de score : plusieurs équipes ont développé des logiciels de type « réseaux de neurones » permettant de prédire de manière efficace le risque de mortalité des patients en ICA.(188,189)

En outre, une fois que le choix de l'orientation du patient est fait, il semble essentiel que celui-ci soit placé dans une filière de soins dédiée que ce soit en ambulatoire ou en hospitalisation. Notre étude sur les parcours de soins a montré que l'intervention d'un cardiologue au cours de la prise en charge améliorait le pronostic. De même, la prise en charge rapide par un cardiologue des patients d'une étude prospective rentrant à domicile après consultation aux urgences permettait elle-aussi un meilleur pronostic.(190) La création de « parcours de soins » tels qu'entendu par l'association européenne des parcours de soins (European Pathway Association) permettrait une implication systématique et organisée d'un cardiologue dans la prise en charge : il s'agit d'une « intervention complexe de processus de prise de décision et d'organisation des soins pour un groupe de patients bien défini et durant une période bien définie ».(191) Selon une méta analyse portant sur les données de sept études, l'implication dans un parcours de soins des patients en ICA permettrait une diminution de la mortalité intra hospitalière, de la durée d'hospitalisation et du taux de reconsultations sans augmenter le coût des hospitalisations.(192)

En France, il existe plusieurs parcours de soins dédiés à l'insuffisance cardiaque, mis en place au niveau hospitalier ou régional. Par exemple, à l'hôpital Henri Mondor (Créteil), La cellule de coordination de l'insuffisance cardiaque et des cardiomyopathies (CCICC), composée de deux infirmiers, a pour but d'améliorer le parcours intra-hospitalier et la sortie d'hospitalisation des patients en insuffisance cardiaque, d'optimiser le traitement de fond de l'insuffisance cardiaque après la sortie et de télésurveiller les symptômes et le poids par des outils connectés. A l'échelle communale, on peut citer les communautés professionnelles territoriales de santé (CPTS) s'articulant autour de l'insuffisance cardiaque à Rouen, Roanne ou Redon et à l'échelle départementale, le RESIC38, le réseau des insuffisants cardiaques d'Isère, permettant d'articuler le suivi des patients à domicile et leur hospitalisation si besoin. Le déploiement de ce genre de réseaux partout en France, apparait aujourd'hui indispensable.

- ✓ **Prise en charge personnalisée**

Si la mise en place et le suivi de recommandations nationales et internationales permettent une homogénéisation des pratiques et un accès au même niveau de traitement pour les patients présentant un épisode d'ICA, on sait aujourd'hui que le traitement ne peut être exactement identique pour tous les patients. Au plan thérapeutique, nous avons vu qu'il semble préférable d'initier un certain traitement en fonction du profil clinique et biologique du patient, et d'adapter la posologie en fonction de la réponse initiale. On pourrait, à l'avenir, créer un algorithme qui, comme pour la décision d'orientation, permettrait de définir le traitement adéquat selon les caractéristiques de chaque patient. Par ailleurs, en ce qui concerne l'orientation des patients, en plus de facteurs pronostiques évoqués précédemment devant être pris en compte dans la décision d'orientation, il parait aussi important d'intégrer les caractéristiques sociales et la capacité pour le patient et son entourage d'une bonne compréhension du traitement et des signes d'alerte.(120) Si, au lit du malade, il paraît évident qu'un patient consultant pour ICA qui est peu autonome ou mal entouré et donc à risque de mauvaise observance ne devrait pas rentrer à domicile après passage aux urgences, cela n'apparaît pas clairement dans les recommandations de prise en charge. De plus, l'association du patient à cette prise de décision semble elle-aussi inévitable. D'une part parce-que cela entraîne, par la discussion du médecin et de son patient, une meilleure compréhension du diagnostic et du traitement et d'autre part, cela respecte le principe d'autonomie du patient.

- ✓ **Implication du médecin urgentiste**

Pour finir, les recommandations sur la prise en charge de l'ICA étaient jusqu'à présent écrites principalement par des cardiologues, alors que cette prise en charge, dans les premières heures, est réalisée principalement par des médecins urgentistes. Ainsi, dans les recommandations de l'ESC, le paragraphe sur la prise en charge de l'ICA en préhospitalier indique que seule la VNI devrait y être administrée, même si les autres traitements « sont parfois disponibles ». Ce texte contraste avec la réalité du terrain : il est plus aisé de traiter un patient lorsque toute une équipe – médicalisée ou non - lui est entièrement dédiée. A l'inverse, aux urgences, les temps d'attente et la multiplicité des patients retardent inévitablement la prise en charge. De nombreux groupes de recherche de médecins urgentistes travaillent aujourd'hui sur l'ICA et pourraient être consultés à ce sujet.(158,164,193–195) D'ailleurs, en France, les sociétés savantes des différentes spécialités (médecine d'urgence, cardiologie et gériatrie) se sont enfin réunies afin de rédiger des recommandations communes.(196) Nous espérons que ce sera bientôt le cas pour les recommandations internationales.

- **Limites**

Les résultats de deux des trois études de ce travail ne sont pas statistiquement significatifs : 1° l'introduction de VNI en préhospitalier ou aux urgences n'avait pas d'impact significatif sur le pronostic et 2° la dose de diurétiques ou de dérivés nitrés administrée au cours des 4 premières heures n'avait pas d'impact significatif sur le pronostic. Trois hypothèses apparaissent au regard de ces résultats. La première est qu'il n'y a réellement pas d'association entre initiation de la VNI d'une part et doses des diurétiques et dérivés nitrés d'autre part avec les critères de jugements respectifs. Cette hypothèse a été développée dans les discussions respectives de ces deux études. La seconde hypothèse est que le nombre de patients analysés n'était chaque fois pas suffisant, aboutissant à un manque de puissance. Enfin, la troisième hypothèse est que les analyses statistiques mises en place n'ont pas permis de mettre correctement en évidence une ou plusieurs associations existantes. Plusieurs éléments peuvent être à l'origine d'une analyse statistique non concluante.

Tout d'abord, les critères de jugement ont pu être mal choisis, conduisant à tort à des résultats non concluants. Un critère de jugement est un élément ou un évènement cliniquement pertinent pour le patient et pour le professionnel de santé, en lien direct avec l'objectif de l'étude et facilement mesurable et reproductible.(197,198) On en distingue classiquement trois types: 1° les évènements pronostiques à court, moyen ou long terme (décès, reconsultation) qui sont des critères solides mais nécessitant parfois un nombre plus élevés de patient et dont l'imputation à l'évènement initial n'est pas toujours aisée, 2° les éléments d'évolution cliniques (congestion, évolution de la dyspnée, « aggravation intra-hospitalière de l'insuffisance cardiaque ») et 3° les éléments de substitutions, censés être corrélés au pronostic du patient et permettant un temps de suivi moins long et un coût moins élevé.(198–203) Dans ce travail, les critères de jugement principaux étaient tous trois des évènements pronostiques fréquemment utilisés et cliniquement pertinents (davantage, par exemple, qu'une évolution de la SpO_2) : 1° mortalité à 30 jours (étude sur les parcours de soins) qui permet de prendre en compte les décès survenus de manière progressive à la suite de l'épisode aigu, tout en excluant les décès à plus long terme potentiellement imputables à d'autres facteurs ; 2° nombre de jours vivant hors de l'hôpital (étude sur les posologies initiales) qui intègre à la fois mortalité, durée d'hospitalisation et réhospitalisations uniques ou itératives ; et 3° critère composite regroupant mortalité à 30 jours, et reconsultation aux urgences en lien avec l'ICA (étude sur la VNI préhospitalière) qui permet en théorie en augmentant le nombre d'évènements positifs, de réduire le nombre de sujets

nécessaire et/ou la durée de suivi, d'analyser davantage de facteurs, d'éviter la compétition des risques et d'augmenter le nombre de patients avec données disponibles.(198,199,204)

Deuxièmement, le choix de nos variables d'ajustement était peut-être inapproprié, conduisant à des résultats non significatifs dans les deux études mentionnées. En fonction du modèle choisi et des facteurs pris en compte, une analyse statistique peut, pour un même jeu de données et un même effet étudié, donner des résultats très différents voire de sens contraires. Lorsqu'on teste une association entre variables explicatives et variables à expliquer, le modèle statistique doit permettre d'éliminer l'effet que peuvent avoir d'autres variables « facteurs confondants », sur les critères de jugement (biais de confusion). Cet ajustement permet d'augmenter la puissance d'une analyse jusqu'à 20% mais à l'inverse, si les variables incluses dans le modèle ne sont pas pronostiques cela peut diminuer la précision de l'analyse.(205) Il n'existe à ce jour pas de standardisation du moyen de sélection des variables à inclure dans le modèle.(206) Une possibilité est de sélectionner les variables qui diffèrent entre les groupes étudiés. Une autre possibilité est de sélectionner les variables qui sont associées au critère de jugement, comme nous l'avons fait dans l'étude sur les parcours de soins et dans l'étude sur l'initiation de la VNI en préhospitalier. Cette sélection se fait alors par une analyse univariée où sont retenues toutes les variables dont la p-value est inférieure à un certain seuil (dans ce travail, < 0.1 ou < 0.2). En cas de nombre trop élevé, plusieurs modèles peuvent alors être testé par le logiciel statistique afin de trouver le plus efficace ; on parle de procédure « pas-à-pas », celle-ci a été utilisée dans l'étude sur les parcours de soins. Une troisième possibilité est d'utiliser des variables d'ajustement définies à priori, parce qu'elles sont cliniquement importantes ou parce qu'elles ont montré, dans la littérature, une association avec le critère de jugement. C'est la stratégie utilisée dans l'étude sur la posologie des traitements initiaux. Celle-ci semble davantage préconisée par les experts.(207,208)

Ces incertitudes méthodologiques, soulevées toutes deux par des rewievers lors de la soumission des articles de ce travail, pourrait expliquer en partie l'absence de résultats significatifs. On ne peut toutefois pas exclure la première hypothèse d'une absence d'association entre les éléments testés (posologie des traitements initiaux ; initiation de la VNI en péhospitalier) et les critères de jugements.

VII. CONCLUSION

La prise en charge de l'insuffisance cardiaque aiguë aux urgences, bien qu'établie dans ses grandes lignes, nécessite certains ajustements afin d'optimiser la pratique de l'urgentiste et d'améliorer le pronostic des patients. En particulier, ce travail a permis de mettre en évidence la nécessité potentielle d'une administration de forte dose de dérivés nitrés et d'une faible dose de diurétiques de l'anse dans les 4 premières heures de prise en charge ; l'intérêt d'une initiation de la VNI en préhospitalier chez les patients qui en ont l'indication et l'intérêt d'une hospitalisation dans un service de cardiologie.

VIII. REFERENCES

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IX. ANNEXES

Tableau 1 : études portant sur la posologie des diurétiques de l'anse dans l'ICA

Etude	Type d'étude	Intervention	Conclusions
Hasselblad 2007 European Journal of Heart Failure	Analyse secondaire de l'étude ESCAPE 395 patients	Dose maximale journalière de furosémide (variable continue)	Forte dose associée à mortalité à 6 mois avec seuil à 300mg/j
Peacock 2008 Cardiology	Observationnelle Registre ADHERE 82540 patients	Dose furosémide les 24 premières heures ≥ ou < 160 mg	Patients recevant < 160mg avaient moins de mortalité intra hospit, d'hospitalisation prolongée, d'effets secondaires rénaux et séjours en réa plus court
Yilmaz 2011 European Journal of Heart Failure	Observationnelle Registre ALARM-HF 3308 patients	Dose furosémide IV les 24 premières heures > ou < 1mg/kg	Pas de différence de mortalité intra hospitalière après appariement sur score de propension
Felker 2011 New England Journal of Medicine	Interventionnelle randomisée Etude DOSE 308 patients prenant 80-240 mg en dose de fond	Furosémide - dose quotidienne - 2.5x dose quotidienne En IVSE ou bolus	Meilleure perte de poids et d'eau dans le groupe forte dose, et tendance non significative à meilleure régression des symptômes mais plus de WRF
Ruocco 2019	Analyse post-hoc Étude DIUR-HF 121 patients	Dose quotidienne furosémide IV ≥ ou < 125 mg	Patients recevant < 125 mg avaient moins de décès/réhospitalisation pour ICA et moins bonne réponse aux diurétiques

Tableau 2 : études portant sur le mode d'administration des diurétiques de l'anse

Étude	Type d'étude	Intervention	Conclusions
Lawson (209) 1978 BMJ	Observationnelle 10 patients	Patients « réfractaires » ont reçu 120 mg IVSE de furosémide	Diurèse satisfaisante
Lahav (31) 1992 Chest	Interventionnelle randomisée 9 patients	Furosémide - IVSE - bolus x3/j	Meilleure diurèse avec IVSE
Dormans (32) 1996 JACC	Interventionnelle randomisée cross-over 20 patients	Furosémide - 1 bolus par jour - IVSE sur 8h 250 à 2000 mg/j, même dose IVSE et bolus	Diurèse et natriurèse plus importante avec traitement IVSE
Pivac (33) 1998 Int J clin pharmacol	Interventionnelle randomisée en cross over 20 patients	Furosemide 80 mg - bolus x2/j - IVSE	Meilleure diurèse dans le groupe IVSE
Allen (210) 2010 Am J cardiol	Interventionnelle randomisée 41 patients	Furosémide - bolus /12h - IVSE Pas de dose prédéfinie	Pas de différence sur créatinine, diurèse, durée d'hospitalisation et mortalité
Thomson (34) 2010 J card fail	Interventionnelle randomisée 56 patients	Furosemide - IV intermittent - IV continu	Plus grande diurèse et plus courte hospitalisation dans le groupe IV continue
Felker (30) 2011 New England Journal of Medicine	Interventionnelle randomisée Étude DOSE 308 patients 80-240 mg en dose de fond	Furosémide - IVSE - bolus /12h Dose quotidienne ou 2.5x	Pas de différence sur les symptômes ou la fonction rénale
Llorens (211) 2013 Emergency Medicine Journal	Interventionnelle randomisée 109 patients	Furosemide - IVSE 10mg/h - bolus 20mg/6h - bolus 20mg/8h	Plus de diurèse avec IVSE mais plus d'hypokaliémie et pas de différence sur amélioration clinique ou fonction rénale
Palazzuoli (29) 2014 Crit care	Interventionnelle randomisée 82 patients	Furosémide - IVSE - Bolus /12h Pas de dose pré définie	Meilleure diminution du BNP mais plus de WRF, d'hyponatrémie, de durée d'hospit, de mortalité et réhospit à 6 mois dans le groupe IVSE
Yayla (212) 2015 Herz	Interventionnelle randomisée 43 patients	Furosémide - 160 mg IVSE sur 16h - bolus 80mg /12h - Bolus 160 mg + SSH x1/j	Pas de différence sur fonction rénale Groupe avec SSH avait moins longue durée d'hospitalisation
Frea (213) 2019 cardiology	Interventionnelle randomisée Etude DRAIN 80 patients	Furosémide - bolus /12h - IVSE Dose 120 ou 240 mg /j	Meilleure diurèse et moins d'échec de traitement dans le groupe IVSE
Sager (214) 2020 J geriatr cardiol	Interventionnelle randomisée 40 patients "âgés"	- Bolus 20-100 mg 1 ou plusieurs fois par jour - IVSE 4-10h par jour, 100-500mg	Mortalité plus importante dans le groupe IVSE. Pas de changement poids, DFG, créat

Fudim (215) 2021 Am heart J	Analyse post-hoc Étude ASCEND-HF 5738 patients	Furosémide/torsémide/bumétanide les 24 premières heures IVSE vs bolus vs PO	Pas de différence sur diurèse, fonction rénale ou mortalité à 30 et 180 jours
Zheng (216) 2021 ESC heart fail	Interventionnelle randomisée 94 patients IR modérée	Furosémide - 1 bolus par jour - IVSE sur 6h 160 ou 200 mg selon DFG	Meilleure diurèse et moins longue hospit dans le groupe IVSE, pas d'association avec mortalité ou insuffisance rénale

Tableau 3 : études portant sur l'efficacité des dérivés nitrés

Etude	Type d'étude	Intervention	Conclusions
Hockings (74) 1981 American Journal of Cardiology	Interventionnelle randomisée 50 patients post IDM	- nitroprusside 33 µg/min puis ajustement selon PAPO - furosémide 40 à 80 mg +/- doublement de la dose /15 min selon PAPO (max 1000mg)	Diminution plus rapide de la PAPO dans le groupe nitroprusside. Pas de différence de morbimortalité à 6 mois ou 1 an.
Cohn (75) 1982 NEJM	Interventionnelle randomisée 812 patients post IDM	- nitroprusside 10 µg/min +/- majoration /5min de 10 µg /min - placebo	Pas de différence de mortalité
Nelson (76) 1983 The Lancet	Interventionnelle 28 patients post IDM	- Furosémide 1mg/kg bolus - ISDN 50 µg/kg/h, majoration selon PA	Meilleure diminution de la pression artérielle, des résistances périphériques et de la PAPO dans le groupe ISDN
Beltrame (77) 1998 Journal of cardiac failure	Interventionnelle randomisée 69 patients pas en IDM	- furosémide 40 mg ou dose quotidienne +/- 2e bolus + morphine 10 mg en titration - NTG 2.5 µg/min +/- majoration jusqu'à 10 µg /min + N-acetylcystéine	Pas de différence en termes de PaO_2/FiO_2 ou de nécessité de ventilation mécanique
Levy (78) 2007 Annals of Emergency medicine	Interventionnelle comparative non randomisée 69 patients avec PAs ≥ 160 mmHg ou PAm ≥ 120 mmHg	- NTG : bolus 2mg puis IVSE 0.3 to 0.5 µg/kg/min+/- majoration de 20 µg/min toutes les 1 à 3 min +/- bolus de 2mg toutes les 3 à 5 min pendant 30 min - pas de NTG	Une forte dose de NTG semblait associée à moins d'intubation ou de complication cardiovasculaire, mais pas de comparaison statistique réalisée
Mullens (79) 2008 JACC	Rétrospective 175 patients	- nitroprusside 10-40 µg /min puis titration - pas de vasodilatateur	Avec nitroprusside, meilleure amélioration hémodynamique, moins de mortalité. Pas de différence fonction rénale ou réhospitalisation
Breidthart (81) 2009 Journal of Internal medicine	Interventionnelle, comparative non randomisée 128 patients	- soins usuels - 1.6 mg nitrate sublingual + patches transdermiques 10 mg et majoration à 6h	Meilleure diminution du BNP et tendance non significative à moins d'admission en soins intensifs dans le groupe avec dérivés nitrés
Aziz (80) 2011 Hospital pratique	Rétrospective 430 patients	3 groupes : - ni diurétiques ni NTG - diurétiques seuls - diurétiques + NTG	Plus faible mortalité à 2 ans dans le groupe diurétiques + NTG. Pas de différence sur les reconsultations pour ICA à 30 jours.
Kozhuharov (82) 2019 JAMA	Interventionnelle randomisée 788 patients	- soins usuels - stratégie de vasodilatation intensive : NTG sublingual + NTG transdermique majorée après 6h + hydralazine	Pas de différence de décès ou réhospitalisation à 180 jours Baisse initiale plus rapide de la pression artérielle dans le groupe vasodilatation

Tableau 4 : études portant sur la posologie des dérivés nitrés

Etude	Type d'étude	Intervention	Conclusions
Cotter (85) 1998 The Lancet	Interventionnelle randomisée 110 patients	- ISDN 3mg /5 min ou - furosémide 80mg /15 min + ISDN 1mg/h avec majoration débit de 1mg/h toutes les 10 min	Moins de ventilation mécanique, d'infarctus du myocarde ou d'évènements indésirables (hors décès) dans le groupe avec forte doses d'ISDN
Sharon (86) 2000 JACC	Interventionnelle randomisée 40 patients	- BiPAP + ISDN 10 µg/min majoré de 10 µg/min toutes les 5-10 min - ISDN bolus de 4mg toutes les 4 min	Moins d'intubation et de survenue d'IDM dans le groupe ISDN en bolus forte dose
Freund (84) 2011 European journal of emergency medicine	Retrospective 136 patients ≥ 75 ans	- ISDN en bolus - ISDN en IVSE ou pas de dérivés nitrés	Pas de différence de survenue d'hypotension, de mortalité intra hospitalière ou de durée de séjour. Plus d'admission en soins intensifs chez les patients du groupe bolus.
Houseman (217) 2023 American journal of emergency medicine	Rétrospective 67 patients avec détresse respiratoire, PAs ≥ 160mmHg et ayant reçu NTG ≥ 100 µg/min	1 seul groupe	37% ont été en soins intensifs, 21% intubés, 13% avec insuffisance rénale aiguë et 4% d'hypotension.

Tableau 5 : études portant sur l'efficacité de la VNI

Etude	Type d'étude	Intervention	Conclusions
Räsänen (96) 1985 American Journal of Cardiology	Interventionnelle randomisée 40 patients	- Oxygène au masque - PPC	Meilleure amélioration de la FR et des gaz du sang après 10 minutes dans le groupe PPC
Bersten (97) 1991 NEJM	Interventionnelle randomisée 39 patients	- Oxygène - BiPAP	Meilleure amélioration FR et gaz du sang après 30 minutes dans le groupe PPC mais pas après 24 heures. Moins d'intubation dans le groupe PPC. Pas de différence de mortalité intra hospitalière
Masip (98) 2000 The Lancet	Interventionnelle randomisée 37 patients	- Oxygène - PPC	Moins d'intubation et résolution des symptômes plus rapide dans le groupe BiPAP
Delclaux (99) 2000 JAMA	Interventionnelle randomisée 123 patients	- oxygène - PPC	Après 1h, amélioration de la dyspnée et de PaO2/FiO2 dans le groupe PPC. Pas de différence d'intubation ni de durée de séjour en réanimation.
Levitt (100) 2001 Journal of emergency medicine	Interventionnelle randomisée 38 patients	- Oxygène au masque - BiPAP	Pas de différence sur l'évolution de FC, PAs, PAd, FR, SpO2, ou des gaz du sang Moins d'intubation ou d'IDM dans le groupe BiPAP, sans différence significative
Kelly (101) 2002 European Herat journal	Interventionnelle randomisée 58 patients	- Oxygène au masque - PPC	Moins de dyspnée à 1h, moins d'échec de traitement et résolution plus rapide de FR, FC et acidose et tendance à réduction de la mortalité dans le groupe PPC
Nava (102) 2003 American journal of respiratory and critical care	Interventionnelle randomisée 130 patients	- Oxygénothérapie - PPC	Pas de différence d'intubation, de mortalité intra hospitalière ou de durée de séjour Amélioration plus rapide de la dyspnée et de PaO_2/FiO_2 dans le groupe PPC
Park (103) 2004 Critical care medicine	Interventionnelle randomisée 80 patients	- Oxygène - PPC - BiPAP	Meilleure amélioration de la dyspnée et de la PaO2/FiO2 dans les 24h, moins d'intubation et moins de mortalité à 15 jours avec la VNI Pas de différence de survenue d'IDM
L'Her (104) 2004 Intensive care medicine	Interventionnelle randomisée 89 patients ≥ 75 ans	- Soins usuels -Soins usuels +PPC	Meilleure amélioration de la FR et de la SpO2 à 1h, moins d'évènements indésirables et de mortalité à 48h dans le groupe PPC
Tallman (218) 2008 Academic emergency medicine	Analyse du registre ADHERE Cas-témoins 37372 patients	4 groupes : - Pas de ventilation - Succès de VNI - Échec de VNI (intubation secondaire) - Intubation immédiate	Moins de mortalité intra hospitalière pour le groupe succès de VNI que pour les patients intubés, et tendance vers un meilleur pronostic pour les patients intubés secondairement que pour les patients intubés dans l'immédiat

Gray (105) 2008 NEJM	Interventionnelle randomisée 1069 patients	- Oxygène - PPC - BiPAP	Pas de différence de mortalité à 7 jours entre oxygène et VNI, mais meilleure amélioration de la dyspnée et des gaz du sang après 1 heure
Miro (219) 2018 European Journal of internal medicine	Analyse du registre EAHFE 11152 patients	- Pas de VNI - VNI	Pas de différence de mortalité à 30 jours

Tableau 6 : évolution des recommandations sur l'utilisation des diurétiques de l'anse

Recommandations ESC		
2005(220)	- DdA IV indiqués en cas de surcharge - Dose : personnalisée puis titrée selon réponse - Dose de charge puis IVSE - Si résistance : forte dose ou associer thiazidique ou ARA (favoriser combinaison)	**IB** **IIbC**
2008(222)	- DdA recommandé si surcharge - Dose initiale 20-40mg furosémide (0.5-1mg bumétanide, 10-20mg torsémide), à majorer si traitement de fond et/ou altération DFG - Bolus ou IVSE. - Dose totale < 100mg/6h ou < 240mg/24h - Si résistance : forte dose ou asso thiazidique ou ARA (favoriser combinaison)	**IB**
2012(224)	- DdA recommandé pour améliorer dyspnée et congestion. - La dose optimale est incertaine. - En cas d'œdème résistant, combinaison avec thiazidique à considérer	**IB**
2016(225)	- DdA IV recommandé si congestion - Dose 20-40mg ou dose quotidienne - Bolus ou IVSE - Si effet insuffisant ou résistance, asso avec thiazidique ou ARA	**IC** **IB** **IB** **IIbC**
2021(4)	- DdA IV recommandé si congestion - Dose : 20-40mg furosémide (10-20mg torsémide) - 2-3 bolus/j ou IVSE +/- dose de charge - Considérer asso avec thiazidique - Traitement séquentiel : Évaluation de la réponse après 2 ou 6h (Bonne réponse = Na_u > 50-70mEg/L ou diurèse > 100-150mL/h) Si réponse insuffisante, on double la dose et on réévalue après 2-6h. Une fois dose maximale atteinte, ajout de thiazidique ou acétazolamide	**IC** **IIaB**

ARA, anti récepteur de l'angiotensine; DdA, diurétique de l'anse; DFG, débit de filtration glomérulaire; ESC, European society of cardiology; IV, intraveineux; IVSE, intraveineux à la seringue électrique

Recommandations ACC/AHA		
2009(221)	- DdA indiqué si surcharge, dose suffisante pour symptômes en évitant effets secondaires - Si réponse insuffisante, majoration de la dose	**IC** **IC**
2013(223)	- DdA recommandés si surcharge - Dose : titration selon symptômes et pour éviter hypotension - Si réponse insuffisante, majoration de la dose ou ajout d'un autre diurétique - Association possible avec dopamine	**IB** **IB** **IIaB** **IIbB**
2022(5)	- DdA recommandés si congestion - Dose : au moins 2 fois la dose quotidienne de base et titration selon la réponse - Si réponse insuffisante, majoration de la dose ou ajout d'une autre molécule	**IB** **IB** **IIaB**

ACC, American college of cardiology; AHA, American heart association; DdA, diurétique de l'anse

Tableau 7 : évolution des recommandations sur l'utilisation des vasodilatateurs

Recommandations ESC		
2005(220)	- Vasodilatateurs recommandé si mauvaise réponse aux diurétiques et pas d'hypotension - Indication à dérivés nitrés PO ou IV - Diminuer dose si PAs < 90-100mmHg - Favoriser nitroprusside si insuffisance cardiaque sévère et/ou insuffisance mitral - Utilisation possible du nesiritide	IB IB IC
2008(222)	- Vasodilatateurs recommandés sauf si PAs < 90 ou hypotension symptomatique ou rétrécissement valvulaire - Utiliser avec précaution si PAs 90-110 - NTG ou ISDN ou nitroprusside ou nesiritide	IB
2012(224)	- Dérivés nitrés IV doivent être considérés chez patients avec PAs >110 mmHg, en l'absence de rétrecissement aortique ou mitral sévère - Nitroprusside IV doivent être considérés chez patients avec PAs >110 mmHg, en l'absence de rétrécissement aortique ou mitral sévère. Faire attention en cas de patient avec IDM	IIaB IIbB
2016(225)	- Vasodilatateurs doivent être considérés si PAs > 90 mmHg sans hypotension symptomatique pour améliorer signes de congestion - Utiliser avec prudence si rétrécissement mitral ou aortique - NTG ou ISDN ou nitroprusside ou nesiritide	IIaB
2021(4)	- Vasodilatateurs IV peuvent être considérés en phase initiale pour améliorer les symptômes et diminuer la congestion - Indiqué si PAs > 110mmHg - Effet favorable en cas de rétrécissement aortique et dysfonction ventriculaire gauche - NTG ou ISDN ou nitroprusside	IIbB

ESC, European society of cardiology; IV, intraveineux; ISDN, isosorbide dinitrate; NTG, nitroglycérine; PAs, pression artérielle systolique; PO, per os

Recommandations ACC/AHA		
2009(221)	- Vasodilatateurs peuvent être bénéfiques si signes de surcharge, en plus des diurétiques ou en cas de résistance - NTG IV ou nitroprusside ou nesiritide	IIaC
2013(223)	- Vasodilatateurs IV peuvent être considérés en plus des diurétiques chez les patients stables avec insuffisance cardiaque, en l'absence de signe d'hypotension - NTG ou nitroprusside ou nesiritide	IIbA
2022(5)	- Vasodilatateurs IV peuvent être considérés en l'absence d'hypotension, en plus des diurétiques, pour soulager la dyspnée - En particulier en cas d'hypertension, d'ischémie coronaire ou d'insuffisance mitral significative. - Nitroprusside à favoriser en cas de dysfonction sévère du ventricule gauche - NTG ou nitroprusside	IIbB

ACC, American college of cardiology; AHA, American heart association; IV, intraveineux; NTG, nitroglycérine

Tableau 8 : évolution des recommandations sur l'utilisation de la VNI

Recommandations ESC		
2005(220)	- Il y a un consensus fort que la VNI doit être utilisée avant intubation - L'utilisation de PPC et de BiPAP diminue le recours à l'intubation	**IIaA**
2008(222)	- La VNI doit être considérée dès que possible chez les patients en ICA hypertensive vu qu'elle améliore les symptômes - Il faut appliquer une PEP de 5-7.5 cmH_2O et titrer jusqu'à 10 cmH_2O selon réponse, avec une $F_iO_2 > 0.40$, pendant une durée de 30 minutes à 1 heure	**IIaB**
2012 (224)	- La VNI peut être utilisée en traitement adjuvant pour soulager les symptômes en cas d'échec du traitement médicamenteux - La VNI (ex. PPC) doit être considérée chez les patients avec FR > 20 pour améliorer la dyspnée et réduire hypercapnie et acidose - Ne pas utiliser en cas d'hypotension.	**IIaB**
2016(225)	- La VNI doit être considérée chez les patients en détresse respiratoire (fréquence respiratoire >25 /min, SpO2 <90%) et débutée dès que possible pour diminuer les symptômes et éviter l'intubation	**IIaB**
2021(4)	- La VNI doit être considérée chez les patients en détresse respiratoire (fréquence respiratoire >25 /min, SpO2 <90%) et débutée dès que possible pour diminuer les symptômes, améliorer les échanges gazeux et éviter l'intubation	**IIaB**

BiPAP, bilevel positive airways pressure; ESC, European society of cardiology; F_iO_2, fraction inspirée en oxygène; FR, fréquence respiratoire; ICA, insuffisance cardiaque aiguë; PEP, pression expiratoire positive; PPC, pression positive continue; VNI, ventilation non invasive

Recommandations ACC/AHA		
2009(221)	Non évoqué	
2013(223)	Non évoqué	
2022(5)	Non évoqué	

ACC, American college of cardiology; AHA, American heart association

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Low compliance to guidelines in the management of acute heart failure in emergency elderly patients: a multicenter pilot prospective study

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In western countries, acute heart failure syndrome (AHFS), a rapid onset or worsening of symptoms and/or signs of heart failure, is the most common primary diagnosis in patients aged greater than or equal to 75 years visiting the emergency department (ED) [1]. This syndrome is reportedly associated with a median length of hospital stay of 10 days, a mortality around 10% at 30 days, and a readmission rate of 25–30% at 30 days [2]. Despite this high rate of morbidity and mortality, the management of AHFS has not changed for several decades and most clinical studies failed to show a positive impact of new drugs on patients' prognosis. European guidelines include the use of diuretics, nitrates, oxygen, and noninvasive ventilation when indicated along with the treatment of any potential AHFS triggers (precipitating factors). However, these guidelines are based on moderate levels of evidence and subsequent moderate strength of recommendations (IB and IIaB), and high-quality randomized-controlled trials data are lacking [3].

EDs play a crucial role in the early management of AHFS as most of their admissions are subsequent to an ED visit. The recommended treatment should be started as early as possible. Before implementing an interventional randomized-controlled trial that will test a comprehensive care bundle of early and intensive management of AHFS, we aimed to assess in an observational pilot study the adherence of French emergency physicians to the European guidelines.

During a 7-day period in 2017, we prospectively enrolled from 8 French academic EDs (rural and urban) consecutive patients aged 75 years and older presenting with a diagnosis of AHFS made by the treating emergency physician on the basis of an association of clinical, biological, and radiological criteria. We recorded all treatments and investigations ordered in the ED. The primary endpoint was the initiation of the recommended treatment: IV nitrates (if systolic blood pressure > 110 mmHg) and a diuretic. The secondary endpoints included the work-up and treatment of acute coronary syndrome (ACS) as a potential precipitating factor and a composite endpoint of global compliance to guidelines in terms of treatment of AHFS and management of an ACS (work-up and treatment). The work-up for ACS was a troponin measurement and the recommended treatment for ACS was the initiation of dual antiplatelet therapy and coronary angiography.

Among the 73 enrolled patients during the 7-day period (median: 8 per center, range 5–13), the median age was 86 years and 47 (64%) were women. The recommended treatment was initiated in 25 (34%) patients, and an ACS was sought in 59 (81%) patients. Among the 18 patients with evidence of ACS, the recommended treatment of this precipitating factor was initiated in four (22%) patients. Altogether, global compliance to the guidelines (symptomatic treatment of AHFS and work-up for precipitating factor and treatment if any) was present in 12 (16%) cases.

In this multicenter prospective cohort study, we found a low compliance rate to the diagnostic and therapeutic guidelines for AHFS. Although 64 (88%) patients were treated with a diuretic, only 25 (34%) also received nitrates. Intravenous vasodilators represent a cornerstone of early AHFS treatment, and we confirmed the findings of previous studies that elderly patients do not often receive this therapy [4].

The treatment of any precipitating factor is clearly recommended in current guidelines as it directly impacts patients' outcome [5]. An ACS is present in up to 30% of AHFS in the elderly and is easy to diagnose with a troponin measurement. However, it appears that only a few patients with positive troponin and ACS criteria receive the recommended treatment. The limitations of the present study include the absence of ECG analysis for the diagnosis of ACS and the definition of ACS based only on a troponin value. We may also lack external validity as all centers were French EDs.

These often forgotten aspects of the management of AHFS in the elderly need to be promoted in the EDs,

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and a clear course of action could probably reduce the heterogeneity and low compliance to guidelines that we found. Once again, we report suboptimal care for elderly patients in the ED.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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New European Society of Cardiology guidelines for the management of patients with ST-elevation myocardial infarction: effect on physician's compliance and patient's outcome

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The recent European Society of Cardiology (ESC) guidelines have changed the management of patients with ST-elevation myocardial infarction (STEMI) [1]. The implication of delay in the decision making, from pain to first medical contact and from first medical contact to angioplasty, has been simplified. A unique delay, 120 min from first medical contact to angioplasty, has been proposed. The previous target was 90 and 60 min in 'early presenters' [2]. In addition, specific guidelines for the management of 'early presenters' have been omitted. However, as the authors underlined, there is no recent evidence to support these changes [1].

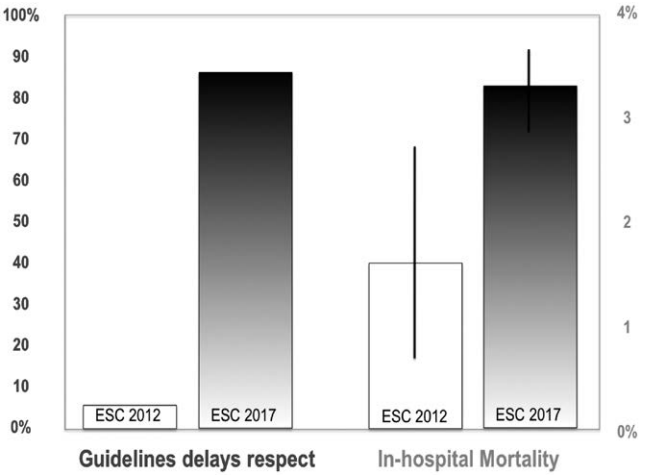
We undertook an analysis of our registry, to compare compliance with the guidelines and patient outcomes with the previous guidelines (2012) and with the new ones (2017) [1,2]. We analyzed data from a prospective, 15-year-old registry of patients with STEMI (<24 h) managed in prehospital settings in the Great Paris area (e-MUST). In accordance with the French SAMU system, patients with STEMI are managed (and thereby included in the registry) by 41 mobile ICUs with an emergency physician on board.

Early presenters (i.e. delay from pain to first medical contact <2 h) who benefitted from a prehospital strategy of primary percutaneous coronary intervention (PCI) were included in our analysis. Patients treated with a pharmacoinvasive strategy (prehospital lytics before PCI), patients who did not benefit from a reperfusion strategy, patients who died before arrival at the hospital and patients for whom information about the delay was missing were excluded.

We then compared the rates of compliance with previous and recent guideline delays reported by physicians (correspondingly the preferred 60 min for 'early presenters' in the 2012 guidelines vs. 120 min for all patients in the 2017 guidelines), and the in-hospital mortality rates corresponding to those delays. These criteria were retrospectively applied to all patients of the cohort.

Among 22 160 patients managed in prehospital settings from 2003 to 2015, 13 569 (61%) were 'early presenters.' Among the population of 'early presenters', 7684 (35%) were included. Excluded were 2839 patients treated with lytics in a prehospital setting, 637 patients for whom

Fig. 1



Comparison of the rates of patients managed in compliance with the guideline delays (ESC 2012 vs. 2017) and corresponding in-hospital mortality rates in the prehospital registry of the Great Paris area (E-Must 2003–2015; ***N*** = 7684). ESC, European Society of Cardiology.

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Trials

STUDY PROTOCOL Open Access

Early and comprehensive care bundle in the elderly for acute heart failure in the emergency department: study protocol of the ELISABETH stepped-wedge cluster randomized trial

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Background: Acute heart failure (AHF) is one of the most common diagnoses for elderly patients in the emergency department (ED), with an admission rate above 80% and 1-month mortality around 10%. The European guidelines for the management of AHF are based on moderate levels of evidence, due to the lack of randomized controlled trials and the scarce evidence of any clinical added value of a specific treatment to improve outcomes. Recent reports suggest that the very early administration of full recommended therapy may decrease mortality. However, several studies have highlighted that elderly patients often received suboptimal treatment. Our hypothesis is that an early care bundle that comprises early and comprehensive management of symptoms, along with prompt detection and treatment of precipitating factors should improve AHF outcome in elderly patients.

Methods/design: ELISABETH is a stepped-wedge, cluster randomized controlled, clinical trial in 15 emergency departments in France recruiting all patients aged 75 years and older with a diagnosis of AHF. The tested intervention is a care bundle with a checklist that mandates detection and early treatment of AHF precipitating factors, early and intensive treatment of congestion with intravenously administered nitrate boluses, and application of other recommended treatment (low-dose diuretics, non-invasive ventilation when indicated, and preventive low-molecular-weight heparin). Each center is randomized to the order in which they will switch from a "control period" to an "intervention period." All centers begin the trials with the control period for 2 weeks, then after each 2-week step a new center will enter the intervention period. At the end of the trial, all clusters will receive the intervention regimen. The primary outcome is the number of days alive and out of the hospital at 30 days.

Discussion: If our hypothesis is confirmed, this trial will strengthen the level of evidence of AHF guidelines and stress the importance of the associated early and comprehensive treatment of precipitating factors. This trial could be the first to report a reduction in short-term morbidity and mortality in elderly AHF patients.

Trial registration: ClinicalTrials.gov, ID: NCT03683212. Prospectively registered on 25 September 2018.

Keywords: Elderly, Acute heart failure, Emergency department

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Background

Acute heart failure (AHF) is a syndrome defined as new-onset or worsening of symptoms and signs of HF, often requiring rapid escalation of therapy and hospital admission. The clinical presentation of AHF typically includes symptoms or signs related to congestion and volume overload rather than to hypoperfusion [1]. Acute heart failure represents 5% of all emergency hospitalizations, and is the most common primary diagnos in patients aged ≥75 years visiting the emergency department (ED) [2, 3]. The EDs are the main entry to the hospital for AHF, with 64% of these admissions being subsequent to an ED visit [4]. This syndrome is reportedly associated with poor outcomes, with a 80% rate of hospital admission, a median length of hospital stay of 10 days and a mortality around 10% at 30 days, and a readmission rate of 25–30% at 30 days [5–7]. Despite a high rate of morbidity and mortality, the management of AHF has not changed for several decades and most clinical studies failed to demonstrate a positive impact of new drugs on patients' prognosis [8, 9]. European guidelines include the use of diuretics, nitrates, oxygen and non-invasive ventilation (NIV) when indicated along with the treatment of any potential AHF triggers (precipitating factors). However, these guidelines are based on moderate levels of evidence (IB and IIaB), and high-quality randomized controlled trial (RCT) data are lacking [10–12].

In 1998 and 2000, the two cornerstone trials of Cotter et al. provided evidence of the benefits associated with early vasodilator therapy with nitrates, although on a very small sample of patients (less than 200 in total) [13, 14]. Since then, every prospective trial on AHF management failed to report a clinically significant improvement of outcomes. Equipoise remains on many questions regarding the recommended therapeutics: the optimum dose and route of administration of diuretics are not clear, the use of nitrates is also debated, and the benefit of NIV is unclear [15–17]. Despite these controversies, recommendations and guidelines are published by international societies (European Society of Cardiology (ESC), American Heart Association (AHA), etc.) and constitute the basis of our understanding and standard of care [10, 11]. However, a large proportion of elderly patients in AHF do not receive adequate care, including low rates (30–50%) of nitrate therapy [7, 18]. We recently conducted a preliminary analysis in eight French EDs participating in the present ELISABETH trial. For a 7-day period, we evaluated all consecutive patients aged 75 years and older with a diagnosis of AHF in the ED. Among the 73 consecutive AHF patients, 23 patients (32%) had not been investigated for the findings of precipitating factors of AHF (namely infection, acute coronary syndrome (ACS) or atrial fibrillation). In total, only 18 elderly ED patients (23%) were managed according to the existing guidelines [19].

The lack of solid evidence regarding the efficacy of full recommended therapeutic management of AHFS on outcomes may have been caused by several shortcomings that we will address in the present ELISABETH trial:

1) The previous RCTs did not include in their protocol of care the systematic early assessment for precipitating factors, and their subsequent treatment. The main reported triggers are ACS, infection and atrial fibrillation [20, 21]. As the outcomes of AHF patients has been linked with the triggering factors, we make the hypothesis that early (i.e., in the ED) and comprehensive discovery and treatment of these precipitating factors may improve the prognosis [22]
2) The majority of previous RCTs only assessed the impact of single drugs, and not of a comprehensive care bundle. Due to polyfactorial causes of poor outcomes in elderly patients with AHF, we believe that an intervention that focuses only on the administration of a single drug may have a lesser effect than a care bundle
3) The delay between ED arrival and randomization may have been too long: in recent large RCTs, this timeframe varied from 6 to > 24 h [8, 23]. It has, however, been suggested that the introduction of decongestion treatment within hours in the ED is associated with better outcomes [24–26]. In the present study, nitrates and loop diuretics will be given within 1 h of first medical contact in the ED
4) Although the elderly are described as suffering most from AHF, with worse outcomes, specific RCTs in this frail population are lacking (e.g., the recent True-AHF RCT, which evaluated the effect of ularitide infusion, excluded elderly patients) [8]. Thus our trial, focused on older AHF patients, will be, to the best of our knowledge, the first to evaluate the impact of an early intensive approach in this target population

The hypothesis of our trial is that an early and comprehensive care bundle, that associates prompt treatment of congestion with intravenously administered (IV) nitrate boluses and early recognition and treatment of potential precipitating factors, will improve short-term morbidity and mortality.

Methods/design

The ELISABETH trial (NCT03683212) is a stepped-wedge clinical trial in France [27]. The primary objective of this study is to assess the change in the early (1-month) morbidity and mortality of AHF in elderly patients with the implementation of an early and comprehensive care bundle in the ED.

Experimental plan of the stepped-wedge design

In this stepped-wedge clinical trial, patients will be recruited in 15 EDs in France, academic and non-academic, rural and urban (Table 1). All clusters will begin the trial with the "control period" where included AHF patients will be routinely managed by the emergency physicians. After a first step of 2 weeks, every 2 weeks, one center will randomly be assigned to switch to the "intervention period" where the ELISABETH care bundle will be implemented. After 32 weeks, all centers will be in the "intervention period" for the four remaining weeks of the trial (Table 2).

We decided to choose this design for the following reasons:

- As we implement a new protocol, there is a risk of contamination. An emergency physician, who would have already treated patients via the care bundle protocol, would be subsequently influenced by this trial, and could have difficulty in providing the former "standard of care." Therefore, a randomization at the patient level or a cross-over design would induce bias through contamination
- The present ELISABETH trial focuses on a severe condition, in EDs that are often busy places; therefore, the need for randomization at the patient level could be an impediment to inclusion, and, therefore, limit our ability to recruit consecutive patients
- A cluster, stepped-wedge design prevents contamination that could arise from a cluster cross-over design, as centers will first be allocated to standard care before implementing the intervention. Furthermore, a stepped-wedge design would also prevent a potential "period effect" that could have resulted from a simple before/after design

Selection of participants

The ELISABETH trial focuses on elderly patients with AHF in the ED. Therefore, all patients aged 75 years and over, affiliated to French social security with a diagnosis of AHF in the ED, defined by the association of:

- At least one of the following symptoms: acute or worsening dyspnea, orthopnea
- *and* at least one of the following:
  - Bilateral pulmonary râles or peripheral edema
  - Signs of pulmonary congestion on chest radiography or cardiac echography
  - Increased natriuretic peptides (brain natriuretic peptide (BNP) or NT-proBNP)

A written informed consent signed by the patient will be necessary prior to inclusion. If the patient is unable to consent, then the physician will seek consent from a trustworthy person, family member or close relative. If none are available, the physician will be able to proceed to an emergency inclusion and then the written informed consent will be signed by the patient (if need be by a trustworthy person, family member or close relative) as soon as possible (article L1122-1-2 of the French Public Health Code).

Patients are excluded if they have any of the followings:

- Other obvious cause of acute illness (severe sepsis, ST-elevation myocardial infarction)
- Systolic blood pressure less than 100 mmHg

Table 1 List of investigators and recruiting centers

Name	First name	City	Country	Hospital	Expected recruitment
Freund	Yonathan	Paris	France	Pitié-Salpêtrière	34
Adnet	Frederic	Paris	France	Avicenne	34
Yordanov	Youri	Paris	France	Saint-Antoine	34
Feral	Anne-Laure	Paris	France	HEGP	34
Laribi	Said	Tours	France	CHU Tours	34
Claret	Pierre-Geraud	Nîmes	France	CHU Nîmes	34
Chouihed	Tahar	Nancy	France	CHU Nancy	34
Charpentier	Sandrine	Toulouse	France	CHU Rangueuil	34
Truchot	Jennifer	Paris	France	Lariboisiere	34
Dumas	Florence	Paris	France	Cochin	34
Occelli	Celine	Nice	France	CHU Nice	34
Khellaf	Mehdi	Creteil	France	CHU H Mondor	34
Beaune	Sebastien	Boulogne	France	CHU A Paré	34
Ganansia	Olivier	Paris	France	CH St Joseph	34
Desmettre	Thibaut	Besancon	France	CHU Besancon	34

Table 2 Experimental design of the stepped-wedge methodology

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Step 9	Step 10	Step 11	Step 12	Step 13	Step 14	Step 15	Step 16
Center 1	C	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Center 2	C	C	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Center 3	C	C	C	I	I	I	I	I	I	I	I	I	I	I	I	I
Center 4	C	C	C	C	I	I	I	I	I	I	I	I	I	I	I	I
Center 5	C	C	C	C	C	I	I	I	I	I	I	I	I	I	I	I
Center 6	C	C	C	C	C	C	I	I	I	I	I	I	I	I	I	I
Center 7	C	C	C	C	C	C	C	I	I	I	I	I	I	I	I	I
Center 8	C	C	C	C	C	C	C	C	I	I	I	I	I	I	I	I
Center 9	C	C	C	C	C	C	C	C	C	I	I	I	I	I	I	I
Center 10	C	C	C	C	C	C	C	C	C	C	I	I	I	I	I	I
Center 11	C	C	C	C	C	C	C	C	C	C	C	I	I	I	I	I
Center 12	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I	I
Center 13	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I	I
Center 14	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I	I
Center 15	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	I

Each step lasts for 2 weeks, except for step 1 and step 16 which last for 4 weeks. *I* Intervention, *C* Control

- Any contra-indication to nitrates (severe mitral or aortic stenosis, or severe aortic regurgitation)
- Known chronic kidney injury on dialysis
- Time from ED entrance to inclusion > 6 h
- Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom

Trial objectives and outcomes

The main objective of the present trial is to compare the efficacy of an early and comprehensive management strategy of AHF in elderly patients to the usual care on morbi-mortality at 30 days. Our primary endpoint is the number of days alive and out of hospital at 30 days after the index ED visit. This endpoint is considered as relevant by the group of experts of the ESC [28]. In their consensus paper, the experts stated that although mortality should be captured, repeated hospitalizations should also be recorded. Especially in elderly patients, where the rate of readmission to the ED and rehospitalization is elevated: up to 40% of heart failure admissions to the hospital are actually repeated admission for recurrence of symptoms within 30 days of a previous AHF event [3, 6]. We chose the timeframe of 30 days because a shorter timeframe would not catch recurrence and morbidity, and a longer timeframe would catch events that are more likely linked to chronic morbidity of the patients than to the AHF syndrome [22, 28, 29].

The primary endpoint (days alive and out of hospital at day 30) will be measured at the end of the 30-day follow-up period, either by hospital visit or phone interview, and medical chart review. Vital status, date of death and date of discharge will be collected.

A death during the follow-up period will correspond to 0. An ED visit will correspond to "1 day" at the hospital. For example, a patient not admitted (at day 0), with no return visit to the hospital, and alive at day 30 will have 30 days alive and out of hospital. A patient who is admitted (at day 0) and stays 8 days in the hospital before being discharged and has no readmission and no return visit to the ED would have "22 days alive and out of hospital at 30 days." A patient who is admitted and dies at 13 days, either at home or in hospital will score 0. A patient who is admitted for 10 days, discharged home for 5 days then admitted at day 16 for 15 days will have 5 days alive and out of hospital (namely days 11, 12, 13, 14 and 15).

The secondary endpoints include:

- 30-day all-cause mortality
- 30-day cardiovascular mortality
- Hospital readmission at 30 days
- Length of in hospital stay truncated at 30 days
- Changes of more than twofold in creatinine level from inclusion to day 30 or to discharge, whichever comes first

Creatinine will be measured at day 0 in the ED, and at discharge day or day 30, whichever comes first.

Description of the intervention

This is an intervention study, where the intervention comprises the application of recommendations and guidelines for the management of AHF, ACS and infection.

Control period: Acute heart failure standard therapy:

- Treatments are given at the discretion of the treating emergency physician
  The guidelines and standard of care will be recalled to the emergency physicians at the beginning of the trial in each center when the control period will start.

Intervention period: Early intensive care bundle:
The care bundle comprises a list of items to follow and tick on a handover checklist (Fig. 1) within 4 h of ED management:

a) Treatment of the congestion: (*international guidelines and recommendations* [10, 11])
   - 40 mg of IV furosemide (or usual daily dose) if not already given pre-hospital
   - IV nitrates given in boluses of 3 mg every 5 min. After 1 h of bolus titration, then continuous infusion with an hourly dose of at least half of the total given during the first hour of nitrate administration. Blood pressure (BP) will be monitored every 5 min during the titration (then hourly), and nitrates will be discontinued if BP drops < 100 mmHg

b) Treatment of precipitating factors:
   - Administration of antibiotic therapy (accordingly to local guidelines amoxicillin and clavulanic acid in most cases) in the presence of at least two of the following: fever > 38 °C, leucocytes > 12,000 G/L, radiological signs suggestive of lower respiratory tract infection or elevated C-reactive protein (CRP) or procalcitonin (PCT)
   - Administration of dual antiplatelet therapy and transfer to cardiac intensive care unit in the presence of at least two of the followings: chest pain, ischemic signs on an electrocardiogram (ECG), elevated troponin concentration or change in troponin concentration. These patients will be transferred for coronary angiography if indicated by the cardiologist, as recommended [30]
   - In case of atrial fibrillation: administration of heparin, heart rate control strategy (digoxin or amiodarone as indicated) to reduce heart rate under 100 bpm, early admission to a cardiac intensive care unit if elevated troponin is associated

c) NIV if respiratory distress with hypercapnia and pH < 7.35 in the absence of any contraindication [11]
d) Preventive low-molecular-weight heparin (LMWH) if there is no pre-existing anticoagulation therapy [11]

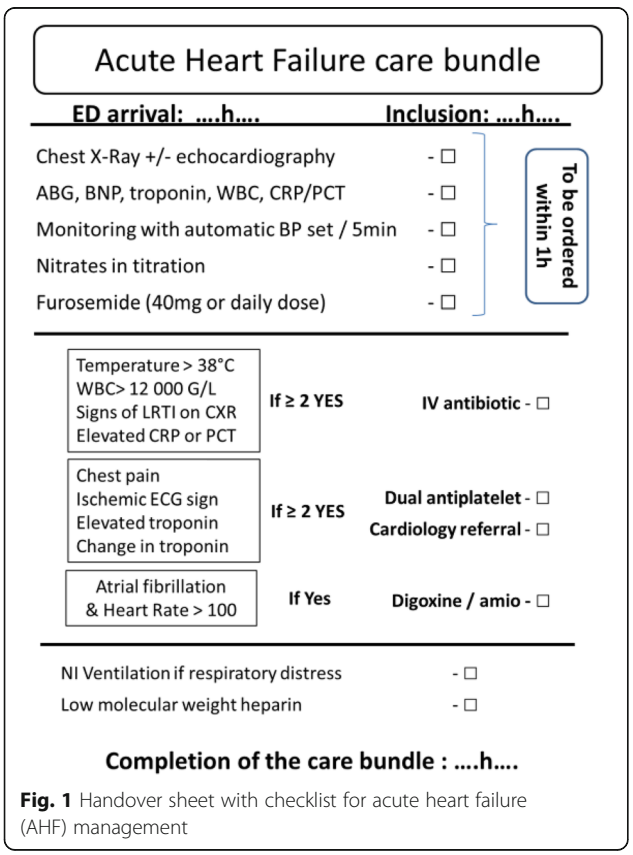

Fig. 1 Handover sheet with checklist for acute heart failure (AHF) management

All treatments will be initiated in the ED, and their continuation or discontinuation will be evaluated by the treating physician during the subsequent hospital stay.

Statistical analysis

No interim analysis is planned. Analysis will be performed at the end of the study after data review and freezing of the data base. Analyses will be performed using SAS® software (version 9.3 or updated version). Principal analysis will be realized according to the intention-to-treat (ITT) principle.

Baseline patient characteristics will be considered at both with the cluster (center) and patient level. For the center level, characteristics at the beginning of the study will be described (there are no expected changes between the two periods for cluster characteristics). Baseline characteristics of patients will be described globally and according to the period. Continuous variables will be summarized using descriptive statistics, i.e., number of subjects, mean, standard deviation (SD), median, inter quartile range, minimum and maximum. Qualitative variables will be summarized by frequency and percentage.

The number of days alive and out of hospital will be calculated based on date of admission, vital status, date of death and date of discharge will be collected.

This primary endpoint will be analyzed using a linear-regression mixed model with a random effect for each cluster, considered fixed effects will be: strategy and, for the stepped-wedge design, time representing each step. In case of non-normal distribution of the interest variable, a transformation could be realized.

All-cause mortality at 30 days, cardiovascular mortality at 30 days and hospital readmission at 30 days will be compared between groups by using Pearson's chi-square test or Fisher's exact test.

If possible, a generalized linear-regression mixed model with Poisson distribution will be performed. If the number of events is sufficient, a generalized linear-regression mixed model using the logit link will be performed. The length of stay in hospital in days will be compared between the two periods by using Student's *t* test or the Wilcoxon rank-sum test as needed. If possible, a linear-regression mixed model will be performed. A random effect for each cluster will be considered and considered fixed effects will be: strategy and, for the stepped-wedge design, time representing each step. In case of non-normal distribution of the interest variable, a transformation could be realized. The percentage of patients with a change of more than twofold in creatinine between inclusion and 30 days will be compared between groups by using Pearson's chi-square test or Fisher's exact test. If possible, a generalized linear-regression mixed model with Poisson distribution will be performed. If the number of events is sufficient, a generalized linear-regression mixed model using the logit link will be performed.

A second analysis will be performed on the per-protocol population.

All tests will be performed with an alpha set at 5%.

Sample size calculation

From our previous cohort, the mean number of days alive and out of hospital at 30 days was 14 ± 9. To be clinically relevant, we estimate that the new approach should increase this endpoint of 3 days at least (a relative increase of 20%). With a power of 80% and alpha = 5%, 283 patients are needed to be included. Considering the stepped-wedge design and after specification of the following elements: 15 clusters, intra-cluster correlation (ICC) = 0.0001, the design effect is estimated at 1.609, increasing to 454 subjects who need to be included. Taking into account 10% of non-evaluable patients, it is necessary to include 500 patients – two per cluster for each 2-week period (Additional file 1).

Discussion

Despite a small improvement in the outcomes of elderly patients admitted for AHF within the past decades, its morbidity and mortality remains severe with a 10% rate of 30-day mortality, and 25–30% of early readmission rate [6, 7, 18, 31]. In the majority of cases, treatment can be initiated in the ED. However, many studies have shown that a majority of these patients are still not receiving recommended therapies in the ED – either for AHF per se, or for precipitating factors of AHF, especially ACS or infection [7, 16, 18].

In this context, there is an urgent need for a multidisciplinary management program for patients with AHF in the ED and following ED care to ensure better results and adherence [32]. The great outcome improvements provided by early treatment in the ED have long been established for other pathologies (e.g., sepsis, myocardial infarction). Unfortunately, AHF has not been considered with this regard until recently. Some reports suggest the importance of time to introduce therapy in AHF. Data derived from the ADHERE registry indicate that early treatment (< 6 h) in EDs would create a positive impact by decreasing in-hospital mortality and morbidity rates (unadjusted OR for in-hospital mortality 0.77, adjusted OR 0.87 (95%CI [0.76–0.96]) [24]. Very recently, in their large prospective observational study, Matsue et al. reported a significant decreased mortality in AHF following the initiation of decongestion therapy within 1 h in the ED (OR for in-hospital mortality of 0.39 (95%CI [0.20–0.76]) [26].

As expressed by Januzzi and Felker in a recent editorial, "*the failure of novel therapies for AHF requires us to make better use of what we already have. A systematic approach would allow an optimal management of acute HF, and in turn could finally improve outcomes*" [33]. If our hypothesis is confirmed, our trial of this early intensive care bundle will be the first RCT to show a significant reduction in short-term morbidity and mortality in elderly AHF patients, similar to what was achieved for sepsis (with a 15% absolute reduction of in-hospital mortality) [34, 35].

Lastly, it can be stressed that the observed high rate of deviation from the guidelines may be caused in part by their low level of evidence. A positive outcome of the introduction of a care bundle based on these recommendations would increase physician adherence and patient outcomes.

Trial status

This is adapted from version v4–0.2018_11_28 of the ELISABETH protocol (Additional file 2).

Inclusion will start on 10 December 2018 and end on 19 August 2019.

Additional files

Additional file 1: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: recommended items to address in a clinical trial protocol and related documents. (DOC 121 kb)

Additional file 2: This is the full ELISABETH protocol in its 4.0 version of 28 November 2018. (DOCX 356 kb)

Abbreviations
AHF: Acute heart failure; BNP: Brain natriuretic peptide; BP: Blood pressure; ED: Emergency department; ICC: Intra-cluster correlation; ITT: Intention-to-treat; LMWH: Low-molecular-weight heparin; NIV: Non-invasive ventilation; RCT: Randomized controlled trial

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
YF drafted the article. YF, JG, SS, VL, TS and AM participated in the elaboration of the study design and writing of the protocol. MC and TS are responsible for the statistical analysis. JG and AM made substantial contributions to the protocol and this article. All authors take responsibility for this paper as a whole. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Informed consent will be obtained from all study participants whenever possible. If the patient is unable to consent, informed consent from a relative will be obtained. If there is no relative, an emergency consent could be obtained. In all cases, the patient's consent will be obtained as soon as their condition allows it. An Institutional Review Board authorized the study (Comité de Protection des Personnes SOOM 2, ID-RCB: 2018-AO1139–46, 6 September 2018) for all participating centers, as this trial will be conducted in France only.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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JAMA | Original Investigation

Effect of an Emergency Department Care Bundle on 30-Day Hospital Discharge and Survival Among Elderly Patients With Acute Heart Failure
The ELISABETH Randomized Clinical Trial

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IMPORTANCE Clinical guidelines for the early management of acute heart failure in the emergency department (ED) setting are based on only moderate levels of evidence, with subsequent low adherence to these guidelines.

OBJECTIVE To test the effect of an early guideline-recommended care bundle on short-term prognosis in older patients with acute heart failure in the ED.

DESIGN, SETTING, AND PARTICIPANTS Stepped-wedge cluster randomized trial in 15 EDs in France of 503 patients 75 years and older with a diagnosis of acute heart failure in the ED from December 2018 to September 2019 and followed up for 30 days until October 2019.

INTERVENTIONS A care bundle that included early intravenous nitrate boluses; management of precipitating factors, such as acute coronary syndrome, infection, or atrial fibrillation; and moderate dose of intravenous diuretics (n = 200). In the control group, patient care was left to the discretion of the treating emergency physician (n = 303). Each center was randomized to the order in which they switched to the "intervention period." After the initial 4-week control period for all centers, 1 center entered in the intervention period every 2 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was the number of days alive and out of hospital at 30 days. Secondary outcomes included 30-day all-cause mortality, 30-day cardiovascular mortality, unscheduled readmission, length of hospital stay, and kidney impairment.

RESULTS Among 503 patients who were randomized (median age, 87 years; 298 [59%] women), 502 were analyzed. In the intervention group, patients received a median (interquartile range) of 27.0 (9-54) mg of intravenous nitrates in the first 4 hours vs 4.0 (2.0-6.0) mg in the control group (adjusted difference, 23.8 [95% CI, 13.5-34.1]). There was a significantly higher percentage of patients in the intervention group treated for their precipitating factors than in the control group (58.8% vs 31.9%; adjusted difference, 31.1% [95% CI, 14.3%-47.9%]). There was no statistically significant difference in the primary end point of the number of days alive and out of hospital at 30 days (median [interquartile range], 19 [0- 24] d in both groups; adjusted difference, −1.9 [95% CI, −6.6 to 2.8]; adjusted ratio, 0.88 [95% CI, 0.64-1.21]). At 30 days, there was no significant difference between the intervention and control groups in mortality (8.0% vs 9.7%; adjusted difference, 4.1% [95% CI, −17.2% to 25.3%]), cardiovascular mortality (5.0% vs 7.4%; adjusted difference, 2.1% [95% CI, −15.5% to 19.8%]), unscheduled readmission (14.3% vs 15.7%; adjusted difference, −1.3% [95% CI, −26.3% to 23.7%]), median length of hospital stay (8 d in both groups; adjusted difference, 2.5 [95% CI, −0.9 to 5.8]), and kidney impairment (1% in both groups).

CONCLUSIONS AND RELEVANCE Among older patients with acute heart failure, use of a guideline-based comprehensive care bundle in the ED compared with usual care did not result in a statistically significant difference in the number of days alive and out of the hospital at 30 days. Further research is needed to identify effective treatments for acute heart failure in older patients.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03683212

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Visual Abstract

Supplemental content

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Acute heart failure is one of the most common syndromes in older patients visiting the emergency department (ED).[1] In an international observational study that included patients 75 years and older from 2010 to 2013, acute heart failure was associated with a 10% mortality risk and up to 30% risk of hospital readmission at 30 days.[2]

International recommendations and clinical guidelines on acute heart failure include the use of moderate doses of diuretics, early initiation of nitrates, and the use of noninvasive ventilation when indicated, along with the early detection and management of precipitating factors, such as acute coronary syndrome, infection, or atrial fibrillation.[3-5] However, these recommendations are based on low levels of evidence. The cornerstone trials on small samples of patients with acute heart failure reported a clinical benefit with early high-dose intravenous nitrates.[6,7] Subsequent large-scale trials testing novel agents with vasodilator properties failed to confirm improved outcomes, possibly because of effects besides vasodilation that might affect mortality risk.[8,9] As a potential consequence, previous reports confirmed low adherence to these recommendations, leading to underuse of nitrates in the ED.[10,11]

The failure of recent acute heart failure studies to report clinical benefits with specific treatments may be attributable to both the delay from presentation to treatment, because recent studies suggest that an early therapy is associated with better prognosis, and the lack of management of precipitating factors, because acute heart failure prognosis has been reported to be associated with the underlying precipitant of worsening heart failure.[12,13] Whether early ED management of congestion and precipitating factors improves outcomes is unknown.

The aim of this trial was to test the efficacy on clinical outcomes of an early, comprehensive, and guideline-recommended care bundle on older patients with acute heart failure in the ED.[14]

Key Points

Question Does an intervention aimed at improving guideline adherence for the management of acute heart failure, including intensive intravenous nitrate therapy and management of precipitating factors, improve hospital discharge and survival at 30 days?

Findings In this stepped-wedge cluster randomized trial that included 503 patients 75 years and older who presented to the emergency department with acute heart failure, implementation of an early and comprehensive care bundle compared with usual care improved guideline adherence, but had no significant effect on number of days alive and out of hospital at 30 days (median of 19 d in both groups).

Meanings This emergency department care bundle did not improve 30-day outcomes among older patients with acute heart failure.

Methods

Study Design

The protocol and statistical analysis plan of the ELISABETH trial are available in Supplement 1 and have been previously published in detail.[14] This was an unblinded, superiority, stepped-wedge, cluster randomized clinical trial in France aimed at testing the effect of an early comprehensive care bundle for acute heart failure on older patients in the ED. Fifteen EDs in France participated in the study. The trial recruited from December 2018 to September 2019, and follow-up ended in October 2019. The study was approved by an institutional review board (Comité de Protection des Personnes SOOM 2, Toulouse academic hospital, France). Written informed consent was sought for all patients before inclusion. If the patient lacked capacity to give consent, the emergency physician sought consent from a relative of the patient. If no such relative was available, research staff were able to proceed to an emergency inclusion. For the latter, as soon as the patient's clinical condition allowed it, a clinical research technician or a physician informed them about the trial and sought written informed consent. The reporting of this trial followed the Consolidated Standards of Reporting Trials (CONSORT) statement extended to stepped-wedge cluster randomized trials.[15,16]

Patients

Consecutive patients 75 years and older with a clinical diagnosis of acute heart failure in the ED were eligible for inclusion in the trial. Acute heart failure diagnosis was made on the basis of having acute or worsening dyspnea and/or orthopnea and at least 1 of the following: bilateral pulmonary rales or peripheral edema, signs of pulmonary congestion on chest radiography or cardiac echocardiography, or elevation in level of natriuretic peptides (brain natriuretic peptide or N-terminal pro-brain natriuretic peptide). As a pragmatic study, whether the diagnosis of acute heart failure was confirmed was left to the discretion of the physician, and echocardiography was not mandatory.

Patients were not included if they presented with another obvious cause of acute illness (eg, ST-elevation myocardial infarction, severe sepsis), systolic blood pressure less than 100 mm Hg, any contraindication for nitrate therapy (severe mitral or aortic stenosis or severe aortic regurgitation), or a known chronic kidney impairment that required dialysis. Because this trial focused on early management of acute heart failure, patients in whom the time from ED presentation to inclusion was more than 6 hours were also excluded. Patients with no Social Security or who were incarcerated or under guardianship were also excluded.

All patients were followed up at 30 days via hospital visit or phone interview if already discharged. They were instructed to return to the same ED or hospital in the event of recurrent or worsening symptoms. A local clinical research assistant checked for return visits to the ED or admission to the hospital during the follow-up period. The phone interview was performed using a structured questionnaire that recorded length of initial hospital stay, any return visit to the ED, or admission to the hospital. When patients could not be contacted by phone, the patient's general practitioner was contacted. If it was not possible to contact the patient or their

physician, death records were sought from the patient's birth town administrative record.

Randomization

After an initial control period (first step) of 4 weeks in all centers, one of the EDs switched to the "intervention period" every 2 weeks. The order in which they switched was randomized. The first 2 weeks of the intervention period in each center was also a training period, in which a clinical research technician presented and detailed the care bundle and assisted emergency physicians in implementing it. After 32 weeks, all EDs were in the "intervention period" for the 8 remaining weeks of inclusion (eFigure 1 in Supplement 2). Randomization of the order of the switch was performed by an independent statistician. At study commencement, EDs were classified on size based on their annual census. Randomization was stratified on cluster size (small, medium, large). Each set of 3 consecutive time periods would contain 1 small, 1 medium, and 1 large site in random order.

Intervention

This study had an unblinded design, which was chosen because the intervention could not be performed in a blinded fashion for either physicians or patients. In participating EDs and in most French EDs, patients are first seen by a triage nurse then seen by a senior emergency physician, with or without the help of a trainee. Only senior emergency physicians could include patients, and consequently the entirety of the ED medical management was completed by a senior emergency physician. In France, regular emergency medical services (EMS) cannot administer treatments, therefore no patients conveyed by regular EMS received any treatment before inclusion in the ED. However, some patients may have been transported by a physician-staffed EMS (service mobile d'urgence-réanimation), where treatment could have been given. These patients are usually directly admitted to an intensive care unit. If that was not the case, patients in whom treatment was already started before inclusion were excluded.

The intervention of this trial consisted of a guideline-recommended care bundle for the early management of acute heart failure in the ED. In the control period, patient care was left to the discretion of the treating emergency physician (usual care). At the beginning of the trial, the recommendations for acute heart failure management were described to all emergency physicians, including moderate-dose diuretics, high-dose intravenous nitrates, search for and early management of the most frequent precipitating factors, and noninvasive ventilation when indicated.

In the intervention period, after a patient's inclusion, emergency physicians were instructed to follow the early care bundle for acute heart failure, with the help of a handover checklist. This care bundle mandated treatment initiation within 1 hour and completion within 4 hours of early management of pulmonary edema with 40 mg (if not currently receiving diuretics) or a daily dose (if already receiving oral diuretics) of intravenous furosemide or intravenous nitrates in titration (given in 3-mg boluses every 5 minutes for 1 hour, titrated until the patient reached a systolic blood pressure above 100 mm Hg) and detection and management of precipitating factors (specifically acute coronary syndrome, rapid atrial fibrillation, and suspected infection). Suspicion of cardiac injury (based on troponin level measurement, echocardiography, and electrocardiogram analysis) required introduction of antiplatelet therapy and referral to cardiologic intensive care unit for potential admission and coronary angiogram if indicated. Suspicion of respiratory tract infection (based on chest radiograph findings, C-reactive protein, procalcitonin, and leukocytes level) required early introduction of antibiotics. Atrial fibrillation with a heart rate above 100/min required introduction of antiarythmic therapy (amiodarone, digoxin, or β-blockers as indicated). Noninvasive ventilation was administered in the event of respiratory distress or hypercarbia with pH less than 7.35.

All treatments were to be initiated in the ED within the first hour of medical management for at least 4 hours. Their discontinuation was left to the discretion of the admitting physician.

Outcomes

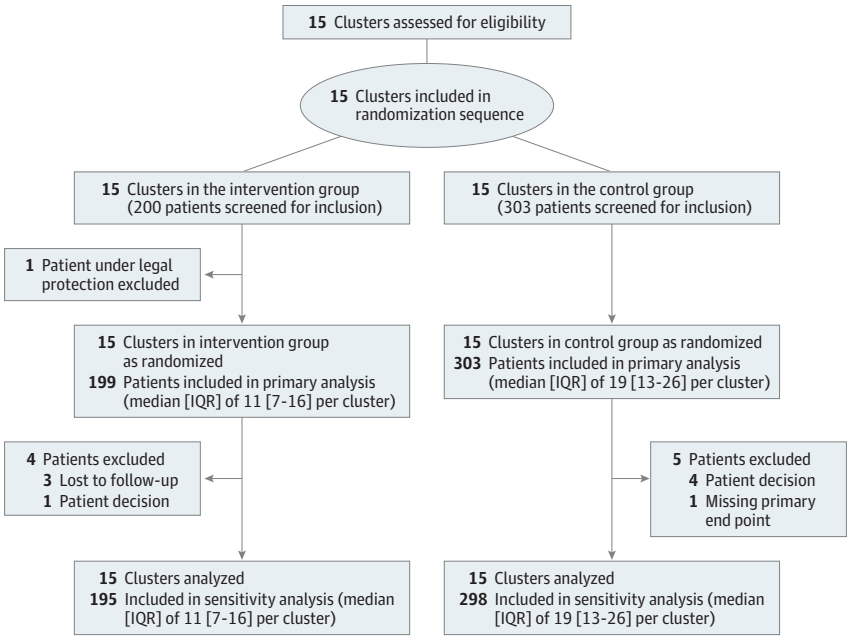
The primary objective of the trial was to test the effect of an early comprehensive guideline-recommended care bundle on morbidity and mortality at 30 days in older patients. The primary end point was the number of days alive and out of hospital during the 30-day period after the ED visit. The choice of this end point allowed for capturing the burden of acute heart failure in terms of mortality, hospital length of stay, and early readmission to the hospital, as recommended by the European Society of Cardiology consensus paper.[17] Patients who died before day 30 were counted as having zero days alive and out of hospital. A return visit to the ED was considered as 1 day in the hospital. Details on the calculation of this end point were previously detailed.[14]

The secondary end points included 30-day all-cause mortality, 30-day cardiovascular mortality, hospital readmission within 30 days, length of in-hospital stay truncated at 30 days, and changes of more than 2-fold in creatinine level from inclusion to day 30 or to discharge (whichever came first). Creatinine was measured at day zero in the ED and at discharge or day 30.

Power Analysis

The full statistical plan and sample size calculation are available in Supplement 1. Sample size was calculated under the superiority hypothesis. Based on previous cohort analysis, the mean (SD) number of days alive and out of the hospital at 30 days was estimated at 14 (9).[10,12,18] To be clinically relevant and consistent with previous literature, it was estimated that the intervention should improve this end point by 20% (ie, ≥3 days).[8,9] For 80% power and an α of 5%, 283 patients needed to be included. Adding the cluster effect for this stepped-wedge design and assuming an intracluster correlation at 0.001, the required sample size was 454 patients. Taking into account a rate of loss to follow-up of 10%, the necessary sample size was 500 patients—2 per cluster for each 2-week period (step). Due to acute heart failure seasonality and fewer cases in the summer period, we had to increase the length of the last inclusion step from 4 weeks to 8 weeks to reach the target.[19,20]

Figure 1. Flow of Patients and Clusters in a Study of the Effect of an Emergency Department (ED) Care Bundle Among Older Patients With Acute Heart Failure



The order in which each of the 15 clusters (EDs) switched to the intervention period was randomized.

Statistical Analysis

The primary analysis included all patients who were randomized (**Figure 1**), with missing outcome data replaced using worst-case imputation (zero days alive and out of the hospital). Baseline characteristics were expressed as numbers and percentages for categorical variables and mean and SD or median and interquartile range (IQR) for continuous variables, depending on their distribution. Unadjusted differences and 95% CIs were calculated using the Wald method with continuity correction for binary variables and using the Brookmeyer and Crowley method for continuous variables. Adjusted differences were calculated using a generalized linear regression mixed model with Bernoulli (binary) distribution and an identity link function with intervention, time period, and cluster size (categorical) as fixed effects and cluster as a random effect for binary variables and using a quantile regression model for continuous variables.[21] The 2-week training period for each site was analyzed as part of the intervention period. Primary and secondary outcomes were analyzed in all randomized patients with a primary outcome available. The number of days alive and out of hospital was analyzed using a generalized linear regression mixed model with negative binomial distribution with intervention, time period, and cluster size as fixed effects and cluster as a random effect.[22] A sensitivity analysis was performed on all patients who completed the trial. All-cause mortality at 30 days, cardiovascular mortality at 30 days, and hospital readmission were compared between groups by using generalized linear regression mixed model with Poisson distribution. The logarithm of the number of patients was included as an offset term in the model. In surviving patients, the hospital length of stay in days was compared between the 2 groups by using a generalized linear regression mixed model with negative binomial distribution. For secondary outcomes, fixed and random effects were defined as previously described. For nonhospitalized patients, length of hospital stay was counted as zero days. The percentage of patients with a change of more than 2-fold in creatinine between inclusion and 30 days were not analyzed because of the presence of a small number of cases and no or negligible differences between the 2 groups.

Because of the potential for type I error due to multiple comparisons, the findings of analyses of secondary end points should be interpreted as exploratory. The original analysis plan was intended to study different extensions of the models as sensitivity analyses, including a time × cluster interaction as a fixed effect and as a random effect. However, due to the structure of the data (low proportion of events by cluster by period), these sensitivity analyses could not be performed. All superiority tests were 2-sided and *P* values <.05 were considered significant. SAS V.9.4 software (SAS Institute Inc) and Stata version 16 (Stata Corp), were used for statistical analyses.

Results

Study Population

Fifteen EDs participated in the trial and 503 patients were recruited. Among them, 1 patient was under guardianship and was excluded, 5 patients withdrew their consent, 3 were lost to follow-up, and 1 was missing the primary end point. Therefore, 502 patients were included in the primary analysis: 303 in the control group and 199 in the intervention group. A total of 493 patients completed the trial and were included in the sensitivity analysis (Figure 1; eFigure 1 and

Table 1. Baseline Characteristics of Participants in a Study of the Effect of an Emergency Department Care Bundle Among Older Patients With Acute Heart Failure

Variable	Intervention (n = 199)	Usual care (n = 303)	Normal values
Age, median (IQR), y	87.0 (81.0-90.0)	87.0 (81.0-91.0)	
Sex, No. (%)			
Women	112 (56.3)	186 (61.4)	
Men	87 (43.7)	117 (38.6)	
Comorbidities, No. (%)[a]			
Chronic pulmonary disease	39 (19.6)	46 (15.2)	
Chronic heart failure	111 (55.8)	158 (52.3) (n = 302)	
Chronic kidney disease	49 (24.6)	73 (24.1) (n = 302)	
Diabetes	54 (27.1)	92 (30.4) (n = 302)	
Myocardial infarction	80 (40.2)	91 (30.0) (n = 302)	
Vital signs at randomization, mean (SD)			
Heart rate/min	86.3 (23.5)	86.6 (23.8)	
Oxygen saturation, %	90.6 (6.7) (n = 185)	91.1 (6.9) (n = 286)	
Respiratory rate/min	26.2 (6.7) (n = 187)	25.9 (7.3) (n = 273)	
Systolic blood pressure, mm Hg	155.3 (28.8) (n = 187)	148.8 (27.9) (n = 273)	
Temperature, °C	36.8 (0.6) (n = 198)	36.7 (0.7) (n = 273)	
Medication at randomization, No. (%)			
ACE inhibitor	58 (29.1)	84 (27.7)	
ARB	41 (20.6)	79 (26.1)	
Antibiotic	18 (9.0)	25 (8.3)	
Anticoagulant	96 (48.2)	147 (48.5)	
Antiplatelet	75 (37.7)	116 (38.3)	
β-Blocker	123 (61.8)	165 (54.5)	
Diuretic	129 (64.8)	222 (73.3)	
Nitrates	13 (6.5)	17 (5.6)	
Laboratory results, median (IQR)[b]			
BNP, ng/L	591.0 (251.5-977.0) (n = 81)	620.0 (319.6-1220.0) (n = 151)	<450
Creatinine, mg/L	11.2 (8.7-14.7) (n = 81)	11.5 (8.9-16.0) (n = 301)	6-12
C-reactive protein, mg/L	13.7 (5.0-47.1) (n = 155)	13.4 (5.0-43.7) (n = 236)	<5
Hemoglobin, mean (SD), g/dL	12.4 (2.0) (n = 155)	12.1 (1.8) (n = 300)	12-17
Leukocytes, G/L	9.0 (6.9-11.9) (n = 155)	8.3 (6.6-10.8) (n = 301)	4-10
NT pro-BNP, ng/L	4.2×10^3 (1.8×10^3-7.9×10^3) (n = 116)	5.0×10^3 (2.3×10^3-9.3×10^3) (n = 144)	2×10^3
Procalcitonin, µg/L	0.1 (0.1-0.2) (n = 54)	0.1 (0.1-0.3) (n = 45)	<0.1
Troponin, µg/L	0.0 (0.0-0.1) (n = 185)	0.0 (0.0-0.1) (n = 243)	<14
pH, mean (SD)	7.4 (0.1) (n = 176)	7.4 (0.1) (n = 210)	7.35-7.45
$Paco_2$, mm Hg	40.0 (33.5-47.0) (n = 176)	39.0 (34.0-45.0) (n = 210)	35-45
Pao_2, mm Hg	74.0 (65.0-91.5) (n = 176)	70.0 (60.0-87.0) (n = 210)	80-100
Bicarbonate, mean (SD), mmol/L	25.8 (5.2) (n = 150)	24.7 (4.4) (n = 221)	22-26

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockade; IQR, interquartile range; NT pro-BNP, N-terminal pro-brain natriuretic peptide.

[a] Comorbidities were recorded by the emergency physician during the ED visit.

[b] Laboratory results were obtained as part of ED care.

eTable 1 in Supplement 2). The mean (SD) number of patients recruited was 34 (12) by center and 31 (20) by step. The median (IQR) age of participants was 87 (81-91) years, 298 (59%) were women, and 269 (54%) had known chronic cardiac failure. Patients' baseline characteristics were similar between the 2 groups and are reported in **Table 1**. Pulmonary congestion was similar between intervention and control groups, including mean (SD) oxygen saturation (90.6% [6.7%] vs 91.1% [6.9%]), respiratory rate (26.2 [6.7] per min vs 25.9 [7.3] per min), and systolic blood pressure (155 [29] mm Hg vs 149 [28] mm Hg).

Treatment in the ED

In the intervention group, compared with the control group, a statistically significantly higher percentage of patients were treated with intravenous nitrates (96% vs 25%; adjusted difference, 71% [95% CI, 62% to 80%]), were given a higher median dose of intravenous nitrates (27.0 mg vs 4.0 mg at 4 hours of initial management; adjusted difference, 24 mg [95% CI, 13.5 to 34.1]), and were treated with diuretics (98% vs 90%; adjusted difference, 6.8% [95% CI, 0.5% to 13.0%]) (**Table 2**). A precipitating factor was present in 45% of patients, and these factors were treated in significantly

Table 2. Treatment of Participants in a Study of the Effect of an Emergency Department (ED) Care Bundle Among Older Patients With Acute Heart Failure

Variable	Intervention (n = 199)	Usual care (n = 303)	Adjusted difference (95% CI), %[a]
Treatment in the emergency department, No. (%)			
Furosemide[b]	195 (98.0)	274 (90.4)	6.8 (0.5 to 13.0)
Dose, median (IQR), mg	40.0 (40.0 to 80.0) (n = 195)	60.0 (40.0 to 80.0) (n = 273)	-13.1 mg (-25.4 to -0.9)
IV nitrates[c]	191 (96.0)	74 (24.5) (n = 302)	71.0 (61.6 to 80.3)
Cumulative dosing at hour 1, median (IQR), mg	18.0 (9.0-30.0) (n = 187)	3.0 (2.0-4.0) (n = 54)	14.9 mg (8.9 to 20.8)
Cumulative dosing at hour 4, median (IQR), mg	27.0 (9.0-53.5) (n = 188)	4.0 (2.0-6.0) (n = 73)	23.8 mg (13.5 to 34.1)
Antibiotics	39 (19.6)	38 (12.5)	10.8 (1.6 to 19.9)
Antiplatelet agents	15 (7.5)	23 (7.6)	0.2 (-7.9 to 8.4)
Dual antiplatelet agents[d]	4 (2.0)	3 (1.0)	
Antiarrhythmics	22 (11.1)	23 (7.6)	2.6 (-5.7 to 10.8)
Noninvasive ventilation	29 (14.6)	29 (9.6)	6.0 (-4.6 to 16.6)
ED discharge disposition, No. (%)			
Home	3 (1.5)	15 (5.0)	-3.1 (-9.4 to 3.2)
ED observation unit	96 (48.2)	137 (45.2)	-2.9 (-16.3 to 10.6)
Hospital ward	60 (30.2)	111 (36.6)	3.2 (-9.7 to 16.2)
Intensive care unit[e]	40 (20.1)	38 (12.5)	9.2 (-1.6 to 20.0)

Abbreviations: IQR, interquartile range; IV, intravenous.

[a] Differences were adjusted for intervention, time period, and cluster size (categorical) as fixed effects and cluster as a random effect.

[b] Furosemide was the only intravenous diuretic used in participating centers.

[c] Cumulative dose of nitrates over the period that includes boluses (first hour) and infusion (between first hour and fourth hour) among patients who were treated with nitrates.

[d] Given the small numbers, no analysis was performed for the dual antiplatelet agents variable.

[e] Including cardiac intensive care unit.

Table 3. Study End Points in the Primary Analysis in a Study of the Effect of an Emergency Department Care Bundle Among Older Patients With Acute Heart Failure

End point	Intervention (n = 199)	Usual care (n = 303)	Difference (95% CI)		Adjusted ratio (95% CI)	Adjusted risk ratio (95% CI)
			Unadjusted	Adjusted[a]		
Primary, median (IQR)						
Time alive and out of hospital at 30 d, d	19.0 (0.0 to 24.0)	19.0 (0.0 to 24.0)	0.0 (-4.0 to 4.0)	-1.9 (-6.6 to 2.8)	0.88 (0.64 to 1.21)	
Secondary, No. (%)						
30-day all-cause mortality	16 (8.0)	29 (9.7) (n = 299)	-1.7% (-7.1% to 3.8%)	4.1% (-17.2% to 25.3%)		1.17 (0.53 to 2.57)
30-day cardiovascular mortality	10 (5.0)	22 (7.4) (n = 299)	-2.3% (-7.0% to 2.3%)	2.1% (-15.5% to 19.8%)		1.12 (0.45 to 2.82)
30-day hospital readmission	22 (14.3) (n = 154)	37 (15.7) (n = 235)	-1.5% (-9.2% to 6.3%)	-1.3% (-26.3% to 23.7%)		0.96 (0.48 to 1.95)
Length of hospital stay, median (IQR), d	8.0 (5.0 to 21.0) (n = 182)	8.0 (5 to 16.0) (n = 269)	0.0 (-1.8 to 1.8)	2.5 (-0.9 to 5.8)	1.22 (0.94 to 1.59)	
2-fold rise in creatinine level[b]	2 (1.0) (n = 192)	4 (1.4) (n = 287)				

Abbreviation: IQR, interquartile range.

[a] Differences, ratios, and risk ratios were adjusted for time period and cluster size (categorical) as fixed effects and cluster as a random effect. The difference is expressed as intervention minus control and the ratio as intervention/control.

[b] Given the small numbers, no analysis was performed for the 2-fold rise in creatinine level end point.

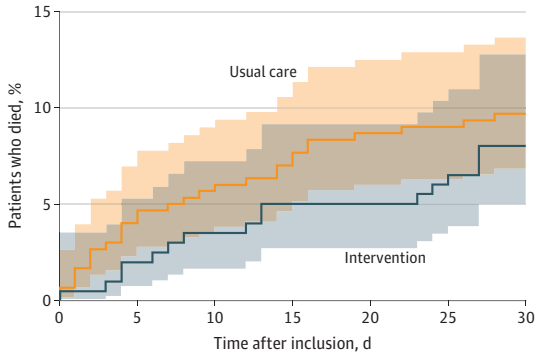
more patients in the ED in the intervention group than in the control group (58.8% vs 31.9%; adjusted difference, 31.1% [95% CI, 14.3% to 47.9%]) (eTable 2 in Supplement 2).

Study End Points

Among the 502 patients included in the primary analysis, the median (IQR) number of days alive and out of hospital at 30 days was 19 (0-24) in the intervention group and 19 (0-24) in the control group (adjusted difference, −1.9 [95% CI, −6.6 to 2.8]); adjusted ratio, 0.88 [95% CI, 0.64-1.21]; P = .44) (**Table 3**). The intraclass correlation coefficient was 0.057. A sensitivity analysis of patients that completed the trial exhibited similar results (eTable 3 and eTable 4 in Supplement 2). There was no statistically significant difference in the intervention vs control groups in all-cause mortality at day 30 (8.0% vs 9.7%; adjusted difference, 4.1% [95% CI, −17.2% to 25.3%]; adjusted risk ratio, 1.17 [95% CI, 0.53-2.57]; reversal in direction due to the adjustment for covariates; **Figure 2**), cardiovascular mortality at day 30 (5.0% vs 7.4%; adjusted difference, −1.3% [95% CI, −15.5% to 19.8%]), median (IQR) length of initial hospital stay (8 [5-21] d vs 8 [5-16] d; adjusted difference, 2.5 [95% CI, −0.9 to 5.8]; adjusted ratio, 1.22 [95% CI, 0.94-1.59]), unscheduled readmission (14.3% vs 15.7%; adjusted difference, −1.3% [95% CI, −26.3% to 23.7%]; adjusted risk ratio, 0.96 [95% CI, 0.48-1.95]), or acute kidney injury at 30 days (1.0% vs 1.4%) (Table 3).

There was a similar rate of nitrate use in the control group (eFigure 2 in Supplement 2) and management of precipitating

Figure 2. Cumulative Incidence of All-Cause Mortality in a Study of the Effect of an Emergency Department Care Bundle Among Older Patients With Acute Heart Failure



No. of patients at risk

Intervention	199	195	192	189	189	187	183
Usual care	299	287	282	278	273	272	270

Shading represents 95% CIs. All patients were observed until date of death or 30 days. Data were missing for vital status in 4 patients.

factors in the 5 centers randomized to later crossover than those in the usual care period (17% vs 15% respectively).

Discussion

In this stepped-wedge cluster randomized trial that included 502 older adults with acute heart failure, an early and comprehensive guideline-recommended care bundle resulted in a significantly higher use of intravenous nitrates and more frequent management of precipitating factors, but did not significantly improve the number of days alive and out of hospital at 30 days nor any other early outcome.

For the past few decades, intravenous nitrates have been recommended for the early treatment of patients with acute heart failure.[6,7] However, the failure of further trials to confirm any clinical benefit of intravenous nitrates in patients with acute heart failure resulted in subsequent moderate level of evidence for this recommendation, hence the reported low adherence in older patients.[11] Several studies suggested that a more comprehensive and early treatment of patients with acute heart failure in the ED could improve prognosis, because prognosis could be dependent on underlying conditions and precipitating factors.[18,23] The implementation of the tested care bundle resulted in a significantly higher adherence to guideline-recommended therapy both in the management of acute pulmonary congestion and of the precipitating factors. The control group in this study received similar treatments to those reported in a 2019 multicenter observational study.[10] In that study, only 34% of 73 patients with acute heart failure received intravenous nitrates and 20% were treated for precipitating factors in the ED. In France, intravenous nitrates are the only nitrates used for patients with acute heart failure, and no other nitrates were used in this study (or in France in general).[24] More patients in the intervention group had to be admitted to an intensive care unit. Whether this was the result of adverse effects of the intervention or of a more proactive approach in this group is unknown.

In the present trial, it is possible that there could have been a Hawthorne effect, in that patients in the control group would receive similar treatments to patients in the intervention group because physicians would be aware that the patients were in the trial and that their treatment decisions were being recorded. This was not the case possibly due to the stepped-wedge cluster-randomization methodology.[10] There was also a low risk of contamination in sites randomized to later crossover, with a similar rate of nitrate use and management of precipitating factors. Furthermore, these results showed an intraclass correlation coefficient estimation of 0.05, higher than the correlation anticipated, which reduced statistical power. However, it seems unlikely that this would have changed the results of the primary outcome.

Regarding management of acute pulmonary congestion, these results are consistent with those from the GALACTIC trial, in which early and sustained vasodilatation therapy was not significantly associated with improved outcomes. The present trial also tested a comprehensive approach with earlier implementation of the intervention: patients were randomized within 6 hours of ED presentation and the care bundle was initiated during the first hour of medical management. With a significantly higher rate of management of precipitating factors, this trial is complementary to the GALACTIC trial and others that tested intervention during the first days of admission for acute heart failure.[8]

This trial focused on older patients, and it is likely that in these patients, who often present with comorbidities, the prognosis is not driven by pulmonary edema but rather by precipitating factors and underlying conditions.[8,9,12,25] Given the study findings, a more specific care pathway for older adults may need to be considered.

Limitations

This study has several limitations. First, only patients 75 years and older were included, because this trial focused on a more homogeneous phenotype of patients.[26] However, this population may still include patients with preserved and reduced systolic cardiac function. This parameter was not assessed in included patients, and it is possible that the intervention may cause different outcomes in different phenotypes of patients. The present trial included mostly "wet and warm" patients, the most common phenotype of acute heart failure.[23] Second, a selection bias may also have occurred because some patients may have refused to be included in the study and some eligible patients may have not been screened by the emergency physicians. Because this number was not recorded, the extent of this bias cannot be ascertained.

Third, the intervention included high-intensity intravenous nitrates, with a median dose of 27 mg of isosorbide dinitrate in the intervention group vs 4 mg in the control group in the first 4 hours. The optimal dose may lie somewhere between those 2 numbers. Fourth, the rate of hypotension that may have been caused by this treatment was not recorded, because the objective was to evaluate the overall effect of the bundle. However, this risk is limited because the intervention included

close monitoring of blood pressure and withholding of nitrate therapy if the systolic blood pressure dropped below 100 mm Hg. Fifth, the potential use in the ED of oral or topical nitrates was not recorded in this study. However, in France, only intravenous nitrates are used for acute heart failure, and the percentage of patients previously treated with topical nitrates for chronic heart failure was similar in both groups (6%). Sixth, a short-term prognosis end point (30 days) was chosen to capture the overall effect of the tested care bundle, and this end point may have been influenced by post-ED therapy in the ward that is not standardized. Seventh, the rate of management of acute coronary syndrome was low in both groups, suggesting a suboptimal management of this precipitating factor, which may have limited the benefit of the intervention.

Conclusions

Among older patients with acute heart failure, use of a guideline-based comprehensive care bundle in the ED compared with usual care did not result in a statistically significant difference in the number of days alive and out of the hospital at 30 days. Further research is needed to identify effective treatments for acute heart failure in older patients.

ARTICLE INFORMATION

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