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Review Article

Effectiveness of interventions to improve cardiovascular healthcare in rural areas: a systematic literature review of clinical trials

Isabel Ruiz-Pérez[a,b,c,*], Ángel Bastos[a], Maria Jesús Serrano-Ripoll[d,e,f], Ignacio Ricci-Cabello[b,d,e]

[a] Andalusian School of Public Health, Cuesta del Observatorio, 4, 18011 Granada, Spain
[b] Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Spain
[c] Ibs. Instituto de Investigación Biosanitaria de Granada, Spain
[d] Balearic Islands Health Research Institute (IdISBa), Spain
[e] Atención Primaria Mallorca, IB-Salut, Spain
[f] Universitat de les Illes Balears (UIB), Departament de Psicologia, Spain

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ABSTRACT

The objective of this systematic literature review is to examine the impact of interventions to improve cardiovascular disease healthcare provided to people living in rural areas. Systematic electronic searches were conducted in Medline, CINAHL, Embase, Scopus, and Web of Knowledge in July 2018. We included clinical trials assessing the effectiveness of interventions to improve cardiovascular disease healthcare in rural areas. Study eligibility assessment, data extraction, and critical appraisal were undertaken by two reviewers independently. We identified 18 trials (18 interventions). They targeted myocardial infarction (five interventions), stroke (eight), and heart failure (five). All the interventions for myocardial infarction were based on organizational changes (e.g. implementation of mobile coronary units). They consistently reduced time to treatment and decreased mortality. All the interventions for heart failure were based on the provision of patient education. They consistently improved patient knowledge and self-care behaviour, but mortality reductions were reported in only some of the trials. Among the interventions for stroke, those based on the implementation of telemedicine (telestroke systems or tele-consultations) improved monitoring of stroke survivors; those based on new or enhanced rehabilitation services did not consistently improve mortality or physical function; whereas educational interventions effectively improved patient knowledge and behavioural outcomes. In conclusion, a number of different strategies (based on enhancing structures and providing patient education) have been proposed to improve cardiovascular disease healthcare in rural areas. Although available evidence show that these interventions can improve healthcare processes, their impact on mortality and other important health outcomes still remains to be established.

1. Introduction

Cardiovascular diseases (CVDs) are the first cause of death globally. It has been estimated that 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million to stroke (Benjamin et al., 2017; Katan and Luft, 2018). Important variations across countries have been observed with regard to CVD risk factors, disease incidence, and mortality (Christensen et al., 2009; Ali et al., 2009; Heuschmann et al., 2009; Timmis et al., 2018; Metra et al., 2016). Although age-adjusted cardiovascular death rates have declined in several developed countries in past decades, rates of CVD have risen greatly in low-income and middle-income countries, with about 80% of the burden now occurring in these countries (Moran et al., 2014; Yusuf et al., 2004a; Mendis et al., 2011; Feigin et al., 2009). Important variations in the burden of CVDs have also been observed within countries. For example, within countries variations in stroke mortality have been identified in countries in Europe (Powles et al., 2002; Bottle et al., 2018), North America (O'Neal et al., 2017), Australia (Jacobs et al., 2018), Asia (Jacobs et al., 2018; Chen et al., 2015; Nishi et al., 2007), or Africa (Powles et al., 2002; Walker et al., 2010; Walker et al., 2000). Similar within countries variations have also been observed for ischemic heart disease (Jiang et al., 2012; Levin and Leyland, 2006; Taylor et al., 1999; Zaman et al., 2007) and heart failure (Teng et al., 2014; Clark et al., 2007; Gamble et al., 2011).

Health inequalities have been defined as differences in health status

* Corresponding author at: Cuesta del Observatorio, 4, 18011 Granada, Spain.
E-mail address: isabel.ruiz.easp@juntadeandalucia.es (I. Ruiz-Pérez).

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or in the distribution of health determinants between different population groups (Kawachi et al., 2002). Gender, socioeconomic or ethnicity related health inequalities have been frequently observed and are well documented in the literature (Camargo, 2011). Geographic (urban-rural) disparities in health have also been studied (Smith et al., 2008; Eberhardt and Pamuk, 2004; Ricci-Cabello et al., 2013). Initially, it was generally perceived that inequalities between rural and urban areas were only restricted to a limited number of conditions or health problems more prevalent in the rural setting, such as occupational accidents or paediatric traumas (Leonhard et al., 2015). However, in the 80's an increased awareness rose about the high prevalence of CVDs, which, until then, had been considered as 'urban' conditions (Lewis et al., 2000). Nowadays is widely accepted that the prevalence of most chronic conditions is higher in rural than in urban areas, and that distance to town is directly associated with a higher prevalence (Corburn and Cohen, 2012; Khanal et al., 2017; Kyte and Wells, 2010).

These geographic inequalities can be partially explained by a higher prevalence in rural areas of important CVD risk factors (abnormal blood lipids, smoking, diabetes, and high blood pressure) (O'Donnell et al., 2010; Yusuf et al., 2004b) which occurs as a result of the higher socioeconomic disadvantage, ethnicity, higher levels of personal risk and more hazardous environmental, occupational and transportation conditions experienced in rural areas (Smith et al., 2008). They can also be explained by the existence of rural inequalities in healthcare provision, which have been described for a number of CVDs, including ischemic heart disease (Terkelsen et al., 2008; Alston et al., 2017; Alston et al., 2016; O'Connor and Wellenius, 2012; Schröder et al., 2016), heart failure (HF) (Havranek et al., 2004; Jin et al., 2003), or stroke (Mullen et al., 2014; Koifman et al., 2016). Geographic differences can determine important limitations in healthcare response to myocardial infarction, such as, for instance, those related to a reduced availability of centres with 24 h angioplasty and delays in receiving assistance due to long distances to reach the appropriate healthcare facilities (Seabury et al., 2017). In relation to stroke, rural areas are less likely than urban areas to have specialized units for patients with this condition (only 1% of individuals in rural areas live within a 60-minute ground ambulance ride of a Primary Stroke Center (Mullen et al., 2014)), have less 24 h brain imaging services, and less access to specialized consultations and to rehabilitation units (Koifman et al., 2016). Although medical thrombolysis is generally available for administration in all hospitals, availability of percutaneous coronary interventions (PCI) is much more limited (e.g., in Australia < 10% of emergency departments are located in hospitals with cardiac catheterisation facilities, and even fewer in hospitals able to perform immediate PCI) (Nadel et al., 2014). Resources for heart failure patients, including but not only rehabilitation services, are clustered in urban areas, with more limited availability for those patients living in rural areas (Jin et al., 2003) - a situation that leads to important inequalities in health outcomes for this group of patients (Gamble et al., 2011).

Therefore, and not surprisingly, substantial efforts have been made during the last two decades to develop and implement interventions to improve CVD healthcare provision in rural areas (Carey et al., 2018; Melvin et al., 2013). However, there is a knowledge gap in relation to the potential efficacy of such interventions in improving processes and outcomes of care, with no previous systematic review assessing the available evidence base in this area.

The aim of this systematic literature review of clinical trials was to examine the impact on processes of care and health outcomes of interventions to improve CVD health care in people living in rural areas, compared with usual care.

2. Methods

The present study is part of a broader program of systematic reviews of interventions to reduce social inequalities in healthcare. The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. Information sources and search strategy

An information specialist designed and implemented a search strategy in Medline (Ovid), CINAHL, Embase, Scopus, and Web of Knowledge. The strategy (available in Supplementary Appendix 1), which combined MeSH terms and keywords, was initially designed for Medline (Ovid) and subsequently adapted to the rest of bibliographic databases.

In addition, a number of searches using free text terms were conducted in Cochrane Library, CRD Databases, metaRegister of Controlled Trials, EURONHEED, CEA Registry, and European Action Program for Health Inequities. Various gray literature sources, as well as reviews in similar topics, were also consulted. The searches were executed in December 2015 and subsequently updated on 31 July 2018. No language or date restrictions were applied. A bibliographical database was created using EndNote X7, which was used to store and manage the references.

2.2. Eligibility assessment

We included studies examining the effectiveness of interventions aimed at decreasing inequalities in the provision of healthcare to patients with CVDs living in rural areas.

We included clinical trials (randomized controlled trials, cluster randomized controlled trials, non-randomized controlled trials, and non-controlled before after studies). We excluded studies not including a quantitative assessment of the impact of the intervention, and pilot studies if data from the full trial was available. In order to reduce the heterogeneity among interventions in countries with different levels of resources, we also excluded studies conducted in countries not members of the OECD at the time of the study identification stage. To maximize the relevance and applicability of this review to the different health systems in different countries, we broadly defined rural areas as those geographic areas which are located outside cities and towns.

The titles and abstracts of the documents retrieved by the search were independently screened by two reviewers for ascertaining eligibility. Those fulfilling the inclusion criteria were selected for full text assessment, after which a new independent assessment was performed, in order to select the studies to include in this review. Disagreements were solved through discussion with a third reviewer.

2.3. Data extraction and quality assessment

We designed and used structured forms to extract all the relevant information from the selected publications, including information about the methods and population characteristics, interventions, comparators, outcomes, timing, settings, and study design.

The methodological quality of the studies was assessed using the "Quality Assessment Tool for Quantitative Studies" (Thomas, 2003), and was classified in three categories (strong, moderate or weak) based on six domains: selection bias, study design, confounders, blinding, data collection, and withdrawals and dropouts. Two independent reviewers extracted the information and conducted the quality assessment. Disagreements were resolved by consensus with a third reviewer.

2.4. Data synthesis and analysis

Given the heterogeneity of the interventions and outcome measures used in the trials identified in this review, it was not possible to conduct a meta-analysis. Instead, a narrative summary of the study characteristics and main findings was conducted. This information was organized and summarized according to the different types of CVDs and of interventions reported in the studies identified.

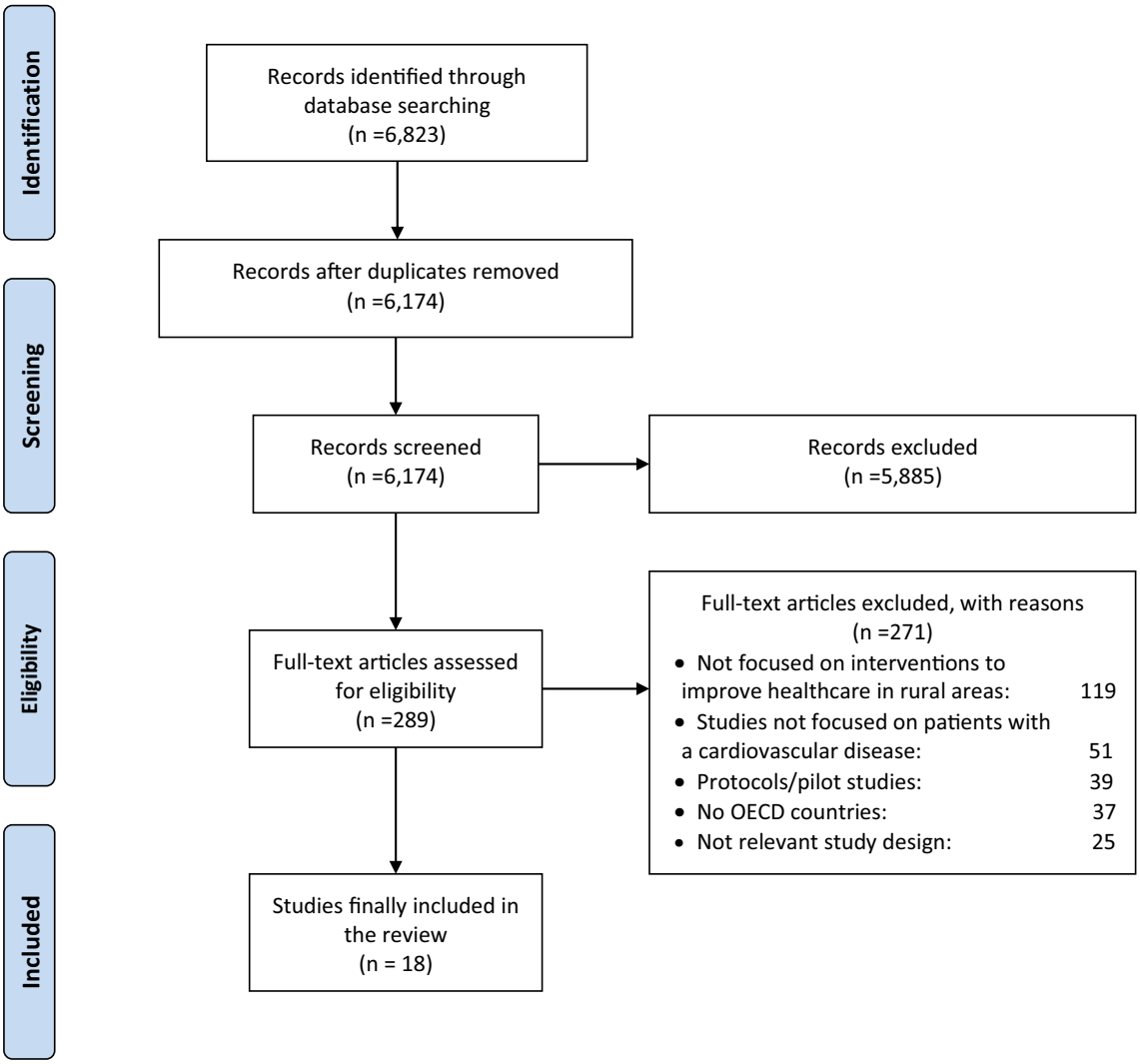

Fig. 1. PRISMA flowchart.

3. Results

3.1. Study identification

The eligibility process of the original studies is summarized in a PRISMA flowchart (Fig. 1). We retrieved a total of 6174 unique citations from database searches, and excluded 5885 based on title and abstract review. We selected for review at the full text level 289 references. Of the 289 full text publications examined, we excluded a total of 271 publications. We finally included in the review a total of 18 trials (Askim et al., 2004; Audebert et al., 2009; Bohmer et al., 2010; Caldwell et al., 2005; Coccolini et al., 1995; Demaerschalk et al., 2010; Dracup et al., 2014; Hebert et al., 2006; Kinsman et al., 2012; Kinugasa et al., 2014; Kitzman et al., 2017; McAleer et al., 1992; O'Callaghan et al., 2012; Park et al., 2017; Roderick et al., 2001; Schweickert et al., 2011; Switzer et al., 2009; Woollard et al., 2005; Young et al., 2016), evaluating 18 different interventions.

3.2. Study characteristics

The characteristics of the included studies are presented in Table 1. Half of the studies (50%) were published from 2010 onwards. Eight were conducted in US, eight in Europe, one in Japan, and one in Australia. The most common study design was randomized controlled trial (56% of the studies), followed by non-randomized controlled trials (28%), and non-controlled before-after studies (17%). The number of study participants ranged from 11 to 3060 (mean = 352), and the study duration ranged from three weeks to 60 months.

In terms of outcomes, two studies (O'Callaghan et al., 2012; Switzer et al., 2009) evaluated the impact of the interventions to improve prevention (e.g. patient knowledge about early detection of stroke), six (Caldwell et al., 2005; Coccolini et al., 1995; Demaerschalk et al., 2010; Kinsman et al., 2012; Switzer et al., 2009; Woollard et al., 2005) evaluated the impact on healthcare processes (diagnosis accuracy, time to treatment, treatment adequacy), and 13 (Askim et al., 2004; Audebert et al., 2009; Bohmer et al., 2010; Caldwell et al., 2005; Coccolini et al., 1995; Demaerschalk et al., 2010; Dracup et al., 2014; Hebert et al., 2006; Kinugasa et al., 2014; Kitzman et al., 2017; McAleer et al., 1992; Roderick et al., 2001; Young et al., 2016) on health outcomes (mortality, hospital readmission, and dependency, among others).

In terms of the risk of bias of the included studies (Fig. 2 and Table 2), six studies presented high methodological quality (Askim et al., 2004; Audebert et al., 2009; Bohmer et al., 2010; Demaerschalk et al., 2010; Dracup et al., 2014; Roderick et al., 2001), six moderate (Caldwell et al., 2005; Coccolini et al., 1995; Hebert et al., 2006; Kinugasa et al., 2014; Switzer et al., 2009; Woollard et al., 2005), and six weak (Kinsman et al., 2012; Kitzman et al., 2017; McAleer et al., 1992; O'Callaghan et al., 2012; Switzer et al., 2009; Young et al., 2016). Most frequent risks of bias were related to inadequate blinding (twelve

Table 1
Study characteristics.

	N 18	%
Publication year		
Prior to 2002	3	17%
2002–2005	3	17%
2006–2009	3	17%
2010–2013	5	28%
2014–July 2018	4	22%
Study design		
Randomized controlled trial	10	56%
Controlled before after study	5	28%
Non-controlled before-after study	3	17%
Number of participants[a]	352	11–3060
Duration (months)[a]	16	0–60
Cardiovascular condition		
Stroke	8	44%
Acute myocardial infarction	5	28%
Heart failure	5	28%
Country		
US	8	44%
UK	3	17%
Norway	2	11%
Japan	1	6%
Australia	1	6%
Italy	1	6%
Germany	1	6%
Ireland	1	6%
Methodological quality		
Strong	6	33%
Medium	6	33%
Weak	6	33%
Setting		
Hospital	10	56%
Medical centre	3	17%
Emergency care	2	11%
Associate centre	1	6%
Mixed	2	11%
Intervention type		
Organizational changes	7	39%
Patient education	5	28%
Multifaceted	6	33%

[a] Mean (range).

studies), selection bias and withdrawals and dropouts (nine studies).

3.3. Characteristics and effectiveness of the interventions

Seven interventions consisted in the implementation of organizational changes aiming at improving healthcare processes in rural areas. They included, among others, setting up mobile coronary care units (McAleer et al., 1992), or implementing new clinical pathways on thrombolytic administration for acute myocardial infarction (Kinsman et al., 2012). Five interventions consisted in the provision of patient education (e.g. to promote adequate self-care in patients with HF (Dracup et al., 2014; Young et al., 2016), or to educate patients at risk of stroke (O'Callaghan et al., 2012)), and six were multifaceted in nature (combining organizational changes with provider or patient education).

Eight intervention targeted healthcare to patients with cerebrovascular diseases (Askim et al., 2004; Audebert et al., 2009; Demaerschalk et al., 2010; Kitzman et al., 2017; O'Callaghan et al., 2012; Roderick et al., 2001; Schweickert et al., 2011; Switzer et al., 2009), five patients with acute myocardial infarction (Bohmer et al., 2010; Coccolini et al., 1995; Kinsman et al., 2012; McAleer et al., 1992; Woollard et al., 2005), and five with HF (Caldwell et al., 2005; Dracup et al., 2014; Hebert et al., 2006; Kinugasa et al., 2014; Young et al., 2016). A summary of the effectiveness of these interventions is provided below and in Table 3.

A. Interventions to improve healthcare provided to patients with myocardial infarction (five trials)

Three trials evaluated interventions to speed-up the provision of treatment for myocardial infarction prior patient arrival to the reference hospital. Two of them (McAleer et al., 1992; Woollard et al., 2005) were based on the provision of medical treatment in mobile coronary care units, whereas the other (Coccolini et al., 1995) examined the impact of a new emergency room in a rural hospital with no coronary care unit. The interventions significantly ($p < 0.05$) reduced median time to treatment (55 min (Woollard et al., 2005) and 75 min (Coccolini et al., 1995)) and mortality rates (30% reduction in 35 days (Coccolini et al., 1995); 13.9% reduction in 1 year (McAleer et al., 1992)).

Another trial (Bohmer et al., 2010) observed that an intervention based on the immediate transfer for percutaneous coronary intervention (PCI) of patients with acute myocardial infarction living in rural areas with > 90-min transfer delays to PCI significantly reduced the composite of death, reinfarction, or stroke at 12 months when compared to usual care (HR: 0.36, 95% CI 0.16 to 0.81). A trial examining the implementation of an acute myocardial infarction clinical pathway and its impact on thrombolytic administration in rural emergency departments (Kinsman et al., 2012) reported no significant ($p > 0.05$) improvements compared to usual care in median time to electrocardiogram, median door-to-needle time, and in the proportion of those eligible receiving a thrombolytic treatment.

B. Interventions to improve healthcare for cerebrovascular diseases (eight trials)

Two trials (O'Callaghan et al., 2012; Schweickert et al., 2011) evaluated educational interventions to increase knowledge of stroke risk factors and promoting early recognition of acute stroke symptoms in elderly patients. One of them (Schweickert et al., 2011) compared face to face vs telematic delivery, observing that both modalities were associated with increased knowledge about stroke, although the telematically delivered was more effective in improving behaviour to decrease vascular risk factors than the face to face modality. Another trial

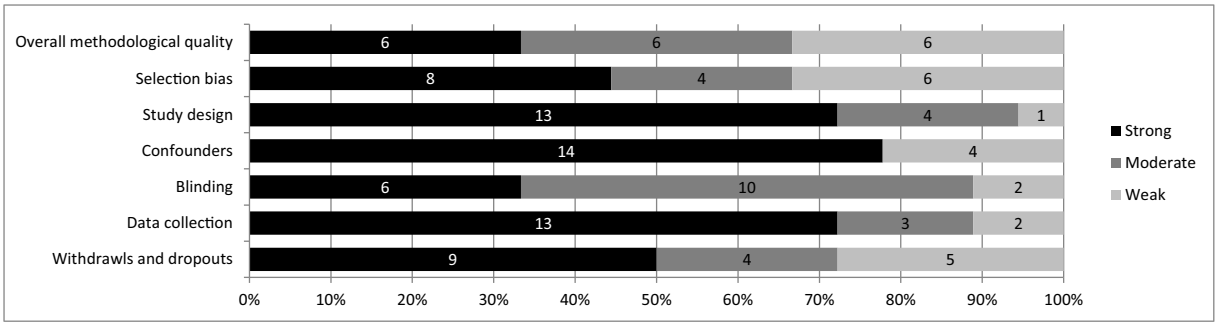

Fig. 2. Risk of bias assessment.

Table 2
Risk of bias of the included studies.

Author (year)	Overall methodological quality	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals and dropouts
Askim et al. (2004)	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Audebert et al. (2009)	Strong	Strong	Strong	Strong	Moderate	Moderate	Strong
Bohmer et al. (2010)	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Caldwell et al. (2005)	Moderate	Weak	Strong	Strong	Moderate	Strong	Moderate
Coccolini et al. (1995)	Moderate	Strong	Weak	Strong	Strong	Strong	Strong
Demaerschalk et al. (2010)	Strong	Moderate	Strong	Strong	Moderate	Strong	Strong
Dracup et al. (2014)/Park et al. (2017)	Strong	Strong	Strong	Strong	Strong	Moderate	Strong
Hebert et al. (2006)	Moderate	Strong	Moderate	Strong	Strong	Strong	Weak
Kinsman et al. (2012)	Weak	Weak	Strong	Strong	Moderate	Strong	Weak
Kitzman et al. (2017)	Weak	Weak	Strong	Weak	Weak	Weak	Moderate
Kinugasa et al. (2014)	Moderate	Moderate	Moderate	Strong	Moderate	Strong	Weak
McAleer et al. (1992)	Weak	Moderate	Strong	Weak	Moderate	Strong	Weak
O'Callaghan et al. (2012)	Weak	Weak	Moderate	Strong	Moderate	Weak	Moderate
Roderick et al. (2001)	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Schweickert et al. (2011)	Weak	Weak	Moderate	Strong	Moderate	Strong	Weak
Switzer et al. (2009)	Moderate	Strong	Strong	Strong	Weak	Strong	Strong
Woollard et al. (2005)	Moderate	Strong	Strong	Weak	Moderate	Strong	Strong
Young et al. (2016)	Weak	Weak	Strong	Weak	Moderate	Moderate	Strong

(O'Callaghan et al., 2012) concluded that a short educational intervention (one session, face to face) substantially improved patients' knowledge about stroke (50% increase in Stroke Knowledge Score, $p < 0.05$) when compared to usual care. A trial examining the impact of using navigators to support community transitions in stroke survivors reported lower rates of 30-day emergency department visits and hospital readmissions in the intervention group (0% and 3.3% respectively) when compared with a usual care control group (83% and 42%) (Kitzman et al., 2017).

Three trials evaluated telehealth systems to remotely examine and monitor stroke survivors (Audebert et al., 2009; Demaerschalk et al., 2010; Switzer et al., 2009). One trial observed that a tele-stroke system intervention was associated with a significant reduction of mean onset-to-treatment time (127.6 min in the intervention group vs 145.9 min in the control group) (Switzer et al., 2009). Another trial (Demaerschalk et al., 2010) compared audio-visual telemedicine system vs telephone consultations, observing no significant differences between both modalities in the proportion of correct treatment decisions (85% vs. 89% in the telemedicine and telephone group respectively), mortality rate (4% vs. 11%) or rates of intracerebral haemorrhage (4% vs. 0%). Another trial (Audebert et al., 2009) compared health outcomes in patients receiving stroke care in hospitals with specialized local stroke wards, continuous medical education, and tele-medical consultation (intervention group) vs. patients receiving stroke care in matched hospitals without those services (control group), observing that, although the intervention did not significantly reduce a composite of "death or institutional care" ($p > 0.05$), it resulted in a significant reduction of "death and dependency" at 12 months (OR, 0.65; 95% CI, 0.54–0.78) and 30 months (OR, 0.82; 95% CI, 0.68–0.98).

Two trials examined the impact of new or improved rehabilitation services for stroke survivors. One of them (Roderick et al., 2001) showed that a domiciliary rehabilitation service for stroke survivors did not significantly improve physical function and social activity when compared with usual care. The other (Askim et al., 2004) observed that an extended stroke unit service with early supported discharge and coordination of further rehabilitation significantly decreased social isolation ($p < 0.05$), but did not improve mortality rates, the proportion of patients independent 52 weeks after stroke onset, or institutionalization time.

C. Interventions to improve healthcare in patients with HF (five trials)

Five trials examined the impact of interventions to improve healthcare in HF patients (Caldwell et al., 2005; Dracup et al., 2014; Hebert et al., 2006; Kinugasa et al., 2014). An education program with a specific focus on disease management (symptom recognition and management of fluid weight) significantly improved knowledge and self-care behaviour but not HF severity (β-natriuretic peptide) in the intervention group (Caldwell et al., 2005). A multifaceted program (mainly based on patient education about how to self-titrate their daily dose of oral diuretics/how to use β-blockers, but also involving open access to the clinic for intravenous diuretics, and phone-based management) was associated with a significant reduction in mortality (adjusted hazard ratio 0.33, $p < 0.001$) when compared with usual care (Hebert et al., 2006). A short (one session) educational self-management intervention followed by follow-up phone calls did not significantly reduce cardiac mortality after two years when compared with usual care (Dracup et al., 2014). A multidisciplinary HF management program involving a number of medical and non-medical interventions (including optimization of HF therapy by cardiologist; cardiac rehabilitation by physical therapist; patient education; pre-discharge assessment of congestion, and; discharge care planning) significantly reduced HF hospitalization and all-cause mortality after ($p < 0.001$ for the comparison pre-post program implementation) (Kinugasa et al., 2014). A 12-week self-management training program delivered by telephone to HF patients discharged from a rural hospital improved patient-reported self-management at 3 and 6 months post-discharge ($p < 0.0005$), but no differences were observed in physical activity, clinical biomarkers and 30-day readmission rates (Young et al., 2016).

4. Discussion

In this systematic review we examined the impact of 18 interventions to improve cardiovascular disease healthcare in rural areas. Most of the interventions for stroke and myocardial infarction consisted in creating new structures or in improving or adapting the existing ones to provide more timely access to healthcare. Although these interventions improved health care processes, a positive impact on mortality or other important health outcomes was not consistently observed. All the interventions for heart failure were based on the provision of patient education. They consistently improved patient knowledge and self-management behaviour, but not mortality rates.

Previous systematic reviews have assessed the efficacy of interventions to improve health care in rural areas for patients with other long term conditions such as diabetes (Ricci-Cabello et al., 2013; Lepard et al., 2015), obesity (Moore et al., 2016; Umstattd Meyer et al., 2016; Cleland et al., 2017; Speyer et al., 2018), chronic obstructive pulmonary disease (Brooke et al., 2017), asthma (Estrada and Ownby, 2017) or cancer (Davis et al., 2018). In line with some of our findings, they provide evidence supporting the use of tele-health services; which

Table 3
Characteristics and effectiveness of the interventions to reduce rural inequalities in cardiovascular healthcare.

Author (reference)/ country	Intervention/control groups	Design/study follow-up	Population	Setting	Intervention delivered by	Intervention type	Outcomes
1. Acute myocardial infarction							
McAleer et al. (1992)/UK	- Intervention group (n = 43): IV streptokinase prehospital by means of a mobile coronary care unit - Control group (n = 102): IV streptokinase in hospital	RCT/24 months	Patients with symptoms of acute myocardial infarction of < 6 h	Hospital	Healthcare providers	Organizational change	Health outcomes: - Mortality at 14 days: 2.3% in the intervention group vs. 11.7% in the control group ($p < 0.05$). - Six month mortality: 4.9% in the intervention group vs. 17.3% in the control group ($p < 0.05$). - Mortality at 1 year: 6.1% in the intervention group vs. 20.0% in the control group ($p < 0.05$).
Coccolini et al. (1995)/Italy	- Intervention group (n = 102): thrombolysis in the Emergency Room of a Rural Hospital with no Coronary Care Unit (followed by a transfer to the main City Hospital with a Coronary Care Unit) - Control group (n = 178): thrombolysis in the main City Hospital with a Coronary Care Unit.	Non-randomized controlled trial/1 month and 5 days	Patients with suspected acute myocardial infarction and with no contra-indications to fibrinolysis, within 6 h of onset of symptoms	Hospital	Healthcare providers	Organizational change	Diagnosis: Accuracy of diagnosis for acute myocardial infarction was 91% and 100%, respectively in the intervention and control group, respectively (statistical significance not examined) Treatment: Median pain to needle time was 90′ in intervention group and 165′ in control group ($p < 0.001$). Health outcomes: - Mortality at 35 days in intervention group was 7.5% vs. 10.7% in control group ($p > 0.05$). - Reduction in Echocardiographic Wall Motion Abnormality Score Index (3.6 intervention vs. 5.6 control group; $p < 0.001$).
Woollard et al. (2005)/UK	- Intervention group (n = 213): transmission from ambulance to a general hospital coronary care unit of ECG, blood pressure, pulse oximetry, and relevant medical history. Cardiology senior house officers then determined each patient's suitability for pre-hospital thrombolysis time, and transmitted this decision back to the ambulance. - Control group (n = 183): standard paramedic treatment	RCT/18 months	Patients with chest pain believed to be of cardiac origin or without a clear alternative cause	Emergency care	Paramedics	Multifaceted (provider education and organizational changes)	Treatment: - Median call to thrombolysis time was 53 min in the intervention group vs108 min in the control group. - Reduction in call to treatment time for telemetry patients recommended for prehospital thrombolysis was 55 min ($p = 0.022$).
Bohmer et al. (2010)/ Norway	- Intervention group (n = 138): immediate transfer for percutaneous coronary intervention - Control group (n = 138): usual care	RCT/12 months	Patients aged 18–75 with symptoms of myocardial infarction present for < 6 h and expected time delay from first medical contact to percutaneous coronary intervention > 90 min.	Emergency care	Research team and healthcare professionals	Organizational changes	Health outcomes: The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the conservative group (6% vs. 16%, hazard ratio: 0.36, 95% CI: 0.16 to 0.81, $p = 0.01$).
		Cluster RCT/27 months		Hospital	Research team	Multifaceted	

(*continued on next page*)

Table 3 (*continued*)

Author (reference)/ country	Intervention/control groups	Design/study follow-up	Population	Setting	Intervention delivered by	Intervention type	Outcomes
Kinsman et al. (2012)/ Australia	- Intervention group (n = 57): Implementation process for an acute myocardial infarction clinical pathway on thrombolytic administration in rural emergency departments (involving clinician engagement; pathway development; reminders; clinician education; audit and feedback). - Control group (n = 51): usual care		Patients presenting within 12 h of onset of ischemic symptoms				Diagnosis: No significant difference between intervention and control groups for median time to electrocardiogram (7 vs. 6 min; p = 0.669). Treatment: No significant difference between intervention and control groups for median door-to-needle time (29 vs. 29 min; p = 0.632), and for proportion of those eligible receiving a thrombolytic treatment (78% versus 84%; p = 0.739).
2. Cerebrovascular disease							
Roderick et al. (2001)/UK	Intervention group (n = 66): new domiciliary rehabilitation service for elderly stroke patients - Control group (n = 74): geriatric day-hospital care (usual care)	RCT/6 months	Stroke patients aged 55 + who required further rehabilitation after hospital discharge or after referral to geriatricians from the community.	Medical centres/ patients' home	Physiotherapist, occupational therapist and consultant geriatrician	Organizational changes	Health outcomes: Non-significant improvement in measures of physical function and social activity was observed in the domiciliary group.
Askim et al. (2004)/ Norway	- Intervention group (n = 31): extended stroke unit service (extended service), with early supported discharge and co-ordination of further rehabilitation in co-operation with the primary health care system - Control group (n = 31): usual care	RCT/13 months	Patients with acute stroke living in the rural municipalities of Malvik, Melhus and Klaebu.	Medical centres/ patients' home	Nurse, occupational therapist, and physician	Organizational change	Health outcomes: - Twelve patients (39%) in the extended service group versus 16 patients (52%) in the ordinary service group were independent according to Modified Rankin Scale at 52 weeks (p = 0.444). - Decreased in social isolation (Nottingham Health Profile) in the extended service group at 26 weeks (p = 0.046). - No significant differences in Barthel Index, Caregiver Strain Index, and length of stay.
Audebert et al. (2009)/ Germany	- Intervention group (n = 1938 patients): set-up of specialized local stroke wards, continuous medical education, and telemedical consultation for patients with acute stroke by 2 stroke centres - Control group (n = 1122 patients): control hospitals without specialized stroke facilities or telemedical support	Non-randomized controlled trial/30 months	Patients with consecutive ischemic or haemorrhagic stroke admitted between July 2003 and March 2005	Hospital	Physicians, nurses and therapists	Multifaceted (provider education and organizational changes)	Health outcomes: - No significant effect of the intervention for reduced "death or institutional care" at 12 months (OR, 0.89; 95% CI, 0.75–1.07; p = 0.23) and 30 months (OR, 0.93; 95% CI, 0.78–1.11; p = 0.40). - Significant reduction of "death and dependency" (Barthel index < 60 or Rankin scale > 3) at 12 months (OR, 0.65; 95% CI, 0.54–0.78; p < 0.01) and 30 months (OR, 0.82; 95% CI, 0.68–0.98; p = 0.031)

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Table 3 (*continued*)

Author (reference)/ country	Intervention/control groups	Design/study follow-up	Population	Setting	Intervention delivered by	Intervention type	Outcomes
Switzer et al. (2009)/US	- Intervention group- (n = 50): telestroke system that allows the stroke consultant to obtain history, examine the patient with live video, and review computed tomography. A recommendation is made regarding the administration of tissue plasminogen activator before patient transport to the tertiary medical centre. - Control group (n = 26): usual care	Non-randomized controlled trial/37 months	Patients treated with tissue plasminogen activator using the REACH system and compared to the data collected on patients treated in the MCG hospital ED during the period of February 2003 to March 2006	Hospital	Healthcare professionals	Organizational changes	Treatment: The mean onset-to-treatment time was 127.6 min (95% CI = 117.1–138.0) in the intervention group vs 145.9 min (95% CI = 126.9–164.9) in the control group.
Demaerschalk et al. (2010)/US	- Intervention group (n = 27): audiovisual telemedicine system designed for remote examination of adult patients with acute stroke. - Control group (n = 27): telephone consultation	RCT/10 months	Adult patients with signs consistent with an acute stroke syndrome, and onset < 3 h.	Hospital	Physicians and nurses	Organizational changes	Treatment: No differences observed in the proportion of correct treatment decision between the intervention (85% correct) and the control group (89% correct) Health outcomes: There were no statistically significant differences in mortality (4% in telemedicine and 11% in telephone) or rates of intracerebral haemorrhage (4% in telemedicine and 0% in telephone)
Schweickert et al. (2011)/US	- Intervention group (n = 5): 20 min stroke education program, delivered through a telehealth platform - Control group (n = 6): 20 min stroke education program, group and face to face delivered.	Non-randomized controlled trial/ < 1 day (completed pre-intervention surveys, received a 20-min group in person or telehealth delivered education session, and then completed the post-intervention surveys)	55–90 years of age and able to give informed consent, participate in a stroke education session	Medical centre	Research team	Patient education	Detection: - Knowledge about stroke increased in both groups after the educational programs (but no statistically significant differences were observed between the intervention and control group) - A significant ($p < 0.05$) improvements in the pre-post score of the likelihood of making behavioural changes to decrease vascular risk factors of the telehealth group in contrast to the in-person group.
O'Callaghan et al. (2012)/Ireland	- Intervention group (n = 200): patient education about stroke (stroke risk factors, warning signs, response to, and treatment available; primary and secondary preventative measures for stroke) delivered face to face over a 90-minute session (n = 200) - Control group (n = 200): usual care	Non-randomized controlled trial/4 weeks	A community-dwelling convenience sample of men and women aged 40 years	Community centre	Stroke consultant, senior dietician, registered nurse and physiotherapist	Patient education	Detection: After adjustment for differences in baseline knowledge and educational attainment, Stroke Knowledge Scores improved by 50% (95% CI, 31%–72%) after the educational session in the intervention group ($p < 0.001$), whereas no differences were observed in the control group (mean score remained unchanged).

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Author (reference)/ country	Intervention/control groups	Design/study follow-up	Population	Setting	Intervention delivered by	Intervention type	Outcomes
Kitzman et al. (2017)/US	- Intervention group (n = 30): To support the transition of individuals with stroke and their caregivers from acute in-patient care back to their rural community through facilitation of communication between the clients and the healthcare providers and acquisition of essential resources (health insurance, medications, follow up appointments, etc.). Contact with the participant is a minimum of 1 ×/week for the first 3 months and a minimum of 1 × every other week for months 4–6 (home and phone visits). - Control group (n = 12): usual care	Non-randomized controlled trial/6 months	Participants with acute stroke receiving care at a regional inpatient rehabilitation hospital in south-eastern (Appalachian) Kentucky	Hospital and home	Trained lay community health worker (navigator)	Multifaceted (organizational changes and patient education)	Health outcomes: Over the assessment period there were no 30-day ED visits by individuals in the Intervention group. In contrast, 83% (n = 10) of control group had visited the ED at least one time within 30 days of discharge from inpatient rehabilitation. One person of intervention group was readmitted to the hospital; in contrast, 42% (n = 5) of the control group reported a readmission to the hospital within 30 days of discharge from acute inpatient rehabilitation.
3. Heart failure							
Caldwell et al. (2005)/US	- Intervention group (n = 20): education program focused on a single component of disease management (symptom recognition and management of fluid weight), and a follow-up phone call focusing on symptom management - Control group (n = 16): usual care	RCT/3 months	Clinically stable New York Heart Association classes II to IV HF patients	Cardiology practice	Research team and nurse	Patient education	Prevention: - Knowledge and self-care behaviour related to daily weights improved significantly at 3 months in the intervention group (p = 0.01 and 0.03, respectively) Health outcomes: No significant differences were observed in heart failure severity (β-natriuretic peptide) between the intervention and control group at three months.
Hebert et al. (2006)/US	- Intervention group (n = 156): heart failure disease management program (patient education about how to self-titrate their daily dose of oral diuretics/how to use β-blockers; provision of open access to the clinic for intravenous diuretics; phone management). - Control group (n = 100): usual care	Non-randomized controlled trial/60 months	Indigent population from rural Louisiana with hospital discharge diagnosis of HF	Hospital	cardiologist, registered nurses, and social worker	Multifaceted (organizational changes and patient education)	Health outcomes: After controlling for differences in demographics, ejection fraction, and comorbidities, participation in the HFDM program was associated with a significant reduction in mortality compared with traditional care (adjusted hazard ratio 0.33, p < 0.001).
Dracup et al. (2014) and Park et al. (2017)/US	- Intervention group 1 (LITE group; n = 200): face to-face education session delivered by a nurse focusing on self-care, and 2 follow-up phone calls - Intervention group 2 (PLUS group; n = 193): face to-face education session delivered by a nurse focusing on self-care, and biweekly calls (mean, 5.3 ± 3.6; range,	RCT/24 months	Adult patients hospitalized with HF within the past 6 month	Medical centre	Nurses	Patient education	Health outcomes: Over 2 years of follow-up, 35% of patients (n = 211) experienced cardiac death or hospitalization for HF, with no difference among the 3 groups in the proportion who experienced the combined clinical outcome (P = 0.06). Although patients in the LITE group had reduced cardiac mortality

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Table 3 (*continued*)

Author (reference)/ country	Intervention/control groups	Design/study follow-up	Population	Setting	Intervention delivered by	Intervention type	Outcomes
	1–19) until the nurse judged the patient to be adequately trained. - Control group (n = 209): usual care						compared with patients in the control group over the 2 years of follow-up (7.5% and 17.7%, respectively; p = 0.003), there was no significant difference in cardiac mortality between patients in the PLUS group and the control group.
Kinugasa et al. (2014)/Japan	- Intervention group (n = 144): multidisciplinary HF management program focused on the comprehensive medical and non-medical interventions. Components of the program included: Optimization of HF therapy by HF cardiologist; Cardiac rehabilitation by physical therapist; patient education; Team conference by multidisciplinary HF team; Pre-discharge assessment of congestion; Discharge care planning. - Control group (n = 133): usual care	Controlled before after study/ 23 months	Hospitalized HF patients in a Japanese rural area	Hospital	HF cardiologist, cardiovascular nurse, pharmacist, dietitian, physical therapist, sonographers, social worker	Multifaceted (organizational changes/patient education)	Health outcomes: The incidence of the composite endpoints (HF hospitalization and all-cause mortality) significantly decreased after introducing the program (p < 0.001). Among a number of interventions, multidisciplinary intensive education was the most effective intervention to improve the primary outcome (p < 0.001).
Young et al. (2016)/US	- Intervention group (n = 51): usual care and the 12-week PATCH intervention comprised of two phases: a one-on-one in-hospital SM training session and 11 post-discharge reinforcement sessions (twice a week for the first 2 weeks, once a week for weeks 3–6, and every other week for weeks 7–12) delivered by telephone. - Control group (n = 49): usual care	RCT/3 months	Adult patients with New York Heart Association classes II to IV symptoms or NYHA class I symptoms and at least one other HF-related hospitalization in the previous year	Hospital and home	Nurses	Patient education (Home Based Intervention)	Health outcomes: Based on self-reported data, patients in the PATCH intervention group had significant improvement in activation scores and SM adherence in weighing themselves daily, following a low-sodium diet and exercising regularly. According to the objective measures (i.e., physical activity measured by accelerometer and daily sodium intake computed from urine sodium), however, the subjects from the intervention group did not reach adherence threshold of sodium restriction and exercise intensity guidelines. Consequently, the reported improvement in SM adherence and behaviours did not improve clinical biomarkers or reduce readmissions. Instead, the 30-day readmission rate was higher in the intervention group than in the control group. Furthermore, the PATCH intervention had no impact on SM knowledge at 3 months.

RCT, randomized controlled trial; HF, heart failure; CI, confidence interval; OR, odds ratio; SM, self-management.

emerge as a strategy to increase access to services in rural and remote communities (Estrada and Ownby, 2017; Banbury et al., 2014) that may be as effective as face-to-face interventions (Speyer et al., 2018). Other reviews conclude that most successful interventions are those including multiple components (multifaceted interventions) (Ricci-Cabello et al., 2013; Davis et al., 2018), interventions targeted to specific challenges (Estrada and Ownby, 2017), as well as community-based (Moore et al., 2016; Cleland et al., 2017; Abbott, 2015) and culturally adapted (Lauckner and Hutchinson, 2016) interventions.

The studies identified in our review evaluating the impact of interventions for acute myocardial infarction observed that these interventions successfully reduced treatment times in patients living in rural areas. It is worth noting however that most of these studies (carried out more than a decade ago) involved the use of therapeutic fibrinolysis, whereas nowadays the gold standard reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) in developed countries (which are the ones our review is focused on) is PCI (Ibanez et al., 2018). According to US and EU guidelines, PCI superiority is however time-dependent, and may disappear if time from STEMI to PCI is higher than 120 min (Ibanez et al., 2018; Alame et al., 2017).

Although efforts should be made to provide a primary service of PCI adherent to times recommended in clinical guidelines, this may be not logistically feasible in all areas - and particularly challenging in those with longer transfer times. Under these circumstances, thrombolysis is still considered the standard procedure (D'Souza et al., 2011). Previous studies have shown that fibrinolysis as a complement to PCI is associated with decreased mortality (Abdel-Qadir et al., 2015).

Despite some heterogeneity in the observed results, telemedicine interventions emerged in our review as a feasible and safe approach to effectively reduce time to treatment, dependency and mortality. The positive findings observed in our systematic review for telemedicine interventions delivered to patients with cerebrovascular disease are generally in line with available evidence from previous studies (Jauch et al., 2013), including, but not only, evidence from randomized controlled trials of telescopic consultation for acute cerebrovascular accident showing the effectiveness (Meyer et al., 2008) and cost-effectiveness (Nelson et al., 2011) of using telestroke to support decision making around the use of thrombolysis.

Telestroke systems enable access to specialized care in rural centres. They allow a two fold increase in the number of patients with ictus who can receive urgent neurological healthcare, and in the number of thrombolytic treatments. Their use significantly reduces time to treatment, and increases the number of patients treated within the first 3 h (Zanaty et al., 2014). The American Heart Association/American Stroke Association currently recommend the use of telestroke systems (Schwamm et al., 2009a), and implementation guidelines are available for a number of different healthcare systems (Schwamm et al., 2009b).

Intervention based on the provision of new or improved rehabilitation services for stroke survivors did not improve mortality, physical function or other important health outcomes, and those based on education about stroke risk factors and early recognition of acute stroke symptoms were effective in increasing knowledge and improving behavioural outcomes.

All the interventions targeted to patients with HF were based on patient education and successfully increased knowledge and improve self-management activities. Reduction in mortality rates were also observed in those cases in which the educational interventions were delivered by multidisciplinary teams which included social workers and members of the community. The limited access to medical care in rural areas could be effectively tackled by using a multidisciplinary approach (Jaarsma et al., 2013), as suggested by several clinical guidelines, which however do not provide a framework that could by universally applied (National CGCU, 2010; Dickstein et al., 2010).

4.1. Strengths and limitations of the systematic review and of the available literature

One of the main strengths of this study is the comprehensiveness of the bibliographic searches. Systematic and manual searches were performed in the most relevant bibliographic databases on biomedical research, as well as in specific sites of gray literature. We applied robust methods for study selection, data extraction and critical appraisal, which were conducted by two independent reviewers to maximize the validity and accuracy of the results of this review.

Our review also has some limitations. First, the review included interventions to improve healthcare in countries with substantially different healthcare systems, which may limit the comparability across countries of the observed results. However, rurality poses similar challenges in healthcare provision, and most of the interventions identified in this review could be relevant in the countries selected for this review. Second, we could not undertake a quantitative synthesis (meta-analysis) of the study results due to the heterogeneity of the interventions and outcomes reported in the studies identified in our review. Finally, as observed in previous systematic reviews of interventions to tackle social inequalities in healthcare provision (Ricci-Cabello et al., 2013; Ruiz-Perez et al., 2017), most of the studies identified focused on developing and evaluating interventions to address the specific needs of the targeted disadvantaged populations (i.e., ethnic minorities, patients living in rural areas, etc.), but did not compare the impact of such interventions in disadvantaged vs. not disadvantaged populations - therefore not being able to determine the extent to which the interventions were successful at reducing geographic inequalities. This, and the lack of studies about other important CVDs (such as peripheral arterial disease, congenital heart disease, deep venous thrombosis or pulmonary embolisms) are important limitations of the available literature that need to be addressed by future research.

5. Conclusions

Evidence from methodologically robust trials suggest that interventions for acute myocardial infarction based on organizational changes (such as the implementation of mobile coronary units) can lead to clinically significant reductions in treatment time - a key aspect for patients with myocardial acute infarction living in rural areas.

For stroke, available evidence shows that the use of telemedicine systems is an effective strategy for monitoring patients in rural areas, and can reduce time to treatment.

Educational interventions for HF patients can improve patient self-management and knowledge about their condition. Management of HF by multidisciplinary teams may decrease rehospitalisation rates and mortality.

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Conflict of interest

None declared.

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References

Abbott, L.S., 2015. Evaluation of nursing interventions designed to impact knowledge, behaviors, and health outcomes for rural African-Americans: an integrative review. Public Health Nurs. 32 (5), 408–420.

Abdel-Qadir, H., Yan, A.T., Tan, M., Borgia, F., Piscione, F., Di Mario, C., et al., 2015.

Consistency of benefit from an early invasive strategy after fibrinolysis: a patient-level meta-analysis. Heart 101 (19), 1554–1561.
Alame, A.J., Karatasakis, A., Karacsonyi, J., Danek, B.A., Resendes, E., Martinez Parachini, J.R., et al., 2017. Comparison of the American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines for the management of patients with non-ST-segment elevation acute coronary syndromes. Coron. Artery Dis. 28 (4), 294–300.
Ali, M., Atula, S., Bath, P.M., Grotta, J., Hacke, W., Lyden, P., et al., 2009. Stroke outcome in clinical trial patients deriving from different countries. Stroke 40 (1), 35–40.
Alston, L.V., Peterson, K.L., Jacobs, J.P., Allender, S., Nichols, M., 2016. A systematic review of published interventions for primary and secondary prevention of ischaemic heart disease (IHD) in rural populations of Australia. BMC Public Health 16, 895.
Alston, L., Allender, S., Peterson, K., Jacobs, J., Nichols, M., 2017. Rural inequalities in the Australian burden of ischaemic heart disease: a systematic review. Heart Lung Circ. 26 (2), 122–133.
Askim, T., Rohweder, G., Lydersen, S., Indredavik, B., 2004. Evaluation of an extended stroke unit service with early supported discharge for patients living in a rural community. A randomized controlled trial. Clin. Rehabil. 18 (3), 238–248.
Audebert, H.J., Schultes, K., Tietz, V., Heuschmann, P.U., Bogdahn, U., Haberl, R.L., et al., 2009. Long-term effects of specialized stroke care with telemedicine support in community hospitals on behalf of the Telemedical Project for Integrative Stroke Care (TEMPiS). Stroke 40 (3), 902–908.
Banbury, A., Roots, A., Nancarrow, S., 2014. Rapid review of applications of e-health and remote monitoring for rural residents. Aust. J. Rural Health 22 (5), 211–222.
Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., et al., 2017. Heart disease and stroke statistics—2017 update: a report from the american heart association. Circulation 135 (10), e146–e603. https://doi.org/10.1161/CIR.0000000000000485.
Bohmer, E., Hoffmann, P., Abdelnoor, M., Arnesen, H., Halvorsen, S., 2010. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). J. Am. Coll. Cardiol. 55 (2), 102–110.
Bottle, A., Ventura, C.M., Dharmarajan, K., Aylin, P., Ieva, F., Paganoni, A.M., 2018. Regional variation in hospitalisation and mortality in heart failure: comparison of England and Lombardy using multistate modelling. Health Care Manag. Sci. 21 (2), 292–304.
Brooke, M.E., Spiliopoulos, N., Collins, M., 2017. A review of the availability and cost effectiveness of chronic obstructive pulmonary disease (COPD) management interventions in rural Australia and New Zealand. Rural Remote Health 17 (3), 4017.
Caldwell, M.A., Peters, K.J., Dracup, K.A., 2005. A simplified education program improves knowledge, self-care behavior, and disease severity in heart failure patients in rural settings. Am. Heart J. 150 (5), 983.
Camargo, KRd, 2011. Closing the gap in a generation: health equity through action on the social determinants of health. Glob. Public Health 6 (1), 102–105.
Carey, T.A., Sirett, D., Russell, D., Humphreys, J.S., Wakerman, J., 2018. What is the overall impact or effectiveness of visiting primary health care services in rural and remote communities in high-income countries? A systematic review. BMC Health Serv. Res. 18 (1), 476.
Chen, R., Hu, Z., Chen, R.-L., Zhang, D., Xu, L., Wang, J., et al., 2015. Socioeconomic deprivation and survival after stroke in China: a systematic literature review and a new population-based cohort study. BMJ Open 5 (1), e005688.
Christensen, M.C., Broderick, J., Vincent, C., Morris, S., Steiner, T., 2009. Global differences in patient characteristics, case management and outcomes in intracerebral hemorrhage: the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial. Cerebrovasc. Dis. 28 (1), 55–64.
Clark, R.A., Eckert, K.A., Stewart, S., Phillips, S.M., Yallop, J.J., Tonkin, A.M., et al., 2007. Rural and urban differentials in primary care management of chronic heart failure: new data from the CASE study. Med. J. Aust. 186 (9), 441–445.
Cleland, V., Squibb, K., Stephens, L., Dalby, J., Timperio, A., Winzenberg, T., et al., 2017. Effectiveness of interventions to promote physical activity and/or decrease sedentary behaviour among rural adults: a systematic review and meta-analysis. Obes. Rev. 18 (7), 727–741.
Coccolini, S., Berti, G., Bosi, S., Pretolani, M., Tumiotto, G., 1995. Prehospital thrombolysis in rural emergency room and subsequent transport to a coronary care unit: Ravenna Myocardial Infarction (RaMI) trial. Int. J. Cardiol. 49, S47–S58 (Suppl).
Corburn, J., Cohen, A.K., 2012. Why we need urban health equity indicators: integrating science, policy, and community. PLoS Med. 9 (8), e1001285.
Davis, M.M., Freeman, M., Shannon, J., Coronado, G.D., Stange, K.C., Guise, J.M., et al., 2018. A systematic review of clinic and community intervention to increase fecal testing for colorectal cancer in rural and low-income populations in the United States - how, what and when? BMC Cancer 18 (1), 40.
Demaerschalk, B.M., Bobrow, B.J., Raman, R., Kiernan, T.E., Aguilar, M.I., Ingall, T.J., et al., 2010. Stroke team remote evaluation using a digital observation camera in Arizona: the initial mayo clinic experience trial. Stroke 41 (6), 1251–1258.
Dickstein, K., Vardas, P.E., Auricchio, A., Daubert, J.C., Linde, C., McMurray, J., et al., 2010. 2010 focused update of ESC guidelines on device therapy in heart failure: an update of the 2008 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur. Heart J. 31 (21), 2677–2687.
Dracup, K., Moser, D.K., Pelter, M.M., Nesbitt, T.S., Southard, J., Paul, S.M., et al., 2014. Randomized, controlled trial to improve self-care in patients with heart failure living in rural areas. Circulation 130 (3), 256–264.
D'Souza, S.P., Mamas, M.A., Fraser, D.G., Fath-Ordoubadi, F., 2011. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. Eur. Heart J. 32 (8), 972–982.
Eberhardt, M.S., Pamuk, E.R., 2004. The importance of place of residence: examining health in rural and nonrural areas. Am. J. Public Health 94 (10), 1682–1686.
Estrada, R.D., Ownby, D.R., 2017. Rural asthma: current understanding of prevalence, patterns, and interventions for children and adolescents. Curr. Allergy Asthma Rep. 17 (6), 37.
Feigin, V.L., Lawes, C.M., Bennett, D.A., Barker-Collo, S.L., Parag, V., 2009. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 8 (4), 355–369.
Gamble, J.M., Eurich, D.T., Ezekowitz, J.A., Kaul, P., Quan, H., McAlister, F.A., 2011. Patterns of care and outcomes differ for urban versus rural patients with newly diagnosed heart failure, even in a universal healthcare system. Circ. Heart Fail. 4 (3), 317–323.
Havranek, E.P., Wolfe, P., Masoudi, F.A., Rathore, S.S., Krumholz, H.M., Ordin, D.L., 2004. Provider and hospital characteristics associated with geographic variation in the evaluation and management of elderly patients with heart failure. Arch. Intern. Med. 164 (11), 1186–1191.
Hebert, K.A., Horswell, R.L., Dy, S., Key Jr., I.J., Butler, M.K., Cerise, F.P., et al., 2006. Mortality benefit of a comprehensive heart failure disease management program in indigent patients. Am. Heart J. 151 (2), 478–483.
Heuschmann, P.U., Di Carlo, A., Bejot, Y., Rastenyte, D., Ryglewicz, D., Sarti, C., et al., 2009. Incidence of stroke in Europe at the beginning of the 21st century. Stroke 40 (5), 1557–1563.
Ibanez, B., James, S., Agewall, S., Antunes, M.J., Bucciarelli-Ducci, C., Bueno, H., et al., 2018. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur. Heart J. 39 (2), 119–177.
Jaarsma, T., Brons, M., Kraai, I., Luttik, M.L., Stromberg, A., 2013. Components of heart failure management in home care; a literature review. Eur. J. Cardiovasc. Nurs. 12 (3), 230–241.
Jacobs, J., Peterson, K.L., Allender, S., Alston, L.V., Nichols, M., 2018. Regional variation in cardiovascular mortality in Australia 2009–2012: the impact of remoteness and socioeconomic status. Aust. N. Z. J. Public Health 42 (5), 467–473. https://doi.org/10.1111/1753-6405.
Jauch, E.C., Saver, J.L., Adams Jr., H.P., Bruno, A., Connors, J.J., Demaerschalk, B.M., et al., 2013. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 44 (3), 870–947.
Jiang, G., Wang, D., Li, W., Pan, Y., Zheng, W., Zhang, H., et al., 2012. Coronary heart disease mortality in China: age, gender, and urban-rural gaps during epidemiological transition. Rev. Panam. Salud Publica 31 (4), 317–324.
Jin, Y., Quan, H., Cujec, B., Johnson, D., 2003. Rural and urban outcomes after hospitalization for congestive heart failure in Alberta, Canada. J. Card. Fail. 9 (4), 278–285.
Katan, M., Luft, A., 2018. Global burden of stroke. Semin. Neurol. 38 (2), 208–211.
Kawachi, I., Subramanian, S.V., Almeida-Filho, N., 2002. A glossary for health inequalities. J. Epidemiol. Community Health 56 (9), 647–652.
Khanal, M.K., Ahmed, M.S., Moniruzzaman, M., Banik, P.C., Dhungana, R.R., Bhandari, P., et al., 2017. Total cardiovascular risk for next 10 years among rural population of Nepal using WHO/ISH risk prediction chart. BMC. Res. Notes 10 (1), 120.
Kinsman, L.D., Rotter, T., Willis, J., Snow, P.C., Buykx, P., Humphreys, J.S., 2012. Do clinical pathways enhance access to evidence-based acute myocardial infarction treatment in rural emergency departments? Aust. J. Rural Health 20 (2), 59–66.
Kinugasa, Y., Kato, M., Sugihara, S., Yanagihara, K., Yamada, K., Hirai, M., et al., 2014. Multidisciplinary intensive education in the hospital improves outcomes for hospitalized heart failure patients in a Japanese rural setting. BMC Health Serv. Res. 14, 351.
Kitzman, P., Hudson, K., Sylvia, V., Feltner, F., Lovins, J., 2017. Care coordination for community transitions for individuals post-stroke returning to low-resource rural communities. J. Community Health 42 (3), 565–572.
Koifman, J., Hall, R., Li, S., Stamplecoski, M., Fang, J., Saltman, A.P., et al., 2016. The association between rural residence and stroke care and outcomes. J. Neurol. Sci. 363, 16–20.
Kyte, L., Wells, C., 2010. Variations in life expectancy between rural and urban areas of England, 2001–07. Health Stat. Q. 46, 25–50.
Lauckner, H.M., Hutchinson, S.L., 2016. Peer support for people with chronic conditions in rural areas: a scoping review. Rural Remote Health 16 (1), 3601.
Leonhard, M.J., Wright, D.A., Fu, R., Lehrfeld, D.P., Carlson, K.F., 2015. Urban/rural disparities in Oregon pediatric traumatic brain injury. Inj. Epidemiol. 2 (1), 32.
Lepard, M.G., Joseph, A.L., Agne, A.A., Cherrington, A.L., 2015. Diabetes self-management interventions for adults with type 2 diabetes living in rural areas: a systematic literature review. Curr. Diab. Rep. 15 (6), 608.
Levin, K.A., Leyland, A.H., 2006. Urban-rural inequalities in ischemic heart disease in Scotland, 1981–1999. Am. J. Public Health 96 (1), 145–151.
Lewis, C., Gadomski, A., Nafziger, A., Reed, R., Jenkins, P., Dennison, B., et al., 2000. Insights from a large rural population laboratory. Health census '89 and '99. Ann. Epidemiol. 10 (7), 454–455.
McAleer, B., Ruane, B., Burke, E., Cathcart, M., Costello, A., Dalton, G., et al., 1992. Prehospital thrombolysis in a rural community: short- and long-term survival. Cardiovasc. Drugs Ther. 6 (4), 369–372.
Melvin, C.L., Corbie-Smith, G., Kumanyika, S.K., Pratt, C.A., Nelson, C., Walker, E.R., et al., 2013. Developing a research agenda for cardiovascular disease prevention in high-risk rural communities. Am. J. Public Health 103 (6), 1011–1021.
Mendis, S., Puska, P., Norrving, B., 2011. Global Atlas on Cardiovascular Disease Prevention and Control. World Health Organization Available at. https://www.who.

int/cardiovascular_diseases/publications/atlas_cvd/en/, Accessed date: 10 December 2018.
Metra, M., Mentz, R.J., Hernandez, A.F., Heizer, G.M., Armstrong, P.W., Clausell, N., et al., 2016. Geographic differences in patients in a global acute heart failure clinical trial (from the ASCEND-HF trial). Am. J. Cardiol. 117 (11), 1771–1778.
Meyer, B.C., Raman, R., Hemmen, T., Obler, R., Zivin, J.A., Rao, R., et al., 2008. Efficacy of site-independent telemedicine in the STRokE DOC trial: a randomised, blinded, prospective study. Lancet Neurol. 7 (9), 787–795.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.
Moore, M., Warburton, J., O'Halloran, P.D., Shields, N., Kingsley, M., 2016. Effective community-based physical activity interventions for older adults living in rural and regional areas: a systematic review. J. Aging Phys. Act. 24 (1), 158–167.
Moran, A.E., Roth, G.A., Narula, J., Mensah, G.A., 2014. 1990–2010 global cardiovascular disease atlas. Glob. Heart 9 (1), 3–16.
Mullen, M.T., Wiebe, D.J., Bowman, A., Wolff, C.S., Albright, K.C., Roy, J., et al., 2014. Disparities in accessibility of certified primary stroke centers. Stroke 45 (11), 3381–3388.
Nadel, J., Hewitt, T., Horton, D., 2014. Acute coronary syndrome in Australia: where are we now and where are we going? Australas Med J 7 (3), 149–156.
National CGCU, 2010. Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update.
Nelson, R.E., Saltzman, G.M., Skalabrin, E.J., Demaerschalk, B.M., Majersik, J.J., 2011. The cost-effectiveness of telestroke in the treatment of acute ischemic stroke. Neurology 77 (17), 1590–1598.
Nishi, N., Sugiyama, H., Kasagi, F., Kodama, K., Hayakawa, T., Ueda, K., et al., 2007. Urban–rural difference in stroke mortality from a 19-year cohort study of the Japanese general population: NIPPON DATA80. Soc. Sci. Med. 65 (4), 822–832.
O'Callaghan, G., Murphy, S., Loane, D., Farrelly, E., Horgan, F., 2012. Stroke knowledge in an Irish semi-rural community-dwelling cohort and impact of a brief education session. J. Stroke Cerebrovasc. Dis. 21 (8), 629–635 (quiz 36-8).
O'Connor, A., Wellenius, G., 2012. Rural–urban disparities in the prevalence of diabetes and coronary heart disease. Public Health 126 (10), 813–820.
O'Donnell, M.J., Xavier, D., Liu, L., Zhang, H., Chin, S.L., Rao-Melacini, P., et al., 2010. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376 (9735), 112–123.
O'Neal, W.T., Judd, S.E., Limdi, N.A., McIntyre, W.F., Kleindorfer, D.O., Cushman, M., et al., 2017. Differential impact of risk factors in blacks and whites in the development of atrial fibrillation: the reasons for geographic and racial differences in stroke (REGARDS) study. J. Racial Ethn. Health Disparities 4 (4), 718–724.
Park, L.G., Dracup, K., Whooley, M.A., McCulloch, C., Jin, C., Moser, D.K., et al., 2017. Symptom diary use and improved survival for patients with heart failure. Circ. Heart Fail. 10 (11).
Powles, J., Kirov, P., Feschieva, N., Stanoev, M., Atanasova, V., 2002. Stroke in urban and rural populations in north-east Bulgaria: incidence and case fatality findings from a 'hot pursuit' study. BMC Public Health 2 (1), 24.
Ricci-Cabello, I., Ruiz-Perez, I., Rojas-García, A., Pastor, G., Gonçalves, D.C., 2013. Improving diabetes care in rural areas: a systematic review and meta-analysis of quality improvement interventions in OECD countries. PLoS ONE 8 (12), e84464.
Roderick, P., Low, J., Day, R., Peasgood, T., Mullee, M.A., Turnbull, J.C., et al., 2001. Stroke rehabilitation after hospital discharge: a randomized trial comparing domiciliary and day-hospital care. Age Ageing 30 (4), 303–310.
Ruiz-Perez, I., Murphy, M., Pastor-Moreno, G., Rojas-Garcia, A., Rodriguez-Barranco, M., 2017. The effectiveness of HIV prevention interventions in socioeconomically disadvantaged ethnic minority women: a systematic review and meta-analysis. Am. J. Public Health 107 (12), e13–e21.
Schröder, S.L., Richter, M., Schröder, J., Frantz, S., Fink, A., 2016. Socioeconomic inequalities in access to treatment for coronary heart disease: a systematic review. Int. J. Cardiol. 219 (Supplement C), 70–78.
Schwamm, L.H., Holloway, R.G., Amarenco, P., Audebert, H.J., Bakas, T., Chumbler, N.R., et al., 2009a. A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association. Stroke 40 (7), 2616–2634.
Schwamm, L.H., Audebert, H.J., Amarenco, P., Chumbler, N.R., Frankel, M.R., George, M.G., et al., 2009b. Recommendations for the implementation of telemedicine within stroke systems of care: a policy statement from the American Heart Association. Stroke 40 (7), 2635–2660.
Schweickert, P.A., Rutledge, C.M., Cattell-Gordon, D.C., Solenski, N.J., Jensen, M.E., Branson, S., et al., 2011. Telehealth stroke education for rural elderly Virginians. Telemed. J. E Health 17 (10), 784–788.
Seabury, S., Bognar, K., Xu, Y., Huber, C., Commerford, S.R., Tayama, D., 2017. Regional disparities in the quality of stroke care. Am. J. Emerg. Med. 35 (9), 1234–1239.
Smith, K.B., Humphreys, J.S., Wilson, M.G., 2008. Addressing the health disadvantage of rural populations: how does epidemiological evidence inform rural health policies and research? Aust. J. Rural Health 16 (2), 56–66.
Speyer, R., Denman, D., Wilkes-Gillan, S., Chen, Y.W., Bogaardt, H., Kim, J.H., et al., 2018. Effects of telehealth by allied health professionals and nurses in rural and remote areas: a systematic review and meta-analysis. J. Rehabil. Med. 50 (3), 225–235.
Switzer, J.A., Hall, C., Gross, H., Waller, J., Nichols, F.T., Wang, S., et al., 2009. A web-based telestroke system facilitates rapid treatment of acute ischemic stroke patients in rural emergency departments. J. Emerg. Med. 36 (1), 12–18.
Taylor, R., Chey, T., Bauman, A., Webster, I., 1999. Socio-economic, migrant and geographic differentials in coronary heart disease occurrence in New South Wales. Aust. N. Z. J. Public Health 23 (1), 20–26.
Teng, T.-H.K., Katzenellenbogen, J.M., Hung, J., Knuiman, M., Sanfilippo, F.M., Geelhoed, E., et al., 2014. Rural–urban differentials in 30-day and 1-year mortality following first-ever heart failure hospitalisation in Western Australia: a population-based study using data linkage. BMJ Open 4 (5).
Terkelsen, C.J., Sorensen, J.T., Nielsen, T.T., 2008. Is there any time left for primary percutaneous coronary intervention according to the 2007 updated American College of Cardiology/American Heart Association ST-segment elevation myocardial infarction guidelines and the D2B alliance? J. Am. Coll. Cardiol. 52 (15), 1211–1215.
Thomas, H., 2003. Quality Assessment Tool for Quantitative Studies. Effective Public Health Practice Project. McMaster University, Toronto.
Timmis, A., Townsend, N., Gale, C., Grobbee, R., Maniadakis, N., Flather, M., et al., 2018. European society of cardiology: cardiovascular disease statistics 2017. Eur. Heart J. 39 (7), 508–579.
Umstattd Meyer, M.R., Perry, C.K., Sumrall, J.C., Patterson, M.S., Walsh, S.M., Clendennen, S.C., et al., 2016. Physical activity-related policy and environmental strategies to prevent obesity in rural communities: a systematic review of the literature, 2002–2013. Prev. Chronic Dis. 13, E03.
Walker, R.W., McLarty, D.G., Kitange, H.M., Whiting, D., Masuki, G., Mtasiwa, D.M., et al., 2000. Stroke mortality in urban and rural Tanzania. Lancet 355 (9216), 1684–1687.
Walker, R., Whiting, D., Unwin, N., Mugusi, F., Swai, M., Aris, E., et al., 2010. Stroke incidence in rural and urban Tanzania: a prospective, community-based study. Lancet Neurol. 9 (8), 786–792.
Woollard, M., Pitt, K., Hayward, A.J., Taylor, N.C., 2005. Limited benefits of ambulance telemetry in delivering early thrombolysis: a randomised controlled trial. Emerg. Med. J. 22 (3), 209–215.
Young, L., Hertzog, M., Barnason, S., 2016. Effects of a home-based activation intervention on self-management adherence and readmission in rural heart failure patients: the PATCH randomized controlled trial. BMC Cardiovasc. Disord. 16 (1), 176.
Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., et al., 2004a. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364 (9438), 937–952.
Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., et al., 2004b. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364 (9438), 937–952.
Zaman, M.M., Ahmed, J., Choudhury, S.R., Numan, S.M., Parvin, K., Islam, M.S., 2007. Prevalence of ischemic heart disease in a rural population of Bangladesh. Indian Heart J. 59 (3), 239–241.
Zanaty, M., Chalouhi, N., Starke, R.M., Tjoumakaris, S.I., Gonzalez, L.F., Deprince, M., et al., 2014. Epidemiology of a large telestroke cohort in the Delaware valley. Clin. Neurol. Neurosurg. 125, 143–147.