Development of local clinical practice guidelines in the real world: an evolving scene in China

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INTRODUCTION

Clinical practice guidelines play a vital and indispensable role in every healthcare system. In China, the comprehensive reform of the healthcare system was initiated in 2009 with the ultimate goal of universal health coverage.¹ The approach to boost government funding to subsidise health expenditures in the form of government health insurance schemes inevitably led to higher demands for healthcare services and a sharp rise in health expenditures.²⁻⁴ This dramatic transformation of healthcare delivery and utilisation highlights the important consideration of ensuring that the health system in China is able to meet the increased demands and provide universal access to effective and consistent healthcare with optimised resource management. At the heart of a sustainable and effective health system is the use of robust and relevant research evidence to inform clinical practice at local and national levels. Successful translation of evidence into practice is achieved by trustworthy clinical practice guidelines, defined by the US Institute of Medicine as 'statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options'.⁵ China is emerging as a new hub for guideline development with the production of Chinese clinical practice guidelines increasing by nearly fourfold over the past few years.⁶ However, unlike their Western counterparts, China lacks a central infrastructure (eg, National Institute for Health and Care Excellence in the UK) to coordinate and monitor guideline development process. Most Chinese clinical practice guidelines are developed by professional societies, such as the Chinese Medical Association. Ideally, guideline recommendations should be formulated de novo with reference to primary research data from Chinese populations due to known ethnic differences in drug responses and diagnostic reference values as well as country-specific health expenditure trends.7 However, enrolment numbers of Chinese patients in global multicentre clinical trials are often modest, and data by ethnic subgroups are typically underpowered and may not be readily available.⁷ In addition, China still falls behind the USA and Europe in the conduct of clinical trials, and most recommendations in Chinese clinical practice guidelines are based on imported knowledge from US and European guidelines.8



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TOWARDS LOCAL CLINICAL PRACTICE GUIDELINES IN CHINA

This somewhat disappointing situation of a lack of high-level, ethnic-specific evidence in

Chinese clinical practice guidelines is changing, as illustrated by the 2016 Chinese guideline for percutaneous coronary intervention (PCI).¹⁰ A major breakthrough of this latest guideline version is the inclusion of multiple Chinese randomised studies. Of the 198 included references, 26 were reports of clinical research conducted entirely within Chinese populations and, of these, 15 (58%) were randomised controlled trials (RCTs) with the majority being multicentre trials and sample size ranging from 60 to nearly 3000 (table 1). Guideline recommendations were derived from five of these RCTs, with three contributing to Class I recommendations. This is a remarkable improvement from previous versions of the guideline, in which only three Chinese observational studies were included, and none were used as evidence base for guideline recommendations (table 2).^{11 12}

EVIDENCE BASE FOR THE 2016 CHINESE GUIDELINE FOR PCI: A CLOSER LOOK

Among the five included RCTs used to formulate recommendations in the 2016 Chinese guideline for PCI, the REVERSE-STEMI study contributed to a unique recommendation of 'As appropriate for healthcare settings in China, primary PCI can be performed by transferring experienced operators to PCI-capable hospitals (with first-medical-contact-to-balloon time of <120 min' (Class IIb recommendation, Level of Evidence B).¹⁰ ¹³ The REVERSE-STEMI study was conducted in a network of five hospitals in Shanghai and aimed to explore whether an interventionalist-transfer strategy was effective in reducing door-to-balloon time and improving outcomes in patients with ST-elevation myocardial infarction (STEMI) within 12 hours of symptom onset presenting to hospitals with catheterisation laboratories (cath labs) but no qualified interventionalists to perform PCI.¹³ The rationale of this one-of-a-kind study is a great illustration of how the Chinese research communities tackle real-world clinical practice questions that are close to home. Guidelines from the Western countries have set ideal time frames for reperfusion strategies in patients with acute STEMI: for those presenting in PCI-capable hospitals, the ideal first-medical-contact to device time is $\leq 90 \text{ min}$, and for those initially presenting in non-PCI-capable hospitals, ≤120 min with door-indoor-out time of $\leq 30 \text{ min.}^{14 \text{ 15}}$ However, for more than 1000 hospitals in China that are equipped with angiographic facilities, many lack qualified and experienced interventional cardiologists to perform PCI.¹⁶ As an example, it has been reported that there were



Table 1	RCTs included in the 2016	Chinese guideline for PCI
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Study ID	N	No. of centres	Enrolment period	Follow-up duration	CoR	LoE	Trial registration no.	
Yang 2008 ³⁴	60	N/R	August–October 2006	90 days				
Zhang 2011 ¹³ (REVERSE-STEMI)	334	5	November 2005–November 2007	1 year	llb	В	NCT00713557	
Han 2013 ³⁵	197	4	Not reported	1 year			NCT01642667	
Zhu 2013 (ICT-AMI) ³⁶	453	N/R	June 2006–March 2010	6 months				
Geng 2014 ³⁷	535	1	March 2012–February 2013	30 days				
Han 2014 (I-LOVE-IT 2) ³⁸	2737	32	October 2012–June 2013	12 months	I	В	NCT01681381	
Han 2014 (TRACK-D) ³⁹	2998	53	December 2008–October 2011	30 days	lla	А	NCT00786136	
Xu 2014 (PEPCAD China ISR) ⁴⁰	220	17	March 2011–April 2012	12 months	1	А	NCT01622075	
Zhou 2015 ⁴¹	621	1	May 2009–May 2013	6 months				
Chen 2015 (DKCRUSH-VI) ⁴²	320	8	November 2011–June 2013	12 months			ChiCTR-TRC-07000015	
Gao 2015 (ABSORB China) ⁴³	480	24	July 2013–March 2014	1 year			NCT01923740	
Li 2015 ⁴⁴	48	1	April–November 2014	6 months			ChiCTR-RCS-14004303	
Han 2015 (BRIGHT) ⁴⁵	2194	82	August 2012–June 2013	1 year	1	А	NCT01696110	
Zhang B 2015 (ISCAP) ⁴⁶	2674	50	N/R	6 months			NCT01293097	
Qian 2016 ⁴⁷	264	1	February 2014–February 2015	90 days			NCT02405377	

ABSORB China, A Clinical Evaluation of Absorb Bioresorbable Vascular Scaffold (Absorb BVS) System in Chinese Population; BRIGHT, Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial; CoR, class of recommendation; DKCRUSH-VI, Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions VI; I-LOVE-IT 2, Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISCAP, Intensive Statin Therapy for Chinese Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention; LoE, Level of Evidence; N/R, not reported; PCI, percutaneous coronary intervention; PEPCAD China ISR, A Prospective, Multicenter, Randomized Trial of Paclitaxel-Coated versus Paclitaxel-Eluting Stent for the Treatment of Drug-Eluting Stent In-Stent Restenosis; RCT, randomised controlled trial; TRACK-D, Rosuvastatin Prevent Contrast Induced Acute Kidney Injury in Patients With Diabetes.

only five experienced interventional cardiologists responsible for four cath labs at a tertiary-care 2000-bed hospital in Urumqi, Xinjiang Province, a large and underdeveloped area in China.¹ Furthermore, resources are known to be uneven across different regions in China. A national survey in 2010 revealed that for major cities with high gross domestic product such as Beijing, Shanghai and Tianjin, the numbers of PCI-capable hospitals per 10 million residents exceeded the national average (8.11) by up to fivefold; in contrast, the average number of PCI-capable hospitals in the Sichuan Province was only one-fourth of the national average.¹⁸ Together with a lack of coordinated emergency medical service and interhospital transfer system, Chinese patients with STEMI in the real world often present to township or district hospitals with no PCI facilities before being transferred to PCI-capable hospitals, where they are required to go through administrative procedures again to register for services,¹⁹ leading to inevitable delays of reperfusion.²⁰ The REVERSE-STEMI study authors reported a significantly reduced door-to-balloon time in the interventionalist-transfer group (n=165) as compared with the patient-transfer group (n=169) (95±20 min vs 147±29 min; p<0.0001), with three times as many patients achieving the 90 min door-to-balloon time window in the interventionalist-transfer group (21.2% vs 7.7%; p < 0.001).¹³ The inclusion of the REVERSE-STEMI study data in the 2016 Chinese PCI guideline represents a major milestone in the pursuit of synthesising and translating relevant, local trial evidence into fit-for-purpose practice recommendations and highlights the need to consider differences between Eastern and Western healthcare systems and the appropriateness of adopting

Western guideline recommendations from use in the Eastern populations.

Another important update of the 2016 Chinese PCI guideline is a new recommendation regarding the need to establish a quality control system within each PCI centre in China (Class I recommendation, Level of Evidence C).¹⁰ This recommendation, formulated by expert consensus, is based on the growing epidemic of coronary artery disease (CAD) and exponential increase in CAD mortality rates in China,²¹ which undoubtedly calls for greater efforts to monitor the overall quality and performance of the high volume of PCI procedures in the real world in order to further understand if clinical practice guidelines are being implemented. The ongoing China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Prospective Study of Percutaneous Coronary Intervention,²² part of the nationwide China PEACE Initiative, is a multicentre prospective cohort study involving 34 tertiary hospitals that aims to evaluate long-term clinical and patient-reported outcomes, adherence to medication for secondary prevention of CAD as well as risk factors in patients following PCI. Also worth highlighting is the nationwide China Acute Myocardial Infarction Registry,²³ which was designed to incorporate the three-tier hospital infrastructure in China: province, prefecture and county. This broad representation of hospitals will ensure that data obtained will reflect current real-world practice trends, patient outcomes and prognosis as well as economic situations in both rural and urban healthcare settings. Although RCTs remain at the top of the evidence hierarchy and are the gold standard for evaluating efficacy, high-quality multicentre registries are extremely

Table 2 Observational studies included in the 2009 Chinese guideline for PCI								
Study ID	Ν	No. of centres	Study period	Follow-up duration	CoR	LoE		
CHANCE Study Group 200548	224	23	May 1997–March 2003	Mean: 15.6±12.3 months	N/A	N/A		
Gao 2008 ⁴⁹	444 (220 historical controls)	1 (controls from 23 centres)	April 2003–February 2006	Mean: 15 months	N/A	N/A		
Li 2008 ⁵⁰	1002	1	January 1999–October 2006	N/R	N/A	N/A		
CHANCE, Chinese Registry of Unprotected Left Main Coronary Artery Stenting; CoR, class of recommendation; LoE, Level of Evidence; N/A, not applicable; N/R, not reported; PCI,								

CHANCE, Chinese Registry of Unprotected Left Main Coronary Artery Stenting; CoR, class of recommendation; LoE, Level of Evidence; N/A, not applicable; N/R, not reported; PCI, percutaneous coronary intervention.

valuable in filling the knowledge gap on questions that may not be answered by RCTs alone, for example, comparative effectiveness, treatment adherence and practice patterns in the real world. Therefore, results of these nationwide large-scale registries should be included in future updates of relevant Chinese guidelines since they reflect real-world practice of PCI and are useful in informing decision makers of potential standards and indicators to measure quality and performance.

CHALLENGES IN THE REAL WORLD

In addition to achieving optimal applicability by using Chinese population study data when formulating guideline recommendations, decision makers within the health system must be able to trust the guidelines before using them. A particularly important marker for trustworthiness is the efficiency in updating guideline recommendations when new evidence emerges in order to guarantee the validity of their recommendations to patients, health professionals and policymakers. A survival analysis reported that guideline recommendations are likely to be out-of-date after 3 years.²⁴ However, a survey of 143 Chinese practice guidelines revealed that only 7.7% (n=11) of the included guidelines had reported to have been updated and for those that were updated, the average update frequency was 5.2 years.²⁵ It took 4 years for the Chinese PCI guideline to be updated, and a staggering 9 years lapsed between the current and previous versions of the Chinese guideline for the management of dyslipidaemia in adults.²⁶ Creating and updating clinical practice guidelines are important yet enormous tasks for guideline developers worldwide, and there is substantial room for improvement for Chinese guideline developers. No formal guidance on how clinical practice guidelines should be updated and how updated guidelines should be reported was available until recently, when the 16-item Checklist for the Reporting of Updated Guidelines (Checkup) was developed to specifically address the presentation and methodology of updated clinical practice guidelines.²⁷ The checklist has come at a crucial time for Chinese guideline developers in particular, since there is currently minimal guidance on how often clinical guidelines should be updated, and it would be worth considering promoting the use of Checkup in China for increased transparency and rigour during guideline development process.

Resource availability is a key factor in developing clinical guidelines that can be successfully implemented in daily practice. It is clear that PCI is an emerging treatment strategy for CAD in China. The number of PCIs performed in urban Chinese hospitals increased 21-fold over the period of 2001-2011²⁸; in 2014 alone, over 500000 cases of PCI were performed.²¹ This is believed to be attributed to the healthcare system reform and expanded health insurance coverage of coronary interventions.²⁹ However, the imbalance of healthcare resource distribution among rural and urban communities will not go away overnight and, coupled with the lack of catheterisation facilities or capable operators to perform PCI, fibrinolysis therefore remains as a viable alternative for patients in whom access is unavailable or falls outside of the recommended therapeutic window. For basic-level rural hospitals without catheterizsation facilities, the use of fibrinolytic therapy should be actively encouraged. Indeed, guidelines from China, Europe and the USA are in sync to recommend the use of fibrinolytic therapy in patients with STEMI within 12 hours of ischaemic symptoms without contraindications if PCI is unavailable within 120 min from first medical contact (Class I recommendation, Level of Evidence A).^{14 30 31} Prompt

actions in subjecting patients with STEMI to timely and effective reperfusion therapy, whether it is PCI or fibrinolysis, remain the ultimate goal in acute care. For local clinical practice guidelines to be truly applicable, we need continual efforts in conducting clinical research in local populations and guideline commendations should be formulated with consideration on resource constraints and cost effectiveness, especially for vast countries with imbalanced economical distributions across regions. The third phase of the Clinical Pathways in Acute Coronary Syndromes (CPACS) programme, CPACS-3, is an ongoing stepped-wedge cluster randomised study designed to investigate the role of a multifaceted quality improvement initiative in clinical outcomes among patients with acute coronary syndromes (ACS) from 104 resource-constrained rural county hospitals without PCI facilities and for which the patient-transfer time to the nearest largest tertiary hospital with cath lab facilities is beyond a 90 min time frame.³² Results of this interesting study will not only provide useful insights as to how best to tackle unequal access to healthcare and thereby strengthen overall CAD care in rural China, but the study data can also serve as useful reference to other low-income and middle-income countries with similar resource constraints. We anticipate the results of CPACS-3 will bring much value to future updates of relevant Chinese clinical practice guidelines.

THE FUTURE IS BRIGHT

Much has changed in China over the past decade, with a steady and promising increase in the ability to synthesise innovative research evidence and translate it into clinical practice and health policies that are appropriate for use at the given times. Strong government support is likely to be a substantial trigger behind the recent advances in clinical research in China: expenditures on research and development reached a total of over 1.5 trillion Renminbi in 2016.³³ Besides financial stability, China has observed successful capacity building in maintaining a sustainable research infrastructure of multiple national clinical research centres, with a recent call for developing a learning healthcare system to drive forward a continual quality improvement initiative.9 The aforementioned China PEACE programme is an excellent demonstration to emphasise the importance of national efforts in conducting authentic, highquality clinical research. It is worth remembering that, the main reason behind the marked improvement in utilising local research evidence in the 2016 Chinese PCI guideline lies with the increasing body of research evidence available for knowledge translation, as PCI is one of the fastest growing fields in Chinese cardiovascular health research. Development of clinical practice guidelines is labour intensive and efforts should not be wasted in guidelines that fail to be implemented at the point of healthcare because practice recommendations do not meet the needs of those in question. Clinical trials and national observational studies conducted in local populations allow for a better understanding of treatment effectiveness and real-world practice trends across rural and urban regions and such ethnic-specific data should form the core evidence base for clinical practice guidelines that are truly trustworthy and useable.

It is clear that the concept of 'using Chinese data for highquality Chinese clinical guidelines, for Chinese patients' is slowly turning into reality. For a transparent and structured guideline development framework to be fully operational in China, there needs to be coordinated, collaborative efforts involving relevant Chinese stakeholders in assuring quality and transparency in the conduct of high-quality primary research, such as reinforcing the importance of trial registration in public trials registries, and effective translation of knowledge into practice in the current era of evidence overload. Although the number of Chinese guidelines for cardiovascular disease management still lags behind those from the USA and Europe,⁹ one should be encouraged by the aforementioned phenomena of steady growth of Chinese clinical practice guidelines and be reassured that China is taking small yet significant steps towards producing trustworthy clinical practice guidelines that are current, fit for purpose and applicable to real-world patients.

Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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